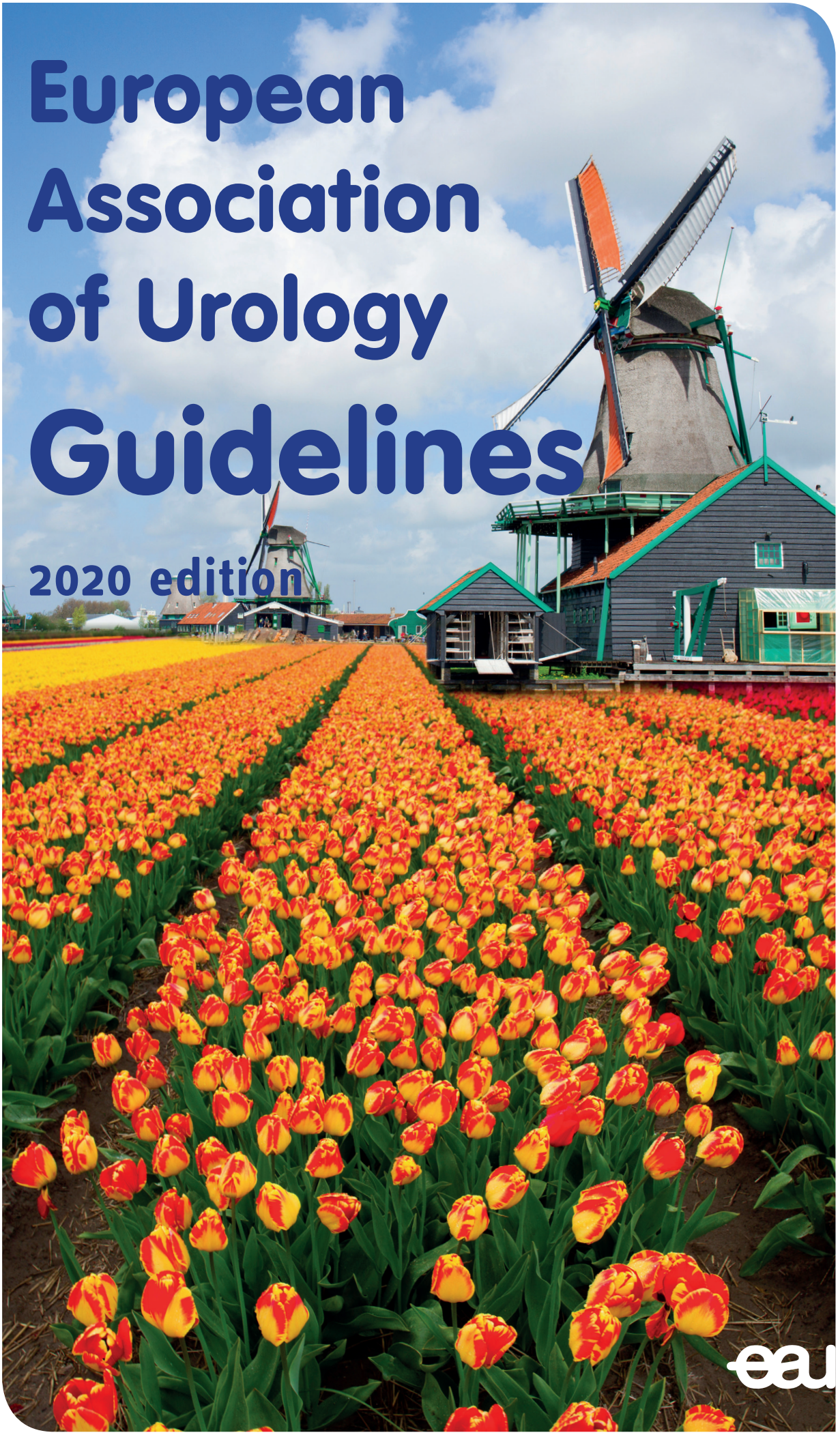
European Association of Urology Guidelines

2020 edition



European Association of Urology

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Guidelines

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Introduction

We are honoured to present the 2020 edition of the European Association of Urology (EAU) Guidelines, the most comprehensive, continuously updated, guidelines available for urologists and clinicians from related specialties. Produced by a dedicated Guidelines Office, involving approximately 250 international experts and endorsed by 72 national and professional societies around the world, the EAU Guidelines are internationally recognised as an excellent, high-quality resource for assisting clinicians in their everyday practice.

For the 2020 edition of the EAU Guidelines, we are proud to present the new EAU Guidelines on Sexual and Reproductive Health which consolidates the work of the former Male Infertility, Male Sexual Dysfunction and Male Hypogonadism Panels. Additionally, numerous guideline recommendations have been updated.

Going forward, the EAU Guidelines Office has a number of plans in place for the coming year, and beyond. We are delighted to announce the formation of a new EAU Guidelines Panel on Non-neurogenic Female LUTS under the leadership of Mr. C.K. Harding (Chair) and Prof.Dr. M.C. Lapitan (vice-chair). The Panel has already begun work on producing the new guideline for publication in 2021. Additionally, the ad-hoc EAU Guidelines on Urethral Strictures, Chaired by Prof.Dr. N. Lumen will also conclude their work in time for publication in 2021.

A further goal for the Guidelines Office in 2020 is a commitment to increasing patient involvement in Guidelines development. Our ultimate aim is to establish an effective framework that can ensure that the voices of patients are captured in the development of future guidelines recommendations in a meaningful and non-tokenistic manner. The EAU Guidelines Office believes that meaningful patient engagement will result in recommendations that lead to better treatment compliance and improved health outcomes aiding the realisation of a truly patient-centred shared-decision making framework. This promises to be a challenging but worthwhile long-term endeavour.

Adherence to clinical guidelines, both national and international, is sub-optimal throughout Europe. The key to increasing adherence to Guidelines, is to understand what are the barriers to adherence, and what might facilitate effective implementation of recommendations. To address these problems, the Guidelines Office IMAGINE group have designed a two-phase programme to: (i) map practice and adherence to key Guideline recommendations across Europe in collaboration with the National Urological Societies; and (ii) to understand the barriers and facilitators to implementation of these recommendations. The IMAGINE project will begin in March 2020 and will facilitate the continued optimisation and harmonisation of urological practice across Europe, ultimately raising the level of urological care and improving patient outcomes.

The yearly publication of the EAU Guidelines would not be possible without the unwavering support of the EAU Executive Committee and Management team, our highly valued Guidelines Panels and young Guidelines Associates, our EAU membership and every user of the Guidelines globally. So, on behalf of the EAU Guidelines Office Board, thank you for your support and inspiration.

We hope you enjoy using the 2020 update of the EAU Guidelines!

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Methodology section

Clinical guidelines development is one of the core activities of the European Association of Urology (EAU), with the 2020 Guidelines covering the majority of the urological field. The EAU clinical guidelines, which are updated based on systematic reviews (SRs) of the available clinical evidence, are developed to support clinicians in making informed decisions in their care of patients.

The Guidelines Office (GO), consisting of more than 300 clinicians, is responsible for the production of these documents. Their efforts are supported by a number of expert Committees, each with specific tasks and responsibilities.

The EAU GO unified production methodology aims to:

- ensure scientific quality, accuracy and currency of information;
- promote sustainable quality improvement;
- contribute to the dissemination and implementation of all EAU Guidelines publications.

All EAU Guidelines can be accessed online through the Association website: www.uroweb.org/guidelines/. All full members of the EAU can collect print copies, of both the full text and pocket Guidelines, at EAU Annual meetings. A mobile app containing the Pocket guidelines is available for download for both iOS and Android devices.

Systematic Review development

The EAU GO have set up a management structure to support development of SRs involving young clinicians (Guidelines Associates) who are supported by methodologists and statisticians. These SRs are based on clinical questions prioritised by the Guideline Panel responsible for each topic and their findings are incorporated into the EAU guidelines as they become available. Benefits and harms of interventions are addressed in detail, both in the development stage of the clinical question and when review findings are being incorporated, and treatment recommendations formulated. Whenever possible, patient input is sought at both the development stage of the SR questions as well as when guidelines recommendations are being drafted. Patient organisations are invited to take part in review of the EAU Guidelines documents prior to publication. This is a rolling programme, with the ambition to address the majority of key clinical questions covered by the EAU guidelines.

All SRs are performed using standard Cochrane SR methodology: (http://www.cochranelibrary.com /about/about-cochrane-systematic-reviews.html). Two independent reviewers screen abstracts and full texts, carry out data abstraction, assess risk of bias and do a GRADING exercise [1-4]. The results are presented in tables showing baseline characteristics and summaries of findings. Meta-analyses are performed only as part of a SR when several randomised controlled trials have addressed the same question and outcomes are reported homogenously. For lower level data, narrative syntheses of the evidence are provided. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance is followed [5].

Independently of these SRs, each Guideline Panel has undertaken a separate systematic search, tailored to their individual guideline. These are broad searches (Scope/Horizon searches) which are developed to:

- ensure that the available clinical evidence is identified in a structured unbiased fashion;
- ensure that significant data are not missed;
- inform on the need to update guidelines documents;
- identify gaps in the literature and prioritise future systematic review activities.

The results of these searches are selected and assessed in a structured fashion by Guideline Associates and Guideline Panel members, although no detailed evidence summaries are produced. The search histories are available online in the Appendices and Publications sections of each guideline topic (www.uroweb.org/guidelines/).

Level of evidence and grading systems

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [3, 4]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomization.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

** Modified from [6].*

References

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5. Moher, D., *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol, 2009. 62: 1006.
6. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
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The following National Urological Associations endorse the EAU Guidelines:

National Societies Endorsements

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The Argentinian Society of Urology
The Armenian Association of Urology
The Urological Society of Australia and New Zealand
The Austrian Urological Society
The Belarusian Association of Urology
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The EAU Guidelines Office is most grateful for the continued support of the European Board of Urology.

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Non-muscle-invasive (Ta, T1 and CIS) Bladder Cancer

Upper Urinary Tract Urothelial Carcinoma

Muscle-Invasive and Metastatic Bladder Cancer

Primary Urethral Carcinoma

Prostate Cancer

Renal Cell Carcinoma

Testicular Cancer

Penile Cancer

Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. benign prostatic obstruction (BPO)

Urinary Incontinence in Adults

Neuro-Urology

Sexual and Reproductive Health

Urological Infections

Urolithiasis

Bladder Stones

Paediatric Urology

Urological Trauma

Chronic Pelvic Pain

Renal Transplantation

Thromboprophylaxis in Urological Surgery

EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Separate EAU Guidelines documents are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2] and primary urethral carcinoma [3]. It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist and a statistician. Members of this Panel have been selected based on their expertise and to represent the professionals treating patients suspected of suffering from bladder cancer. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/nonmuscleinvasive-bladder-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2019 [4], as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Guidelines on Bladder Cancer were first published in 2000. This 2020 NMIBC Guidelines document presents a limited update of the 2019 publication.

*1.4.2 **Summary of changes***

Additional data has been included throughout this document text. In particular in sections:

- 4.7 - Variants of urothelial carcinoma and lymphovascular invasion: this section has been expanded to include further information on variant histologies.
- 7.3 - Treatment of failure of intravesical therapy. This section has been considerably expanded, alongside a revision of Figure 7.2, Table 7.2 (Categories of unsuccessful treatment with intravesical BCG) and 7.7 Guidelines for the treatment of BCG failure.

Recommendations have been changed in sections:

7.5 Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Offer a RC to patients with BCG unresponsive tumours (see Section 7.7).	Strong
Offer patients with BCG unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesial- or systemic immunotherapy; preferably within clinical trials).	Weak

7.7 Guidelines for the treatment of BCG failure

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC)	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak
Late BCG relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.	Strong
	2. Bladder-preserving strategies	Weak
LG recurrence after BCG for primary	1. Repeat BCG or intravesical chemotherapy	Weak
	2. Radical cystectomy	Weak

2. METHODS

2.1 Data Identification

For the 2019 NMIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines was performed. Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults, were included. The search was restricted to articles published between June 8th 2018 and May 16th, 2019. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,124 unique records were identified, retrieved and screened for relevance.

A total of 29 new publications were added to the 2020 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guideline/non-muscle-invasive-bladdercancer/?type=appendices-publications.

For Chapters 3-6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) references used in this text were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM levels of evidence was being used [5].

For each recommendation within the guidelines there is an accompanying online strength rating form based on a modified GRADE methodology [6, 7]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications of systematic reviews were peer reviewed prior to publication. The NMIBC Guidelines were peer-reviewed prior to publication in 2019.

2.3 Future goals

The results of ongoing reviews will be included in the 2020 update of the NMIBC Guidelines. These reviews are performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing projects:

- Individual Patient Data Prognostic Factor Study on WHO 1973 & 2004 Grade and EORTC 2006 risk score in primary TaT1 Bladder Cancer.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered [8]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [8]. In the European Union the age-standardised incidence rate is 19.1 for men and 4.0 for women [8]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [8].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [8]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, partly caused by the different methodologies used and the quality of data collection [9]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [10].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40) this percentage is even higher [11]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [8, 9].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [9, 10, 12, 13] (LE: 3). Low-tar cigarettes are not associated with a lower risk of developing bladder cancer [13]. The risk associated with electronic cigarettes is not adequately assessed; however, carcinogens have been identified in urine [13]. Environmental exposure to tobacco smoke is also associated with an increased risk for BC [9]. Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants, which process paint, dye, metal and petroleum products [9, 10, 14, 15]. In developed industrial settings, these risks have been reduced by work-safety guidelines; therefore, chemical workers no longer have a higher incidence of BC compared to the general population [9, 14, 15].

While family history seems to have little impact [16] and, to date, no overt significance of any genetic variation for BC has been shown; genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [9, 17-21]. This has been suggested to lead to familial clustering of BC with an increased risk for first- and second-degree relatives (hazard ratio [HR]: 1⁄4 1.69, 95% confidence interval [CI]: 1⁄4, 1.47-1.95, $p < 0.001$) [22].

Although the impact of drinking habits is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, also exposure to arsenic in drinking water increases risk [9, 23] (LE: 3). Arsenic intake and smoking has a combined effect [24]. The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [9]. Dietary habits seem to have little impact, recently protective impact of flavonoids have been suggested and a Mediterranean diet, characterised by a high

consumption of vegetables and non-saturated fat (olive oil) and moderate consumption of protein, was linked to some reduction of BC risk (HR: 0.85 [95% CI: 0.77, 0.93]) [25-30].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [9, 23, 31] (LE: 3). The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol and triglycerides) is uncertain [32]. Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC [9] (LE: 3).

3.3 Pathology

The information presented in this text is limited to urothelial carcinoma, unless otherwise specified.

3.4 Summary of evidence for epidemiology, aetiology and pathology

Summary of evidence	LE
Worldwide, bladder cancer (BC) is the eleventh most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system [33]. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term “Non-muscle-invasive BC” represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/carcinoma-of-the-bladder-cystectomy-cystoprostatec). The term ‘superficial BC’ should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2009 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2017 (8th Edn.), but with no changes in relation to bladder tumours (Table 4.1) [33].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: ‘flat tumour’
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall

N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
	M1a Non-regional lymph nodes
	M1b Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 substaging) has been demonstrated to be of prognostic value in retrospective cohort studies [34, 35] (LE: 3). Its use is recommended by the most recent 2016 World Health Organization (WHO) classification [36]. The optimal system to substage T1 remains to be defined [36, 37].

4.4 Histological grading of non-muscle-invasive bladder urothelial carcinomas

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [36, 38] (Tables 4.2 and 4.3, Figure 4.1). In 2016, an update of the 2004 WHO grading classification was published without major changes [36]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [39].

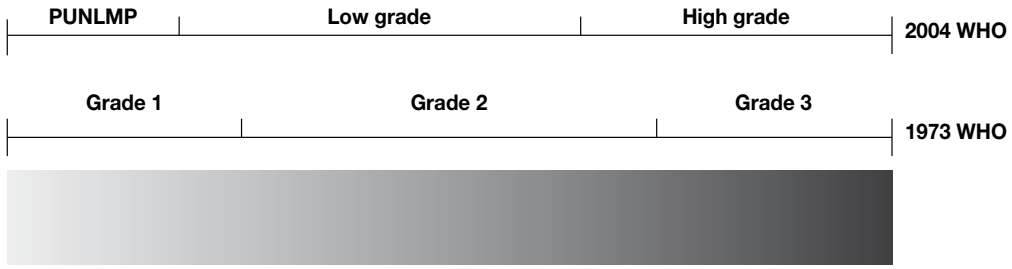
Table 4.2: WHO grading in 1973 and in 2004/2016 [36]

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 WHO grading system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [39] (LE: 2a).

There is a significant shift of patients between the prognostic categories of both systems, for example an increase in the number of HG patients (WHO 2004/2016) due to inclusion of some G2 patients with their better prognosis compared to the G3 category (WHO 1973) [39]. According to a recent multi-institutional IPD analysis, the proportion of tumours classified as PUNLMP has decreased to very low levels in the last decade [40]. As the 2004 WHO system has not been fully incorporated into prognostic models yet, long term individual patient data using both classification systems are needed.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [41]*



**1973 WHO Grade 1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade (LG) carcinomas in the 2004 WHO classification, and Grade 2 carcinomas to LG and high-grade (HG) carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to HG carcinomas (Reproduced with permission from Elsevier).*

4.5 Carcinoma *in situ* and its classification

Carcinoma *in situ* is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts, and prostatic urethra [42].

Classification of CIS according to clinical type [43]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Table 4.3: WHO 2004 histological classification for flat lesions

Non-malignant lesions
• Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects).
• Reactive atypia (flat lesion with atypia).
• Atypia of unknown significance.
• Urothelial dysplasia.
Malignant lesion
• Urothelial CIS is always high grade.

4.6 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [44] (LE: 2a). There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2004 classifications. The general conformity between pathologists in staging and grading is 50-60% [45-48] (LE: 2a). The WHO 2004 classification provides slightly better reproducibility than the 1973 classification [39].

4.7 Variants of urothelial carcinoma and lymphovascular invasion

Currently the following differentiations are used [49, 50]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary urothelial carcinoma;
4. nested variant (including large nested variant) and microcystic urothelial carcinoma;
5. plasmocytoid, giant cell, signet ring, diffuse, undifferentiated;
6. lymphoepithelioma-like;
7. some urothelial carcinomas with other rare differentiation;
8. small-cell carcinomas;
9. sarcomatoid urothelial carcinoma.

Other, extremely rare, variants exist which are not detailed.

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, sarcomatoid) have a worse prognosis than

pure HG urothelial carcinoma [2, 51-58] (LE: 3).

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [59-63] (LE: 3).

4.8 Molecular classification

Molecular markers and their prognostic role have been investigated [64-68]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification are promising, but are not yet suitable for routine application [69, 70].

4.9 Summary of evidence and guidelines for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
For histological classification of NMIBC, both the WHO 1973 and 2004 grading systems are used.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO grading systems.	Strong
Do not use the term ‘superficial’ bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage disease compared to nonvisible haematuria [71]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

5.3 Physical examination

A focused urological examination is mandatory although it does not reveal NMIBC.

5.4 Imaging

*5.4.1 **Computed tomography urography and intravenous urography***

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [72].

Intravenous urography (IVU) is an alternative if CT is not available [73] (LE: 2b), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography provides more information (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [74-76] (LE: 2b). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [75] (LE: 2b). The risk of UTUC during follow up increases in patients with multiple- and high-risk tumours [77] (LE: 2b).

*5.4.2 **Ultrasound***

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [78, 79] (LE: 3). It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

*5.4.3 **Multiparametric magnetic resonance imaging***

The role of multiparametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting in patients with BC was recently published but requires validation [80].

A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI) (LE: 4).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 and high-grade tumours (84%), but low sensitivity in G1/LG tumours (16%) [81]. The sensitivity in CIS detection is 28-100% [82] (LE: 1b). Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours. Positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [83, 84]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, however, in experienced hands specificity exceeds 90% [83] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [85]:

- adequacy of urine specimens (Adequacy);
- negative for high-grade urothelial carcinoma (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade urothelial carcinoma (Suspicious);
- high-grade urothelial carcinoma (HGUC);
- low-grade urothelial neoplasia (LGUN).

The Paris system for reporting urinary cytology has been validated in several retrospective studies [86, 87].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [88]. In patients with suspicious cytology repeat investigation is advised [89] (LE: 2b).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed [90]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity, compared to urine cytology [91-96] (LE: 3).
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [91-93] (LE: 1b).
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow up [high risk, low/intermediate risk]) [92, 93] (LE: 3).
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and complicated laboratory methods required [93, 94, 97-104].
- Positive results of cytology, UroVysion (FISH), Nuclear Matrix Protein (NMP)22®, *Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT)* and microsatellite analysis in patients with negative cystoscopy and upper tract work-up, may identify patients more likely to experience disease recurrence and possibly progression [98, 100, 103-107] (LE: 2b).
- If main aim is to avoid unnecessary cystoscopies, rather than looking for markers with a high sensitivity and specificity, focus should be on identifying a marker with a very high negative predictive value. A test able to predict absence of tumour will have great utility in daily clinical practice [108].
- Promising novel urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies, with a very high negative predictive value [97, 99, 109-112].

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

*5.7.1 **Screening of the population at risk of bladder cancer***

The application of haematuria dipstick, followed by *FGFR3*, NMP22® or UroVysion tests if dipstick is positive has been reported in BC screening in high-risk populations [113, 114]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [106, 114]. Routine screening for BC is not recommended [106, 113, 114].

*5.7.2 **Exploration of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)***

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important.

*5.7.3 **Surveillance of non-muscle-invasive bladder cancer***

Research has been carried out into the usefulness of urinary cytology vs. markers in the follow up of NMIBC [97, 98, 110, 111, 115].

5.7.3.1 Follow-up of high-risk non-muscle-invasive bladder cancer

High-risk tumours should be detected early in follow up and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.

5.7.3.2 Follow-up of low/intermediate-risk non-muscle-invasive bladder cancer

To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology and current urinary markers is their low sensitivity for low-grade recurrences [92, 98] (LE: 1b).

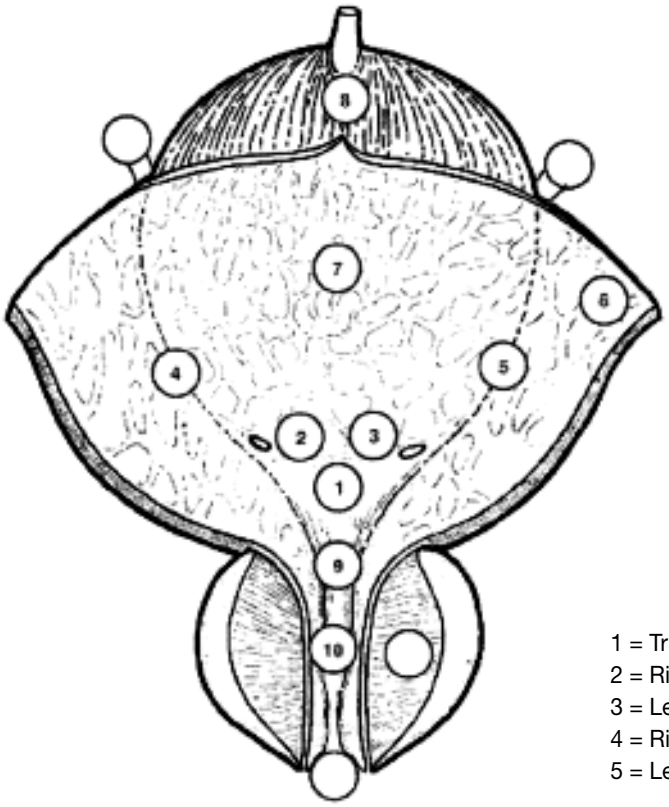
According to current knowledge, no urinary marker can replace cystoscopy during follow up or lower cystoscopy frequency in a routine fashion. One prospective randomised study found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [116] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [116] (see Section 8.1).

5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [117].

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [118, 119] (LE: 1b).

Figure 5.1: Bladder diagram



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 = Posterior urethra

5.9 Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goal of TURB in TaT1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder should be performed systematically in individual steps [120, 121] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to assign disease risk (number of tumours, size, multifocality, characteristics, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), and presence of complications (assessment for perforation) [121, 122]. To measure the size of the largest tumour, one can use the end of cutting loop, which is approximately 1 cm wide as a reference. The characteristics of the tumour are described as sessile, nodular, papillary or flat.

*5.10.2 **Surgical and technical aspects of tumour resection***

5.10.2.1 Surgical strategy of resection (piecemeal/separate resection, en-bloc resection)

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis [120, 123].

- Piecemeal resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [124] (LE: 2b).
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumours. It provides high quality resected specimens with the presence of detrusor muscle in 96-100% of cases [120, 125-128] (LE: 1b).

The technique selected is dependent on the size and location of the tumour and experience of the surgeon.

5.10.2.2 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [129] (LE: 1b). The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required (except in TaG1/LG tumours).

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [130]. Virtual training on simulators is an emerging approach [131]. Its role in the teaching process still needs to be established [121].

5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens. Currently, the results remain controversial [132-135].

5.10.2.4 Office-based fulguration and laser vaporisation

In patients with a history of small, TaLG/G1 tumours, fulguration or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [136, 137] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

5.10.2.5 Resection of small papillary bladder tumours at the time of transurethral resection of the prostate

Only limited, retrospective, data exist on the outcome of incidentally detected papillary bladder tumour during cystoscopy as the initial step of transurethral resection of the prostate. Provided these tumours are papillary by aspect, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate. However, no exact risk-assessment can be provided [138, 139].

*5.10.3 **Bladder biopsies***

Carcinoma *in situ* can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason biopsies from suspicious urothelium should be taken. However, in patients with positive urine cytology, or with a history of HG/G3 NMIBC and in tumours with non-papillary appearance, mapping biopsies from normal-looking mucosa is recommended [140, 141]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [140, 141]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

*5.10.4 **Prostatic urethral biopsies***

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al*. showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% [142] (LE: 2b). The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [143] (LE: 3b). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [142, 144, 145].

5.11 New methods of tumour visualisation

As a standard procedure, cystoscopy and TURB are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

*5.11.1 **Photodynamic diagnosis (fluorescence cystoscopy)***

Photodynamic diagnosis is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly for CIS [146, 147] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [147]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [148].

Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [147]. False-positivity can be induced by inflammation or recent TURB and during the first three months after BCG instillation [149, 150] (LE: 1a).

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, six using 5-ALA and nine HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [151] (LE: 1a).

One RCT has shown a reduction in recurrence and progression with fluorescence guided TURB as compared to white light TURB [152]. These results need to be validated by further studies.

*5.11.2 **Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [153-156] (LE: 3b). An RCT assessed the reduction of recurrence rates if NBI is used during TURB. Although the overall results of the study were negative, a benefit after three and twelve months was observed for low-risk tumours (pTa/LG, < 30 mm, no CIS) [157] (LE: 1b).

*5.11.3 **Additional technologies***

Confocal laser micro-endoscopy is a high resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [158]. The Storz professional image enhancement system (IMAGE1 S, formally called SPIES) is an image enhancement system using four different light spectra but prospective data using this system are lacking [159].

5.12 Second resection

*5.12.1 **Detection of residual disease and tumour upstaging***

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [123] (LE: 1b).

A SR analysing data of 8,409 patients with Ta or T1 HG BC demonstrated a 51% risk of disease persistence and an 8% risk of understaging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [160] (LE: 1a).

Another meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high in a subgroup with detrusor muscle in the resection specimen. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and understaging occurred in 11% of cases [161].

*5.12.2 **The impact of second resection on treatment outcomes***

A second TURB can increase recurrence-free survival (RFS) [162, 163] (LE: 2a), improve outcomes after BCG treatment [164] (LE: 3) and provide prognostic information [165-168] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1G3/HG tumours (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the specimen of the initial resection [169] (LE: 3).

*5.12.3 **Timing of second resection***

Retrospective evaluation showed that a second resection performed 14-42 days after initial resection provides longer RFS and PFS compared to second resection performed after 43-90 days [170] (LE: 3). Based on these arguments, a second TURB is recommended in selected cases two-six weeks after initial resection (for recommendations on patient selection, see Section 5.14).

*5.12.4 **Recording of results***

The results of the second resection (residual tumours and understaging) reflect the quality of the initial TURB. As the goal is to improve the quality of the initial TURB, the results of the second resection should be recorded.

5.13 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [171]. Close co-operation between urologists and pathologists is required. A high quality of resected and submitted tissue and clinical information is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of the T category. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [172, 173]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

5.14 Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour understaging (with the exception of TaLG tumours).	2b
In patients with a history of small TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis is feasible and safe.	3
A second TURB can detect residual tumours and tumour understaging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma *in situ* is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong

Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

Treatment should be based on a patient's prognosis. In order to predict, both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables [174]. The basis for these tables are individual patient data from 2,596 patients diagnosed with TaT1 tumours, who were randomised into seven EORTC trials. Patients with CIS alone were not included. Seventy-eight percent of patients received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathological factors which are shown in Table 6.1. It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 6.2 shows the total scores stratified, into four categories that reflect various probabilities of recurrence and progression at one and five years [174] (LE: 2a).

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for Apple and Android phones and tables, are available for download: https://www.eortc.be/tools/bladdercalculator/download_disclaimer.htm.

The prognosis of intermediate-risk patients treated with chemotherapy has been calculated. Patients with Ta G1/G2 tumours receiving chemotherapy were further stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade, number of tumours and adjuvant chemotherapy [175].

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 month period following TURB, has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received twelve instillations over five-six months. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [176] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this sample.

The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow up in an independent patient population [177, 178] (LE: 2a).

In 1,812 intermediate- and high-risk patients without CIS treated with one to three years of maintenance BCG, the EORTC found that the prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and grade for disease progression and disease-specific survival, while age and grade were the most important prognostic factors for OS. T1G3 patients do poorly, with one- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data the new EORTC risk groups and nomograms for BCG-treated patients were designed [179] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with induction course only) [142, 180] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of the absence of muscle layer in the diverticular wall [181] (LE: 3).
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [166-168] (LE: 3).
- In patients with T1G2 tumours treated with TURB, recurrence at three months was the most important predictor of progression [182] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently available risk tables [177, 183].
- Preoperative neutrophil-to-lymphocyte ratio may have prognostic value in NMIBC. This data, however, needs further validation [184].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [185] (LE: 3). There are no reliable prognostic factors, some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [186, 187] in extended CIS [188] and in CIS in the prostatic urethra [142] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [176-178, 182]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [189, 190] (LE: 2a).

6.3 Patient stratification into risk groups

The Guidelines Panel recommends stratification of patients into three risk groups. Table 6.3 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and, especially, progression.

6.4 Subgroup of highest-risk tumours

Based on prognostic factors, it is possible to sub-stratify high-risk group patients, and identify those that are at the highest risk of disease progression. Patients diagnosed with T1G3/HG tumours associated with concurrent bladder CIS, multiple- and/or large T1G3/HG tumours and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, and T1 tumours with LVI (Table 6.3) are at the highest risk of progression.

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no CIS.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumours	Any of the following: • T1 tumour • G3 (HG**) tumour • carcinoma *in situ* (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present)*.
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.

Sub-stratification of high-risk tumours for clinical purposes is addressed in Table 7.2.

**Low grade is a mixture of G1 and G2.*

*** High grade is a mixture of some G2 and all G3 (see Figure 4.1).*

6.5 Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EORTC scoring system and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with non-muscle-invasive bladder cancer (NMIBC).	2a
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade, number of tumours and adjuvant chemotherapy.	2a-b
In patients treated with 5-6 months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression.	2a
In patients receiving BCG maintenance; prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence. Stage and grade are the most important prognostic factors for disease progression and disease-specific survival; patient age and grade are the most important prognostic factors for overall survival.	2a

Recommendations	Strength rating
Stratify patients into three risk groups according to Table 6.3.	Strong
Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder in individual patients.	Strong
Use the CUETO risk tables and the EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [191, 192] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [181, 193-195] (LE: 3).

7.2 Adjuvant treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [123]. It is therefore necessary to consider adjuvant therapy in all patients.

*7.2.1 **Intravesical chemotherapy***

7.2.1.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [196-199] (LE: 3).

Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [200-203] (LE: 1a). In a SR and individual patient data meta-analysis of 2,278 eligible patients [200], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. Only patients with a prior recurrence rate of less than or equal to one recurrence per year and those with an EORTC recurrence score < 5 benefited from SI. In patients with an EORTC recurrence score ≥ 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment.

No randomised comparisons of individual drugs have been conducted [200-203].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin, have all shown a beneficial effect [200]. Single instillation with gemcitabine was superior to placebo control (saline) in an RCT with approximately 200 patients per arm [204], with remarkably low toxicity rates [204]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [205]. In the Böhle *et al*. study, continuous saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low

recurrence rate in the control arm [205]. Two meta-analyses suggest efficacy of continuous saline irrigation in the prevention of early recurrences [206, 207].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix [196, 208-210] (LE: 3). In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [211]. To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation [212, 213] safety measures should be maintained (see Section 7.5).

7.2.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1, 6.2 and 6.3), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [200, 201] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1, 6.2 and 6.3).

Efficacy data for the following comparisons of application schemes were published:

Single installation only vs. SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [214] (LE: 2a).

Repeat chemotherapy instillations vs. no adjuvant treatment

A large meta-analysis of 3,703 patients from eleven randomised trials showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [215]. This corresponds to an absolute difference of 13-14% in the number of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [216, 217] (see Section 7.2.2.1) (LE: 1a). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [218-220] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [220] (LE: 1a).

Single instillation + further repeat instillations vs. later repeat instillations only

There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [221-224]. An RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at three years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [221] (LE: 2a). Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [225]. The results of this study should be considered with caution since some patients did not receive adequate therapy. An RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC [226].

The optimal schedule of intravesical chemotherapy instillations

The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [224] (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy

7.2.1.3.1 Adjustment of pH, duration of instillation, and drug concentration

The intravesical solution reduced the recurrence rate [227] (LE: 1b). Another trial reported that duration of a one hour instillation of MCC was more effective compared to a 30 minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [228] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [229] (LE: 1b). In view of these data, instructions are provided (see Section 7.5).

7.2.1.3.2 Device-assisted intravesical chemotherapy

Microwave-induced hyperthermia

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [230]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [231] (LE: 1b).

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [232]. The definitive conclusion, however, needs further confirmation.

For application of device-assisted instillations in patients with BCG-unresponsive tumours, see Section 7.3.3.

7.2.1.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	**LE**
In patients with low-risk NMIBC and in those with a prior low recurrence rate (one recurrence per year) and in those with an EORTC recurrence score < 5, a single instillation (SI) significantly reduces the recurrence rate compared to transurethral resection of the bladder alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given.	3
Repeat chemotherapy instillations (with or without previous SI) improve recurrence-free survival in intermediate-risk patients.	2a

7.2.2 ***Intravesical bacillus Calmette-Guérin (BCG) immunotherapy***

7.2.2.1 Efficacy of BCG

Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [218, 233-236] (LE: 1a). Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [237], MMC [238], or epirubicin alone [219] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [219, 238] and was also observed in a separate analysis of patients with intermediate-risk tumours [219]. One meta-analysis [218] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

It has been suggested that the efficacy of MMC may be improved by optimising application through the adjustment of urine pH, in addition to the use of alternative maintenance schedules. Neither aspect is reflected in the literature quoted above since most published studies do not support this approach.

Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [216, 217, 236] (LE: 1a). A meta-analysis carried out by the EORTC Genito-Urinary Cancers Group (GUCG) has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [217]. An RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [219] (LE: 1b). In contrast, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [218].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a

reduction in the risk of progression in high- and intermediate-risk tumours if a BCG maintenance schedule was applied.

Influence of further factors
Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [239]. In the IPD meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [218] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [240] (LE: 1a). According to a cohort analysis, the risk of tumour recurrence after BCG was shown to be higher in patients with a previous history of UTUC [241].

7.2.2.2 BCG strain
Although smaller studies without maintenance demonstrated some differences between strains [241-243], a network meta-analysis identified ten different BCG strains used for intravesical treatment in the published literature but was not able to confirm superiority of any BCG strain over another [244].

Similarly, a published meta-analysis of prospective RCTs [217], recently published data from a prospective registry [245] as well as from a *post-hoc* analysis of a large phase 2 prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients [246] did not suggest any clear difference in efficacy between the different BCG-strains (LE: 2a). The quality of data, however, does not allow definitive conclusions.

7.2.2.3 BCG toxicity
Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [217] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [247] (LE: 1b). The incidence of BCG infections after BCG instillations was 1% In a register-based cohort analysis [248]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [247]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [249]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [250] (LE: 2a). No significant difference in toxicity between different BCG strains was demonstrated [245]. Symptoms may be the result of side-effects of the BCG-treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients [251].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.5). The presence of leukocyturia, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [100, 252, 253] (LE: 3).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g. immunosuppression, human immunodeficiency virus (HIV) infection pose relative contraindications [254], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [255-257] (LE: 3). The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [258, 259] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [259-262]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation b. Perform a urine culture c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity b. With negative culture: quinolones and potentially analgesic anti-inflamatory instillations once daily for 5 days (repeat cycle if necessary) [260].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [261]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [262].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. • Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus.*
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al*. [263]. For optimal efficacy, BCG must be given in a maintenance schedule [216-218, 236] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of ten instillations given in eighteen weeks to 27 over three years [264]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [217]. In their meta-analysis, Bohle *et al*. concluded that at least

one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [216] (LE: 1a).

The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations are not fully known. Moreover, it can be different in each individual patient [265]. In an RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the 3-year arm, however, 36.1% of patients did not complete the 3-year schedule [266] (LE: 1b). In an RCT of 397 patients CUETO suggested that in high-risk tumours, the maintenance schedule with only one instillation every three months for three years may be suboptimal [267] (LE: 1b).

7.2.2.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [268, 269] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [270] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [249, 266] (LE: 1b). The routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose reliably.

7.2.2.6 Indications for BCG

Although BCG is very effective, there is consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patient's risk (Table 6.2). Recommendations for individual risk groups are provided in Section 7.5.

A statement by the Panel on BCG shortage can be accessed online:
https://uroweb.org/guideline/non-muscleinvasive- bladder-cancer/?type=appendices-publications.

7.2.2.7 Summary of evidence - BCG treatment

Summary of evidence	**LE**
In patients with intermediate- and high-risk tumours, intravesical bacillus Calmette-Guérin (BCG) after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

*7.2.3 **Combination therapy***

7.2.3.1 Intravesical BCG + chemotherapy versus BCG alone

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [271]. In an RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [232, 272] (LE: 2). Two meta-analyses demonstrated improved DFS, but no difference in PFS in patients treated with combination treatment comparing to BCG alone [272, 273].

7.2.3.2 Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [274]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [275]. Additionally, an RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [276] (LE: 1b).

*7.2.4 **Specific aspects of treatment of carcinoma in situ***

7.2.4.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [174, 176], in this case further treatment according to the criteria summarised in Sections 7.2.1, 7.2.2, 7.3 and 7.4 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [185] (LE: 3).

7.2.4.2 Cohort studies on intravesical BCG or chemotherapy

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [185-188, 277] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [188, 210, 264, 277] (LE: 3).

7.2.4.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few randomised trials in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [278] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy [217] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [279]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.2.4.4 Treatment of CIS in prostatic urethra and upper urinary tract

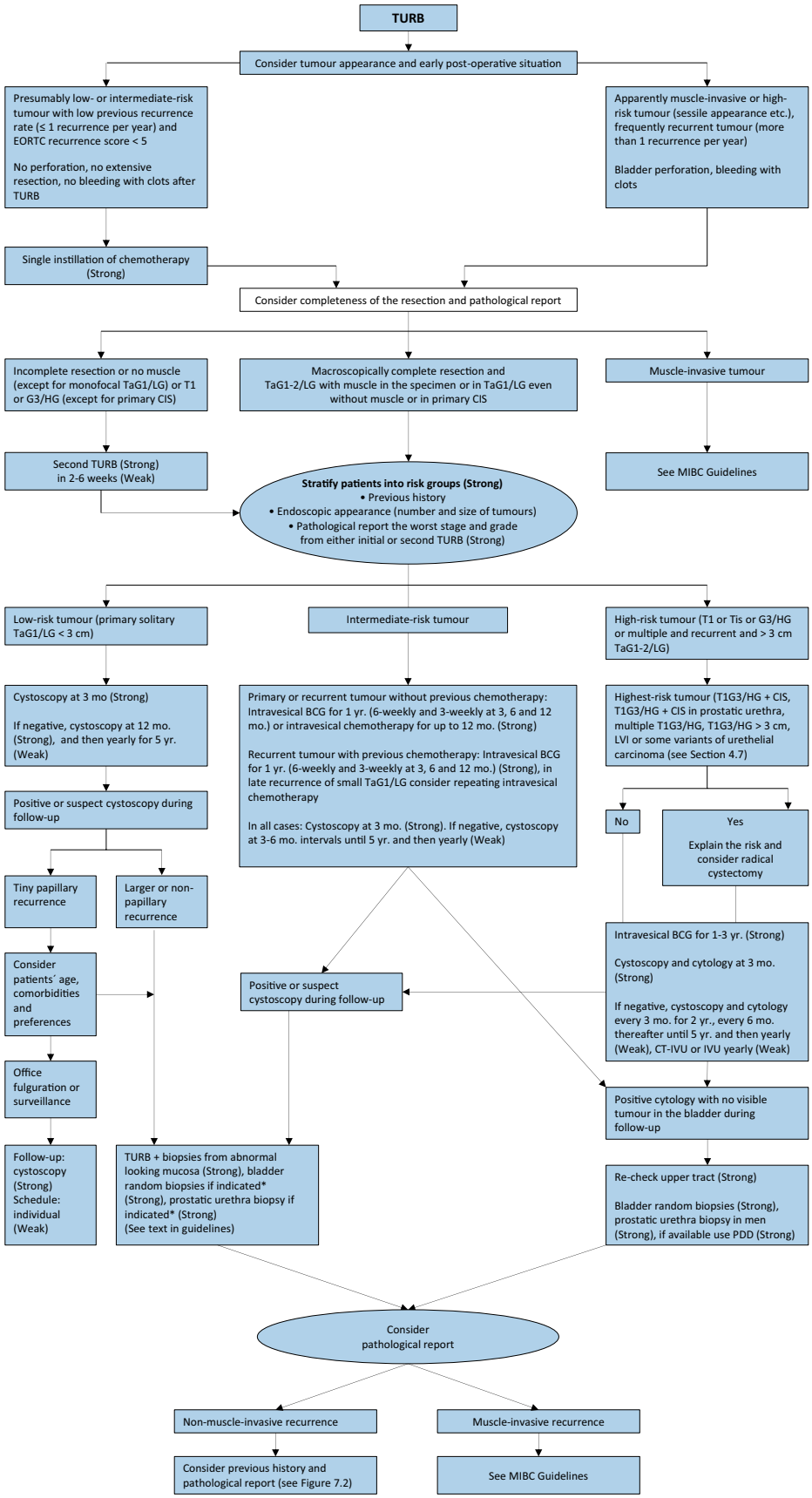
Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al*. found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [280]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [280] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [42]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours), and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [119, 281] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement, there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [281, 282] (LE: 3).

7.2.4.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* (CIS) cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, bacillus Calmette-Guérin treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.	1b

Figure 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*



** For details and explanations see the text of the guidelines.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.3 Treatment of failure of intravesical therapy

7.3.1 Failure of intravesical chemotherapy

Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [218] (LE: 1a).

7.3.2 Recurrence and failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any disease occurrence following therapy, have been proposed (Table 7.2). Non-muscle-invasive BC presenting after BCG can be categorised into BCG refractory, BCG unresponsive and BCG relapse. Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [283]. Recently an updated definition of BCG-unresponsive tumours was introduced to denote a subgroup of patients at higher risk of progression for whom further BCG is not feasible [284]. This definition was developed in consultation with the FDA to allow for single-arm trials to provide primary evidence of effectiveness to support a marketing application since no effective therapy is available for BCG-unresponsive NMIBC [285].

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months [286]. Further conservative treatment with BCG is associated with an increased risk of progression [189, 287] (LE: 3). 2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [42] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [42, 43, 277] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [288] (LE: 3).
BCG unresponsive tumour
BCG refractory or T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure [284] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [259].

** Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

7.3.3 Treatment of BCG failure

Treatment recommendations and options are provided in Sections 7.5 and 7.7. They reflect the categories mentioned in Table 7.2 and tumour characteristics at the time of recurrence.

Patients with BCG unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Additionally, several bladder preservation strategies are under different stages of investigation such as cytotoxic intravesical therapies (271), device assisted instillations (see below), intravesical immunotherapy [289], systemic immunotherapy [290] or gene therapy [291-293].

Changing from BCG to these options can yield responses in selected cases with BCG unresponsive disease [289, 294-303] (LE: 3). In the only RCT on a series of predominantly high-risk NMIBC failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia yielded an overall 35% disease-free survival (DFS) at 2 years as compared to 41% of the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rate in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [304]. Recently, the systemic immunotherapy pembrolizumab was granted FDA approval based on currently unpublished data.

At the present time, treatments other than RC must, however, be considered oncologically inferior in patients with BCG unresponsive disease [189, 286, 287] (LE: 3). Various studies suggest that repeat-BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours, namely those relapsing beyond one year after BCG exposure [294, 305] (LE: 3).

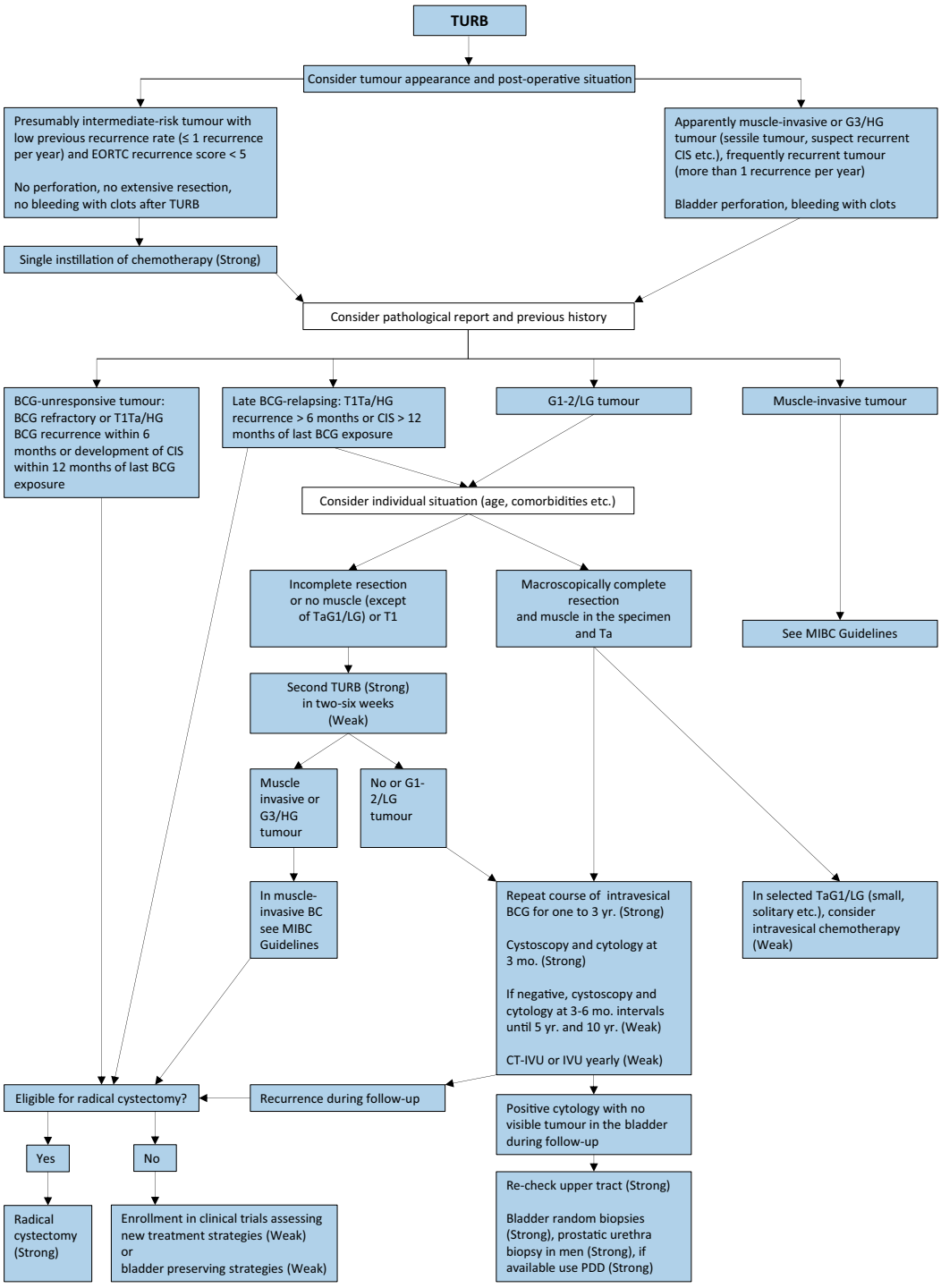
Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Non-high-grade recurrence after BCG is not considered as BCG failure. Treatment decisions should be individualised according to tumour characteristics.

*7.3.4 **Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	**LE**
Prior intravesical chemotherapy has no impact on the effect of bacillus Calmette-Guérin (BCG) instillation.	1a
Treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG unresponsive tumours.	3

Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG*



BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.4 Radical cystectomy for non-muscle-invasive bladder cancer

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC [145, 306-310] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage, have a worse prognosis than those who present with 'primary' muscle-invasive disease [311, 312].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of disease progression (see Section 7.6) [58, 142, 174, 176, 313] (LE: 3).

Early RC is strongly recommended in patients with BCG unresponsive tumours, as mentioned above. A delay in RC may lead to decreased disease-specific survival [314] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [315-317] (LE: 3).

7.5 Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcino*ma in situ*

General recommendations	**Strength rating**
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Table 6.3 and Section 7.6.	Strong
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side-effects and problems connected with BCG shortage.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Discuss immediate radical cystectomy (RC) with patients at the highest risk of tumour progression (see Section 7.6).	Strong
Offer a RC to patients with BCG unresponsive tumours (see Section 7.7).	Strong
Offer patients with BCG unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

7.6 Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS.	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk).	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus 3weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one to three years or radical cystectomy (in highest-risk tumours - see below).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 4.7 and 6.4).	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one to three years.

7.7 Guidelines for the treatment of BCG failure

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC).	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak
Late BCG relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.	Strong
	2. Bladder-preserving strategies.	Weak
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.	Weak
	2. Radical cystectomy.	Weak

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance, following therapy. However, the frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. Using risk tables (see Tables 6.1 and 6.2), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly (see Section 8.1) [174, 176]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of randomised studies investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, TaG1/LG papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [318, 319] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be safe [320] (LE: 3). Multiple authors have suggested active surveillance in selected cases [321-323] (LE: 3/2a).
- The first cystoscopy after TURB at three months is an important prognostic indicator for recurrence and progression [182, 189, 324-326] (LE: 1a). Therefore, the first cystoscopy should always be performed three months after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after five recurrence-free years is low [325] (LE: 3). Therefore, in low-risk tumours, after five years of follow up, discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [326].
- In tumours originally intermediate- or high risk, recurrences after ten years tumour-free are not unusual [327] (LE: 3). Therefore, life-long follow-up is recommended [326].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders).
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [77] (LE: 3).
- Positive urine test results have a positive impact on the quality of follow-up cystoscopy [116] (LE: 1b) supporting the adjunctive role of urine tests during follow-up.
- In patients initially diagnosed with TaG1-2/LG BC, US of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [328].
- No non-invasive method can replace endoscopy.

8.1 Summary of evidence and guidelines for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	Weak
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong

During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=panel.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organization and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Upper Urinary Tract Urothelial Carcinoma

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC). Separate EAU guidelines documents are available addressing non-muscle-invasive bladder cancer [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma (UC). All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/upper-urinary-tracturothelial-cell-carcinoma/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print and as an app for iOS and Android devices, presenting the main findings of the UTUC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available as are a number of translations of all versions of the EAU UTUC Guidelines, the most recent scientific summary was published in 2018 [4]. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/upperurinary-tract-urothelial-cell-carcinoma/.

1.4 Publication history & summary of changes

The first EAU Guidelines on UTUC were published in 2011. This 2020 publication presents a substantial update of the 2019 version.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant. Conclusions and recommendations have been rephrased and added to throughout the current document.

Key changes for the 2020 print:

- Section 3.1 – Epidemiology – has been expanded, resulting changes in Figure 3.1 and the addition of two new recommendations

3.4 Summary of evidence and recommendations for epidemiology, aetiology and pathology

Summary of evidence	LE
Aristolochic acid and smoking exposure increases the risk for UTUC.	2
Patients with Lynch syndrome are at risk for UTUC.	3

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

- Chapter 6 – Prognosis – additional information has been added, resulting in changes to Figure 6.1 and an additional recommendation.

6.7 Summary of evidence and guidelines for prognosis

Summary of evidence	LE
Chronological age should not preclude radical nephroureterectomy with curative intent, where indicated.	3
Important prognostic factors include hydronephrosis, tumour multifocality, size, stage, grade, lymph node metastasis, lymphovascular invasion and variant histology.	3

Recommendations	Strength rating
Use pre-operative factors to risk-stratify patients for therapeutic guidance.	Weak

- Chapter 7 – Disease management, has been restructured, including new information on adjuvant and neoadjuvant therapies. Both Figures 7.1 and 7.2 have been adapted and a number of new recommendations have been added.

7.1.6 Summary of evidence and guidelines for management of high-risk non-metastatic UTUC

Summary of evidence	LE
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Peri-operative chemotherapy may improve survival.	3
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ-confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer peri-operative chemotherapy to patients with muscle-invasive UTUC.	Weak
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

- Section 7.2 – Metastatic disease has been expanded to include the latest information on immunotherapy, both in a first- and second-line setting, resulting in a new summary table.

7.2.4 ***Summary of evidence and guidelines for the treatment of metastatic UTUC***

Summary of evidence	LE
Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.	3
Cisplatin-based combination chemotherapy can improve median survival.	2
Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy in terms of complete response and survival.	3
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PDL-1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Weak
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-treatment line.	Weak

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

2. METHODS

2.1 Data identification

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. For the 2020 UTUC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was restricted to articles published between June 20th (Cochrane)/June 26th 2018 (Embase) and May 31st 2019. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 702 unique records were identified, retrieved and screened for relevance.

Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults were included. The publications identified were mainly retrospective, including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant. A total of 56 new publications were added to the 2020 UTUC Guidelines print. A detailed search strategy is available online: http://uroweb.org/guideline/upper-urinarytract-urothelial-cell-carcinoma/?type=appendicespublications.

For Chapters 3-6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis and Prognosis) references used in this text are assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM LEs has been used [5].

For each recommendation within the guidelines there is an accompanying online strength rating form, based on a modified GRADE methodology [6, 7]. These forms address a number of key elements, namely:

1. The overall quality of the evidence which exists for the commendation references used in this text are graded according to the CEBM Levels of Evidence (see above) [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences [8].

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guidelines/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The UTUC Guidelines have been peer-reviewed prior to publication in 2016. The summary paper published in 2018 was peer-reviewed prior to publication [4].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours in developed countries [9]. They can be located in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90-95% of UCs and are the most common urinary tract malignancy [1]. Upper urinary tract UCs are uncommon and account for only 5-10% of UCs [9] with an estimated annual incidence in Western countries of almost two cases per 100,000 inhabitants. This rate has risen in the past few decades as a result of improved detection and improved bladder cancer survival [10]. Pyelocaliceal tumours are approximately twice as common as ureteral tumours whilst multifocal tumours are found in approximately 10-20% of cases [11]. The presence of concomitant carcinoma *in situ* of the upper tract is between 11 and 36% [10]. In 17% of cases, concurrent bladder cancer is present [12] whilst a prior history of bladder cancer is found in 41% of American men but in only 4% of Chinese men [13]. This, along with genetic and epigenetic factors, may explain why Asian patients present with more advanced and higher grade disease compared to other ethnic groups [10]. Following treatment, recurrence in the bladder occurs in 22-47% of UTUC patients [14] compared with 2-6% in the contralateral upper tract [15].

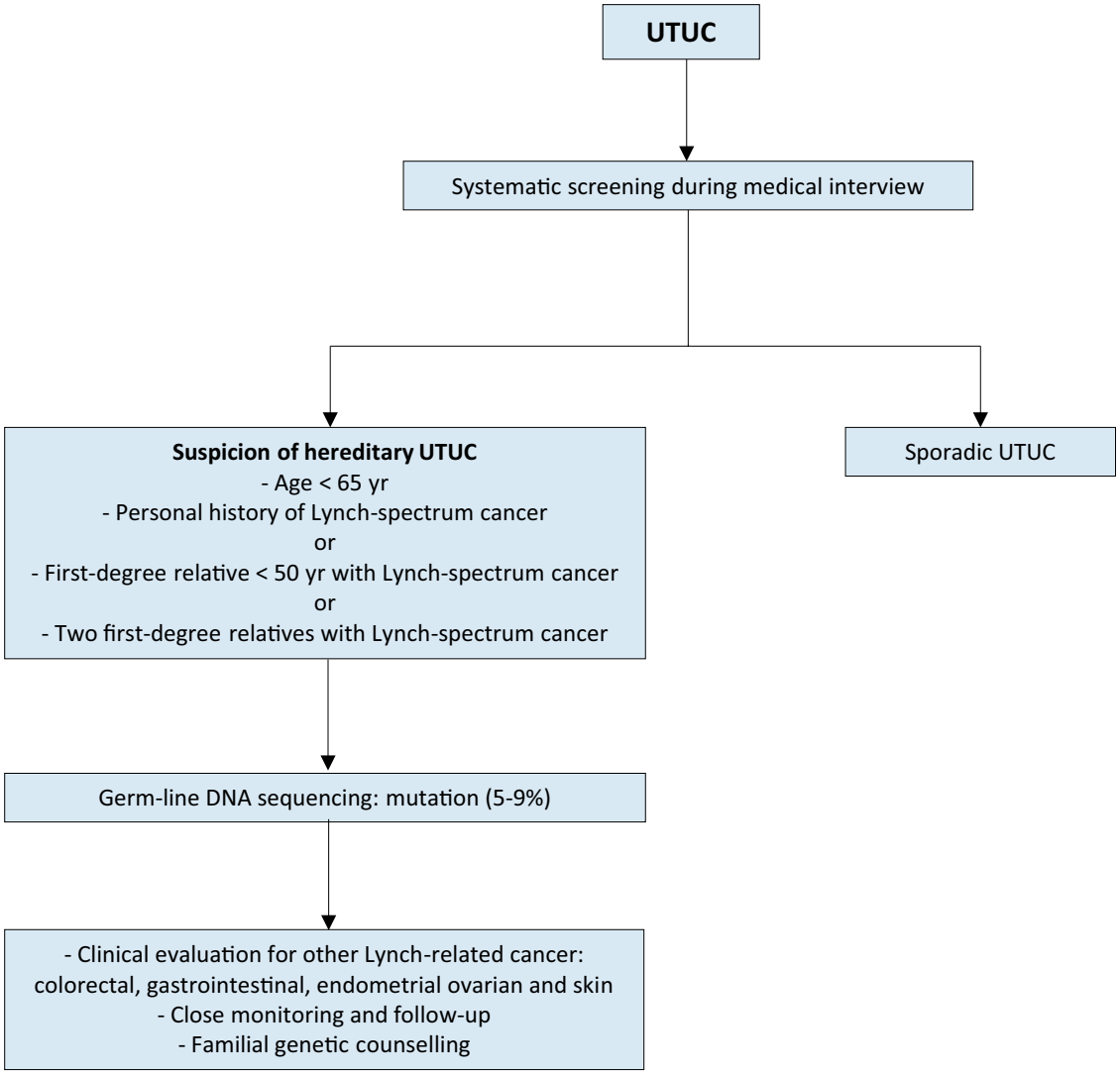
With regards to UTUC occurring following an initial diagnosis of bladder cancer, a series of 82 patients treated with bacillus Calmette-Guérin (BCG) who had regular upper tract imaging between years 1 and 3 showed a 13% incidence of UTUC, all of which were asymptomatic [16], whilst in another series of 307 patients without routine upper tract imaging the incidence was 25% [17]. More recently, a multicentre cohort study (n = 402) with a 50 month follow-up has demonstrated a UTUC incidence of 7.5% in NMIBC receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder [16]. Following radical cystectomy for MIBC, 3-5% of patients develop a metachronous UTUC.

Approximately two-thirds of patients who present with UTUCs have invasive disease at diagnosis compared to 15-25% of patients presenting with bladder tumours [18]. Approximately 7% of patients present with metastasis [10, 19]. Upper urinary tract UCs have a peak incidence in individuals aged 70-90 years and are three times more common in men [20].

Upper tract UC and bladder cancer exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumours, bladder cancer and UTUC were always clonally related. Genomic characterisation of UTUC provides information regarding the risk of bladder recurrence and can identify tumours associated with Lynch syndrome [21].

The Amsterdam criteria are a set of diagnostic criteria used by doctors to help identify families which are likely to have Lynch syndrome [22]. In Lynch-related UTUC, immunohistochemistry analysis showed loss of protein expression corresponding to the disease-predisposing MMR (mismatch repair) gene mutation in 98% of the samples (46% were microsatellite instable and 54% microsatellite stable) [23]. The majority of tumours develop in MSH2 mutation carriers [24]. Patients identified at high risk for Lynch syndrome should undergo DNA sequencing for patient and family counselling [25, 26]. Germline mutations in DNA MMR genes defining Lynch syndrome, are found in 9% of patients with UTUC compared to 1% of patients with bladder cancer, linking UTUC to Lynch syndrome [27]. A recent study of 115 consecutive UTUC patients, reported that 13.9% screened positive for potential Lynch syndrome and 5.2% had confirmed Lynch syndrome [28]. This is one of the highest rates of undiagnosed genetic disease in urological cancers, which justifies screening of all patients under 65 presenting with UTUC and those with a family history of UTUC (see Figure 3.1) [29, 30].

Figure 3.1: Selection of patients with UTUC for Lynch syndrome screening during the first medical interview



UTUC = upper urinary tract urothelial carcinoma.

3.2 Risk factors

A number of environmental factors have been implicated in the development of UTUC [11, 31]. Published evidence in support of a causative role for these factors is not strong, with the exception of smoking and aristolochic acid. Tobacco exposure increases the relative risk of developing UTUC from 2.5 to 7.0 [32-34]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than a 9% of the cohort being UTUC patients, clustering was not seen in upper tract disease. This may suggest that the familial clustering of urothelial cancer is specific to lower tract cancers [35].

In Taiwan, the presence of arsenic in drinking water has been tentatively linked to UTUC [36]. Aristolochic acid, a nitrophenanthrene carboxylic acid produced by Aristolochia plants, exerts multiple effects on the urinary system. Aristolochic acid irreversibly injures renal proximal tubules resulting in chronic tubulointerstitial disease, while the mutagenic properties of this chemical carcinogen lead predominantly to UTUC [37-39]. Aristolochic acid has been linked recently to bladder cancer, renal cell carcinoma, hepatocellular carcinoma and intrahepatic cholangiocarcinoma [40]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by Aristolochia plants, as reported for Balkan endemic nephropathy [41]; and (ii) ingestion of Aristolochia-based herbal remedies [42, 43]. Aristolochia herbs are used worldwide, especially in China and Taiwan [39]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [44]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [9]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [40, 45].

However, fewer than 10% of individuals exposed to aristolochic acid develop UTUC [38].

Two recent retrospective series found that aristolochic acid-associated UTUC is more common in females [46, 47]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts.

Alcohol consumption is associated with development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has evidenced a significantly higher risk of UTUC in ever-drinkers compared to never-drinkers (OR: 1.23; 95% CI: 1.08-1.40, p = 0.001). Compared to never-drinkers, the risk threshold for UTUC was > 15 gr. of alcohol/day. A dose-response was observed [48].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper urinary tract UCs may share some risk factors and described molecular pathways with bladder UC [21]. So far, two UTUC-specific polymorphisms have been reported [49].

3.3 Histology and classification

*3.3.1 **Histological types***

Upper urinary tract UC with pure non-urothelial histology is rare [50, 51] but variants are present in approximately 25% of cases [52, 53]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [54-57]. Urothelial carcinoma with divergent squamous differentiation is present in approximately 15% of cases [55]. Upper urinary tract UCs with variant histology are often high-grade and have a worse prognosis compared with pure UC [53, 58]. Other variants, although rare, include sarcomatoid and UCs with inverted growth [59].

However, collecting duct carcinomas, which may seem to share similar characteristics with UCs, display a unique transcriptomic signature similar to renal cancer, with a putative cell of origin in the distal convoluted tubules. Therefore, collecting duct carcinomas are considered as renal tumours [60].

3.4 Summary of evidence and recommendations for epidemiology, aetiology and pathology

Summary of evidence	LE
Aristolochic acid and smoking exposure increases the risk for UTUC.	2
Patients with Lynch syndrome are at risk for UTUC.	3

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [1]. It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential and low- and high-grade papillary UC) [61], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma.

4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [62]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of UCs which provides a different patient stratification between individual categories compared

to the older 1973 WHO classification [63, 64]. In 2016, an update of the 2004 WHO grading classification was published without major changes [63]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [61].

4.4 Future developments

A number of recent studies focussing on molecular classification have been able to demonstrate genetically different groups of UTUC by evaluating DNA, RNA and protein expression. Four molecular subtypes with distinct clinical behaviours were identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment [65].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [62]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TNM = Tumour, Node, Metastasis (classification).

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. The most common symptom is visible or nonvisible haematuria (70-80%) [66, 67]. Flank pain occurs in approximately 20% of cases [68, 69]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt evaluation for metastases associated with a worse prognosis [68, 69].

5.2 Imaging

*5.2.1 **Computed tomography urography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [70]. A meta-analysis of 13 studies comprising 1,233 patients revealed a pooled sensitivity of CT urography for UTUC of 92% (CI: 88-98) and a pooled specificity of 95% [71].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial “flat lesions” without mass effect or urothelial thickening are generally not visible with CT.

The presence of enlarged LNs is highly predictive of metastases in UTUC [72].

*5.2.2 **Magnetic resonance urography***

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [73]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [73]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of

nephrogenic systemic fibrosis. Computed tomography urography is generally preferred to MR urography for the diagnosis and staging of UTUC.

5.3 Cystoscopy and urinary cytology

Urethrocystocopy is an integral part of UTUC diagnosis to rule out concomitant bladder cancer [10, 12]. Abnormal cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 74, 75]. Cytology is less sensitive for UTUC than bladder tumours and should be performed selectively for the affected upper tract [76]. Retrograde ureteropyelography remains an option to detect UTUCs [70, 77, 78]. Urinary cytology of the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography because it may cause deterioration of cytological specimens [78, 79]. In a recent study, barbotage cytology detected up to 91% of cancers, being as effective as biopsy histology [80].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 50% and therefore its use in clinical practice remains unproven [81-83].

5.4 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used to visualise the ureter, renal pelvis and collecting system and for biopsy of suspicious lesions. Presence, appearance and size of tumour can be determined using URS. In addition, ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [84]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if kidney-sparing treatment is chosen [85]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [78, 86, 87]. Stage assessment using ureteroscopic biopsy is inaccurate.

Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing therapy [87, 88]. While some studies suggest a higher rate of intravesical recurrence after RNU in patients who underwent diagnostic URS pre-operatively [89, 90], one study did not [91].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions [92]. Narrow-band imaging is a promising technique, but results are preliminary [88, 93, 94]. Optical coherence tomography and confocal laser endomicroscopy (Cellvizio®) have been used *in vivo* to evaluate tumour grade and/or for staging purposes, with a promising correlation with definitive histology in high-grade UTUC [95, 96]. Recommendations for the diagnosis of UTUC are listed in Section 5.6.

5.5 Distant metastases

Prior to any treatment with curative intent, it is essential to rule out distant metastases. Computed tomography is the diagnostic technique of choice for lung- and abdominal staging for metastases [71].

5.6 Summary of evidence and guidelines for the diagnosis of UTUC

Summary of evidence	LE
The diagnosis and staging of UTUC is best done with computed tomography urography and URS.	2
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma *in situ*.	3
Urethrocystoscopy can detect concomitant bladder cancer.	2

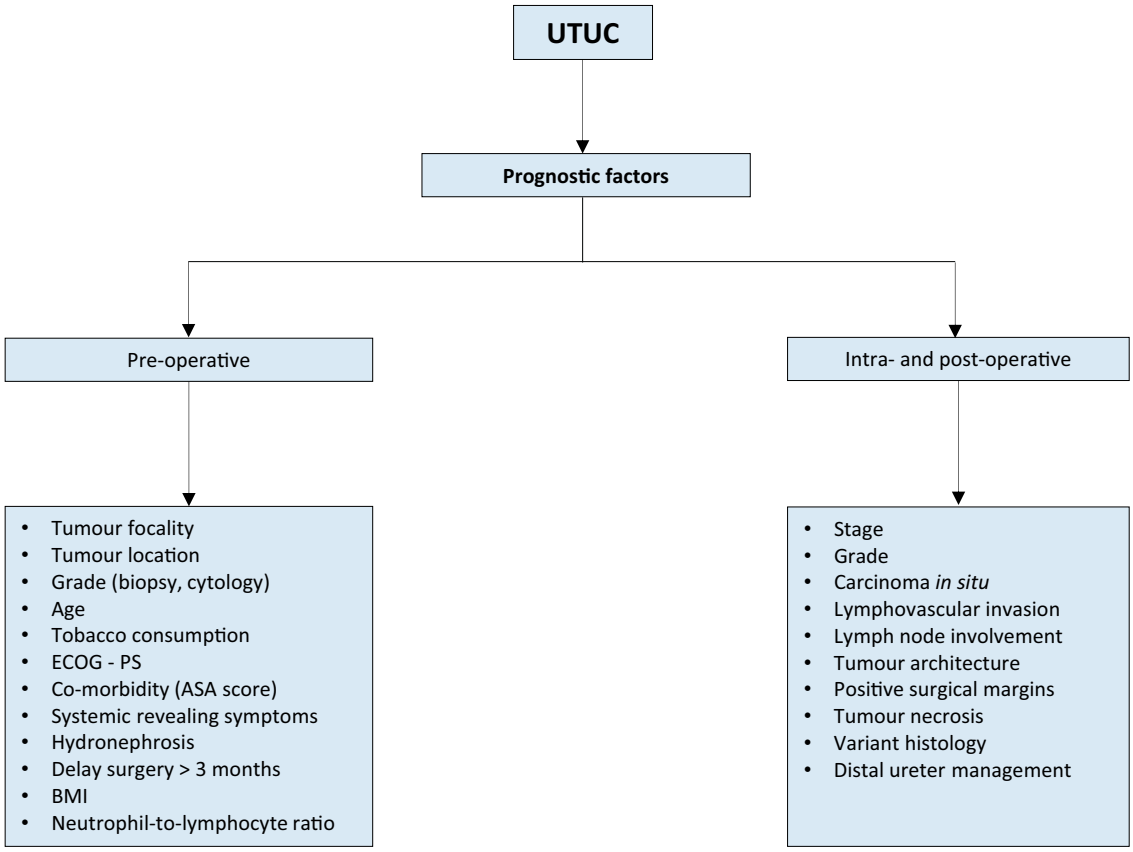
Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform a computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour.	Strong
Magnetic resonance urography may be used when CT is contra-indicated.	Weak

6. PROGNOSIS

6.1 Prognostic factors

Upper urinary tract UCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 UTUC [97-100]. The main prognostic factors are briefly listed in the text. Figure 6.1 shows a more exhaustive list of those patients with the most increased risk.

Figure 6.1: Upper urinary tract urothelial cell carcinoma - prognostic factors



ASA = American Society of Anesthesiologists; BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; UTUC = upper urinary tract urothelial cell carcinoma.

6.2 Pre-operative factors

6.2.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [98, 101, 102] (LE: 3). However, even elderly patients can be cured with RNU [103]. Therefore, chronological age alone should not be a contraindication to RNU [102, 103]. Gender has no impact on prognosis of UTUC [20, 98, 104].

6.2.2 Ethnicity

One multicentre study of academic centres did not show any difference in outcomes between races [105], but U.S. population-based studies have indicated that African-American patients have worse outcomes than other ethnicities (LE: 3). Whether this is related to access to care or biological and/or patterns of care remains unknown. Another study has demonstrated differences between Chinese and American patients at presentation (risk factor, disease characteristics and predictors of adverse oncologic outcomes) [13].

6.2.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [106, 107] and recurrence within the bladder [108] (LE: 3). There is a close relationship between tobacco consumption and prognosis; smoking cessation improves cancer control.

*6.2.4 **Tumour location, multifocality, size and hydronephrosis***

Initial location of the UTUC is a prognostic factor in some studies [109, 110] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than patients diagnosed with renal pelvic tumours [98, 109-114]. Hydronephrosis is associated with advanced disease and poor oncological outcome [68, 72, 79].

*6.2.5 **Surgical delay***

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made, the procedure should be carried out within twelve weeks, when possible [115-119] (LE: 3).

*6.2.6 **Other***

A higher American Society of Anesthesiologists score confers worse CSS after RNU [120] (LE: 3), as does poor performance status [121]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [122] (LE: 3). High pre-treatment-derived neutrophil-lymphocyte ratio [123, 124] and low albumin [125] have been associated with worse cancer-specific mortality.

6.3 Post-operative factors

*6.3.1 **Tumour stage and grade***

The primary recognised prognostic factors are tumour stage and grade [18, 87, 98, 126, 127].

*6.3.2 **Lymph node involvement***

Lymph node metastasis and extranodal extension are powerful predictors of survival outcomes in UTUC [128, 129]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [100, 129-131] (LE: 3).

*6.3.3 **Lymphovascular invasion***

Lymphovascular invasion (LVI) is present in approximately 20% of UTUCs and is an independent predictor of survival [132-134]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [132, 135, 136] (LE: 3).

*6.3.4 **Surgical margins***

Positive soft tissue surgical margin is associated with a higher disease recurrence after RNU. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour [137] (LE: 3).

*6.3.5 **Other pathological factors***

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [138, 139] (LE: 3). The architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [140, 141] (LE: 3). Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [142, 143] (LE: 3). Macroscopic infiltration or invasion of peri-pelvic adipose tissue confers a higher risk of disease recurrence after RNU compared to microscopic infiltration of renal parenchyma [52, 144].

6.4 Molecular markers

Several studies have investigated the prognostic impact of molecular markers related to cell adhesion (E-cadherin [145] and CD24), microsatellite instability [146], cell differentiation [147, 148], angiogenesis, cell proliferation (Ki-67), epithelial-mesenchymal transition, mitosis), apoptosis, vascular invasion, programmed death(ligand) 1 (PD-1/PDL-1) expression [149] and c-MET protein [98, 150].

Because of the rarity of UTUC, the main limitations of molecular studies are their retrospective design and, for most studies, small sample size. None of the markers have yet fulfilled the criteria necessary to support their introduction in daily clinical decision making.

6.5 Predictive tools

There are three pre-RNU models aiming at predicting which patient has muscle-invasive/non-organ-confined disease [151-153].

Five prognostic nomograms based on pathological characteristics are available [100, 154-158].

6.5.1 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [159] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

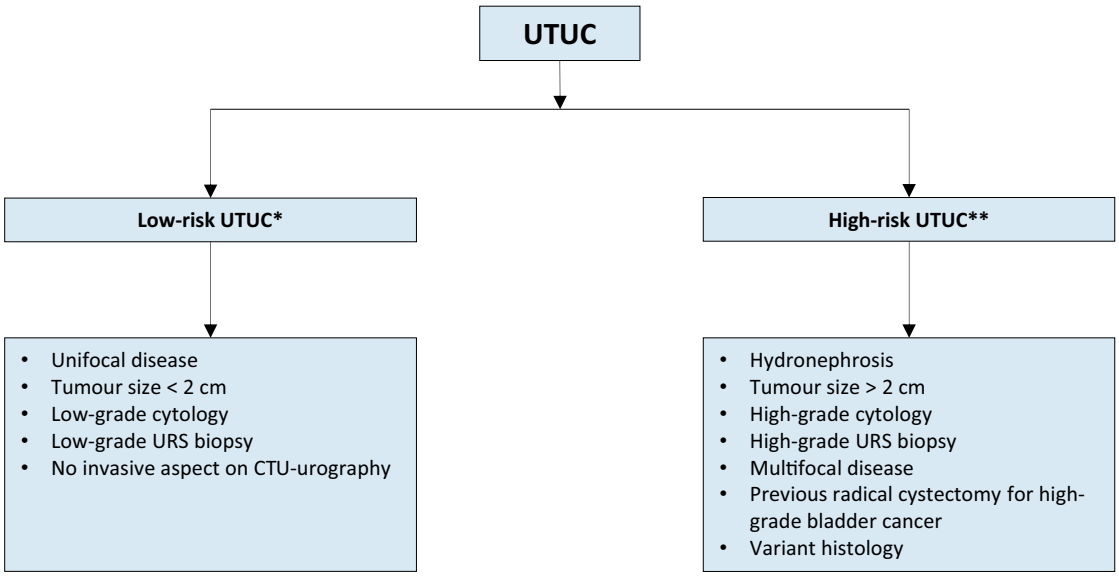
1. Patient-specific factors such as male gender, previous bladder cancer, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis.
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [159].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [89, 90] (LE: 3). Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of non-metastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [119-121].

6.6 Risk stratification of non-metastatic UTUC

As tumour stage is difficult to assert clinically in UTUC, it is useful to "risk stratify" UTUC between low- and high-risk tumours to identify those patients who are more likely to benefit from kidney-sparing treatment [160, 161] (Figure 6.2).

Figure 6.2: Risk stratification of non-metastatic UTUC



CTU = computed tomography urography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
**All these factors need to be present.*
***Any of these factors need to be present.*

6.7 Summary of evidence and guidelines for the prognosis of UTUC

Summary of evidence	LE
Chronological age should not preclude radical nephroureterectomy with curative intent, where indicated.	3
Important prognostic factors include hydronephrosis, tumour multifocality, size, stage, grade, lymph node metastasis, lymphovascular invasion and variant histology.	3

Recommendations	Strength rating
Use pre-operative factors to risk-stratify patients for therapeutic guidance.	Weak

7. DISEASE MANAGEMENT

7.1 Localised non-metastatic disease

*7.1.1 **Kidney-sparing surgery***

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with radical surgery (e.g. loss of kidney function), without compromising oncological outcomes [162]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [162]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney. In addition, it can also be considered in select patients with a serious renal insufficiency or having a solitary kidney (LE: 3). Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.1.5.

7.1.1.1 Ureteroscopy

Endoscopic ablation should be considered in patients with clinically low-risk cancer [163, 164]. A flexible ureteroscope is necessary in management of pelvicalyceal tumours [165]. The patient should be informed of the need and be willing to comply with an early second-look URS [166] and stringent surveillance; complete tumour resection or destruction is necessary [166]. Nevertheless, a risk of disease progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [167].

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [164, 168] (LE: 3). This may also be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. However, this approach is being used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopes [164, 168]. Moreover, a risk of tumour seeding remains with a percutaneous access.

7.1.1.3 Ureteral resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading while preserving the ipsilateral kidney. Lymphadenectomy can also be performed during segmental ureteral resection [162]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [169, 170] (LE: 3).

Distal ureterectomy with ureteroneocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically and for high-risk tumours when kidney-sparing surgery for renal function preservation is desired [99, 169, 170] (LE: 3). A total ureterectomy with an ileal-ureteral substitution is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [171].

Partial pyelectomy or partial nephrectomy is extremely rarely indicated. Open resection of tumours of the renal pelvis or calices has almost disappeared.

7.1.1.4 Upper urinary tract instillation of topical agents

The antegrade instillation of BCG or mitomycin C in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [143, 172] (LE: 3). Retrograde instillation through a single J open-ended ureteric stent is also used. Both the antegrade and retrograde approach can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used but this approach is suboptimal because the drug often does not reach the renal pelvis [173-176]. A recently published systematic review and meta-analysis, assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and adjuvant endocavitary treatment, analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidney-sparing surgery for papillary non-invasive (Ta-T1) UTUCs and of adjuvant BCG for the treatment of UT CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and overall survival (OS). Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [177]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

7.1.1.5 Guidelines for kidney-sparing management of UTUC

Recommendations	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Offer kidney-sparing management to patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to patients with solitary kidney and/or impaired renal function, providing that it will not compromise survival. This decision will have to be made on a case-by-case basis with the patient.	Strong

7.1.2 Management of high-risk non-metastatic UTUC

7.1.2.1 Surgical approach

7.1.2.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [18] (LE: 3). Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [18]. Section 7.1.6 lists the recommendations for RNU.

7.1.2.1.2 Minimal invasive radical nephroureterectomy

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases [178, 179]. Several precautions may lower the risk of tumour spillage:

1. avoid entering the urinary tract;
2. avoid direct contact between instruments and the tumour;
3. perform the procedure in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
4. the kidney and ureter must be removed *en bloc* with the bladder cuff;
5. Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for minimal-invasive RNU as the outcome is worse compared to an open approach [180, 181].

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [179, 182-185] (LE: 3). One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ confined UTUC [181] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [186] (LE: 3). A robot-assisted laparoscopic approach can be considered with recent data suggesting oncologic equivalence with the other approaches [187-189].

7.1.2.1.3 Management of bladder cuff

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area and in the bladder [159, 169, 190-192]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques has convincingly been shown to be equal to complete bladder cuff excision [15, 190, 191] (LE: 3).

7.1.2.1.4 Lymph node dissection

The use of an LND template is likely to have a greater impact on patient survival than the number of removed LNs [193]. Template-based and completeness of LND improves CSS in patients muscle-invasive disease and reduces the risk of local recurrence [194]. Even in clinically [195] and pathologically [196] node-negative patients, LND improves survival.

The risk of LN metastasis increases with advancing tumour stage [130]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [197-200], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are planned for RNU. The templates for LND have been described [194, 201, 202].

7.1.3 ***Peri-operative chemotherapy***

7.1.3.1 Neoadjuvant chemotherapy

Several retrospective studies evaluating the role of neoadjuvant chemotherapy have shown promising pathological downstaging and complete response rates [203-207]. In addition, neoadjuvant chemotherapy has

been shown to result in lower disease recurrence and mortality rates compared to RNU alone [208-210]. No randomised controlled trials have yet been published.

7.1.3.2 Adjuvant chemotherapy

Conflicting results are available from retrospective studies evaluating adjuvant chemotherapy [211-213]. A population-based study has shown improved OS rates in pT3/T4 and/or pN+ patients (n = 3,253) [214], while a multicentre cohort study did not in pT2-T4 and/or pN+ patients (n = 1,544) [212].

The main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver full dose cisplatin-based regimen after RNU, given that this surgical procedure is likely to impact renal function [215, 216]. Promising phase II prospective randomised data on the benefit of platinum-based adjuvant chemotherapy for pT2-4, N0-3M0 UTUC has been reported at meetings, with full publication pending.

*7.1.4 **Adjuvant Radiotherapy after radical nephroureterectomy***

Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [217-220]. Moreover, its additive value to chemotherapy remains questionable [219].

*7.1.5 **Post-operative bladder instillation***

The rate of bladder recurrence after RNU for UTUC is 22-47% [161, 191]. Two prospective randomised trials [221, 222] and a meta-analysis [223] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2-10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU (LE: 2). Prior to instillation, a cystogram might be considered in case of any concerns about extravasation.

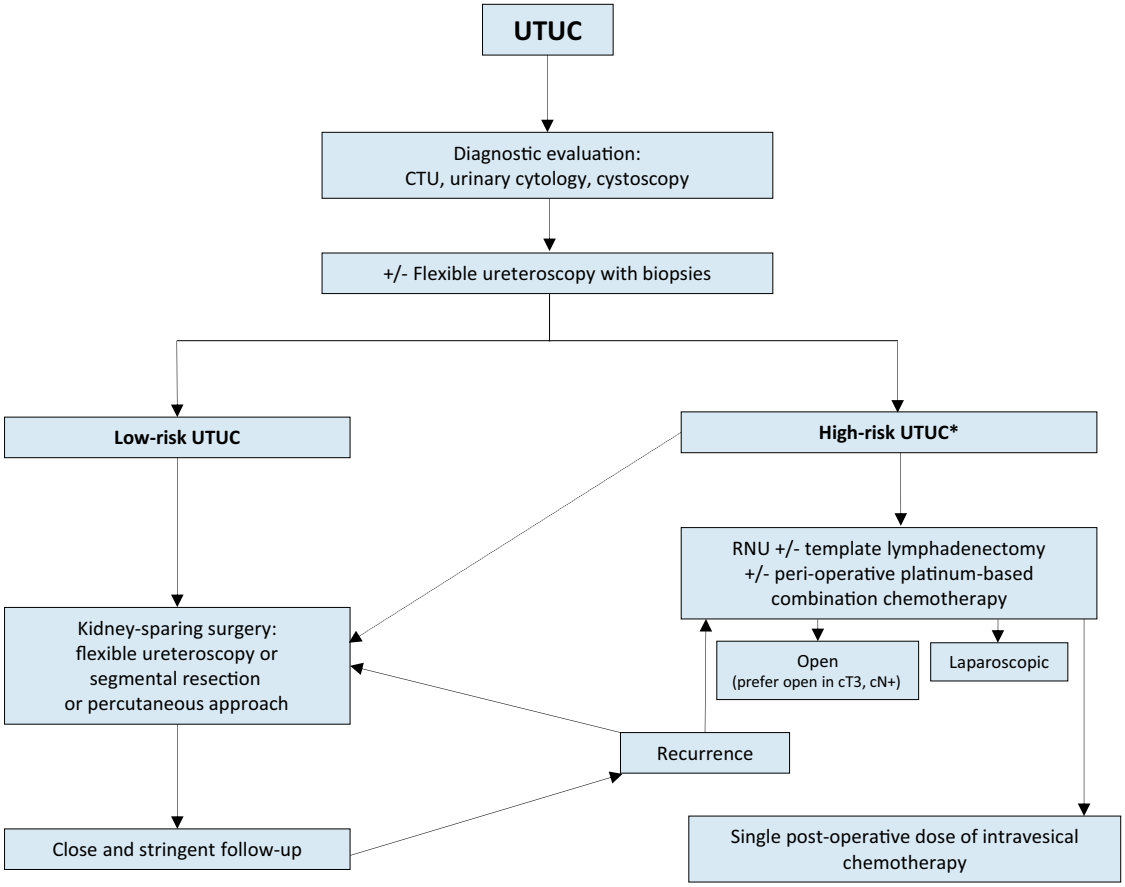
Whilst there is no direct evidence supporting the use of intravesical instillation of chemotherapy after kidney-sparing surgery, single-dose chemotherapy might be effective in that setting as well (LE: 4). Management is outlined in Figures 7.1 and 7.2.

*7.1.6 **Summary of evidence and guidelines for the management of high-risk non-metastatic UTUC***

Summary of evidence	**LE**
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Peri-operative chemotherapy may improve survival.	3
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

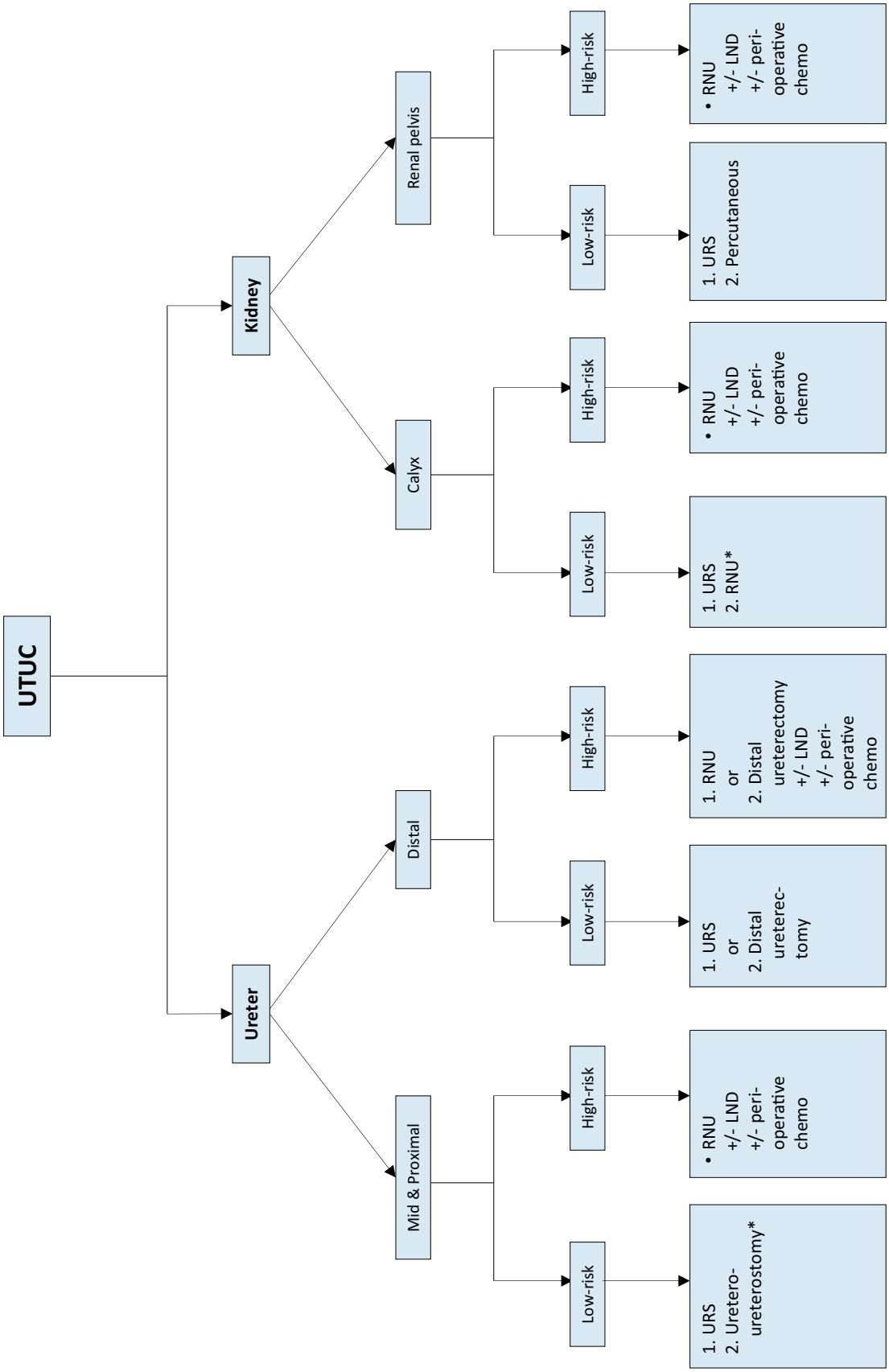
Recommendations	**Strength rating**
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer peri-operative chemotherapy to patients with muscle-invasive UTUC.	Weak
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Figure 7.1: Proposed flowchart for the management of UTUC



**In patients with solitary kidney, consider a more conservative approach.*
CTU = computed tomography urography; RNU = radical nephroureterectomy;
UTUC = upper urinary tract urothelial carcinoma.

Figure 7.2: Surgical treatment according to location and risk status



1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy;
UTUC = upper urinary tract urothelial carcinoma.

7.2 Metastatic disease

*7.2.1 **Radical nephroureterectomy***

The role of RNU in the treatment of patients with metastatic UTUC has recently been explored in several observational studies [224-227]. Although evidence remains very limited, RNU may be associated with cancer-specific [224, 226, 227] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [225, 226]. It is noteworthy that these benefits may be limited to those with only one metastatic site [226]. Nonetheless, given the high risk of bias of the observational studies addressing RNU for metastatic UTUC, indications for RNU in this setting should mainly be reserved for palliative patients, aimed at controlling symptomatic disease [17, 106] (LE: 3). In patients who have a partial or complete response to induction chemotherapy, RNU may be discussed with the patient.

*7.2.2 **Metastasectomy***

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. However, several reports including both UTUC and bladder cancer patients suggested that resection of metastatic lesions could be safe and oncologically beneficial in selected patients with a life expectancy of more than six months [228-230]. This was confirmed in the most recent and largest study to date [231]. Nonetheless, in the absence of data from randomised controlled trials, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically or otherwise) should be done in a shared decision-making process with the patient.

*7.2.3 **Systemic treatments***

7.2.3.1 First-line setting

Extrapolating from the bladder cancer literature and small, single-centre UTUC studies, platinum-based combination chemotherapy – especially using cisplatin – might be efficacious for first-line treatment of metastatic UTUC. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free or OS in patients with locally advanced or metastatic UC treated with platinum-based combination chemotherapy [232].

In addition, the role of immunotherapy has been evaluated in the first-line setting for cisplatin-ineligible UTUC patients but limited data is available in the literature. First, a single-arm phase II trial including 370 patients showed that for the subset of those with UTUC (n = 69/19%), the objective response rate was 22% [233]. In the overall cohort, a PD-L1 expression of 10% was associated with a higher frequency of response to pembrolizumab, which had relative acceptable toxicity. Second, atezolizumab was associated with an objective response rate of 39% in 33 (27.7%) cisplatin-ineligible patients with metastatic UTUC included in a single-arm phase II trial (n = 119) [234]. Median OS in the overall cohort was 15.9 months and toxicity was relatively acceptable. No other data are currently available in the first-line setting but several phase III trials are currently testing pembrolizumab (NCT02853305 [235]) atezolizumab (NCT02807636 [236]) or durvalumab (NCT02516241 [237]) alone, and immunotherapy combinations with nivolumab (NCT03036098 [238]), durvalumab (NCT02516241 [237]) or pembrolizumab (NCT02178722 [239]) for patients with metastatic UC including those with UTUC.

7.2.3.2 Second-line setting

Similar to the bladder cancer setting, second-line treatment of metastatic UTUC remains challenging. In a *post-hoc* subgroup analysis of locally advanced or metastatic UC, vinflunine was reported to be as effective in UTUC as for bladder cancer progressing after cisplatin-based chemotherapy [240].

More importantly, a phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab could decrease the risk of death by almost 50% in those with UTUC (n = 75, 13.8%), although these results were borderline significant [241]. The objective response rate was 21.1% in the overall cohort and median OS was 10.3 months. Interestingly, although no subgroup analysis was available for UTUC patients (n = 65/21%) a single-arm phase II trial demonstrated that atezolizumab has durable activity associated with PD-L1 expression on immune cells in patients with metastatic UC [242]. The objective response rate was 26% in the group of those overexpressing PD-L1 and 15% in the overall population. However, a phase III RCT showed that it was not associated with prolonged OS as compared to chemotherapy in patients overexpressing PD-L1¬including 51 (21.8%) with UTUC, despite a more favourable safety profile [243].

Other immunotherapies such as nivolumab [244], avelumab [245, 246] and durvalumab [247] have shown objective response rates ranging from 17.8% [247] to 19.6% [244] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC overall. These results were obtained from single-arm phase I or II trials only and the number of UTUC patients included in these studies was only specified in evaluating avelumab (n = 7/15.9%) [246] without any subgroup analysis based on primary tumour location.

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC progressing after platinum-based chemotherapy [248]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [249].

7.2.4 Summary of evidence and guidelines for the treatment of metastatic UTUC

Summary of evidence	LE
Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.	3
Cisplatin-based combination chemotherapy can improve median survival.	2
Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy in terms of complete response and survival.	3
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-treatment line.	Strong

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

8. FOLLOW-UP

The risk of recurrence and death evolves during the follow-up period after surgery [250]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours (probability increases over time [251]), local recurrence, and distant metastases. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

Surveillance regimens are based on cystoscopy and urinary cytology for > 5 years [12, 14, 15, 161]. Bladder recurrence is not considered a distant recurrence. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [165, 252, 253]. Despite endourological improvements, follow-up after kidney-sparing management is difficult and frequent, and repeated endoscopic procedures are necessary. As done in bladder cancer, a second look has been proposed after kidney-sparing surgery but is not yet routine practice [2, 166].

8.1 Summary of evidence and guidelines for the follow-up of UTUC

Summary of evidence	LE
Follow-up is more frequent and more stringent in patients who have undergone kidney-sparing treatment compared to radical nephroureterectomy.	3

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every six months for two years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy (URS) at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at three and six months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at three and six months.	Weak

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Separate EAU guidelines documents are available addressing upper urinary tract (UUT) tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) (NMIBC) [2], and primary urethral carcinomas [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist and a radiologist.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/bladdercancermuscle-invasive-and-metastatic/?type=panel.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version.

Several scientific publications are available (the most recent paper dating back to 2017 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website: http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU published its first guidelines on bladder cancer (BC) in 2000. This document covered both NMIBC and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2020 document presents a limited update of the 2019 version.

*1.4.2 **Summary of changes***

New relevant references have been identified through a structured assessment of the literature and incorporated in the various chapters of the 2020 EAU MIBC Guidelines.

Key changes in the 2020 print are:

- New section - 3.2.5 - Metabolic disorders – has been added, also providing a recommendation.

*3.2.9 **Summary of evidence and guidelines for epidemiology and risk factors***

Recommendations	Strength rating
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

- Chapter 6 - Markers – this section has been completely revised.
- Section 7.1 - Treatment failure of non-muscle-invasive bladder cancer – this section has been updated to align with the 2020 NMIBC guidelines; in particular with respect to discussing unsuccessful treatment with intravesical BCG.

7.1.2 ***Guidelines for treatment failure of non-muscle-invasive bladder cancer***

Recommendations	Strength rating
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

- Section 7.4.3.2 - Radical cystectomy in women – this section has been revised.
- Section 7.4.6.1 - Patient selection and preparations for surgery – additional information on thromboprophylaxis has been included, as well as the final findings of the systematic review conducted to assess the impact of hospital and surgeon volume on treatment outcomes, resulting in two new recommendations.

7.4.10 ***Summary of evidence and guidelines for radical cystectomy and urinary diversion***

Recommendations	Strength rating
Perform at least 10, and preferably > 20 radical cystectomies per hospital/per year	Strong
Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong

- Section 7.8 – Metastatic disease – this section has been completely restructured, also incorporating updated information on novel programmed death ligand 1 (PD-1) and PD-L1 inhibitors.

7.8.6 ***Summary of evidence and guidelines for metastatic disease***

Recommendations	Strength rating
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to PD-L1-positive patients.	Strong
Second-line treatment	
Only offer vinflunine to patients for metastatic disease as subsequent-line treatment if immunotherapy or combination chemotherapy or FGFR3-inhibitor therapy or inclusion in a clinical trial is not feasible.	Weak

- Section 7.9 – Quality of life – a new section 7.9.2 - Neoadjuvant chemotherapy has been included.

A number of text sections will include statements resulting from the EAU-ESMO consensus [5, 6], notably:

- Pathology – Section 3.3.4
- Diagnostic evaluation – Section 5.1.10
- Markers - Section 6.5.1
- Treatment failure of NMIBC – Section 7.1.3
- Pre- and post-operative radiotherapy in MIBC – Section 7.3.4
- Radical surgery and urinary diversion - Section 7.4.11
- Unresectable tumours - Section 7.5.1.2
- Bladder-sparing treatments for localised disease - Section 7.6.1.2
- External beam radiotherapy - Section 7.6.2.2
- Multimodality bladder-preserving treatment - Section 7.6.4.2
- Adjuvant therapy – Section 7.7.4
- Oligometastatic disease - Section 7.8.4.1
- Metastatic disease - Section 7.8.7
- Follow up - Section 8.6

2. METHODS

2.1 Data identification

For the 2019 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 1st, 2018 and May 10th, 2019. A total of 1,899 unique records were identified, retrieved and screened for relevance. Sixty-two new publications have been included in the 2020 print. A detailed search strategy is available online: http://uroweb.org/guideline/bladdercancer-muscle-invasive-andmetastatic/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [7, 8] which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The results of a collaborative multi-stakeholder consensus project on the management of advanced and variant bladder cancer have been incorporated in the 2020 MIBC Guidelines update [5, 6]. Only statements which reached the *a priori* defined level of agreement - ≥ 70% agreement and ≤ 15% disagreement - across all stakeholders involved in this consensus project are listed. The methodology is presented in detail in the scientific publications. Some of these statements may be replaced by higher levels of evidence, over time, even though for some areas it is unlikely that clinical trials and prospective comparative studies will be conducted.

2.2 Peer-review

The 2020 MIBC Guidelines have not been peer reviewed.

*2.2.1 **Lay review***

Post publication, the 2018 MIBC Guidelines were shared with seven patients treated for MIBC. Their comments were requested, but not limited to:

- the overall tone of the guidelines content;
- any missing information;
- any information considered incorrect;
- any information which is not presented in a clear fashion;
- any text which is considered redundant and should be omitted;
- any text section that should be more detailed.

Common comments across reviewers:

- In general, the overall tone of the text was considered informational and instructive, but the language used obviously targets medical professionals, which make certain parts of the text difficult to understand for lay persons. The use of many abbreviations is considered an additional hindrance, as are the methodological elements. In case the EAU are considering producing a lay version of this text, the language needs to be adapted and clear instructions are to be provided.
- It is difficult for lay reviewers to comment on what may be omitted since, in their opinion, they lack the expertise.

- Some sections, such as ‘Recurrent disease’ and ‘Markers’ denote areas where less evidence is available. Consequently, the available data is less systematically presented which makes these sections more difficult to understand.
- There is an interest whether screening for BC is a consideration.
- In particular ‘follow up’, ‘quality of life’ and ‘survivorship aspects’ should be elaborated on; providing additional information on what may be expected after treatment is considered very helpful for patients and their families. Also lifestyle elements would be of relevance (healthy living, “what to do to prevent cancer”). For this section, in particular, involvement of patients in the text development was considered missing. Transparency about the process of patient involvement in guidelines development was considered most relevant.

The MIBC Guidelines Panel is most grateful for the unique insights and guidance provided by the lay reviewers.

2.3 Future goals

Topics considered for inclusion in the 2020 update of the MIBC Guidelines:

- development of a diagnostic pathway for the assessment of visible and non-visible haematuria;
- participation in developing strategies to ensure meaningful participation of patients in the development and implementation of the MIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer is the 7th most commonly diagnosed cancer in males, whilst it drops to 11th when both genders are considered [10]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [10]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [11]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [10, 12].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [10]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the different methodologies used in the studies and the quality of data collection [11, 13].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [13, 14].

Approximately 75% of patients with BC present with disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40 years) this percentage is even higher [15]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality (CSM) compared to T2-4 tumours [10, 11].

3.2 Aetiology

*3.2.1 **Tobacco smoking***

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [16]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [17].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [18]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [19]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [16]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [18]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [16].

3.2.2 ***Occupational exposure to chemicals***

Occupational exposure is the second most important risk factor for BC. Work-related cases accounted for 20-25% of all BC cases in several series and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [20]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [21, 22]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [11, 23].

3.2.3 ***Radiotherapy***

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 [24]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy, and EBRT-brachytherapy were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [25].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [26]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life-expectancy are at a higher risk of developing BC [26].

3.2.4 ***Dietary factors***

Several dietary factors have been related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption and only recently an inverse association between dietary intake of flavonoids and lignans and the risk of aggressive BC tumours has been described [27].

3.2.5 ***Metabolic disorders***

In a large prospective study pooling six cohorts from Norway, Sweden, and Austria (The Metabolic syndrome and Cancer project, Me-Can 2.0), metabolic aberrations, especially elevated blood pressure and triglycerides, were associated with increased risks of BC among men, whereas high BMI was associated with decreased BC risk. The associations between body mass index (BMI), blood pressure and BC risk significantly differed between men and women [28].

The association of Diabetes Mellitus (DM) with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, DM was associated with BC or cancer mortality risk especially in men [29]. Thiazolidinediones (pioglitazone and rosiglitazone) are oral hypoglycaemic drugs used for the management of type 2 DM. Their use and the association with BC is still a matter of debate. In a recent meta-analysis of observational studies, the summary results indicated that pioglitazone use was significantly associated with an increased risk of BC which appears to be linked to higher dose and longer duration of treatment [30]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC. Several countries in Europe have removed this agent from the market or included warnings for prescription. Moreover, the benefits of glycaemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

3.2.6 ***Bladder schistosomiasis and chronic urinary tract infection***

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [31]. There is a well-established relationship between schistosomiasis and urothelial carcinoma (UC) of the bladder, which can progress to squamous cell carcinoma (SCC), however, better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [32, 33].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series [34]. However, a recent meta-analysis found no statistical association when pooling data from the most recent and highest quality studies which highlights the need for higher quality data to be able to draw conclusions [35].

Similarly, urinary calculi and chronic irritation or inflammation of the urothelium have been described as possible risk factors for BC. A meta-analysis of case-control and cohort studies suggests a positive association between history of urinary calculi and BC [36].

*3.2.7 **Gender***

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (hazard ratio [HR]: 1.20; 95% CI: 1.09-1.32) compared to male gender after radical cystectomy (RC) [37]. This finding had already been presented in a descriptive nation-wide analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific-survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [38]. However, this higher mortality is questionable once both genders receive the same therapy. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in overall survival (OS), mortality and outcomes were found between males and females following radical therapy [39]. The gender-specific difference in survival for patients with BC was also analysed in the Norway population. Survival was inferior for female patients but only within the first 2 years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [40].

A population-based study from the MarketScan databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [41]. Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [42-44].

*3.2.8 **Genetic factors***

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A recent population-based study of cancer risk in relatives and spouses of UC patients showed an increased risk for first- and second-degree relatives, and suggests genetic or environmental roots independent of smoking-related behaviour [45]. Shared environmental exposure was recognised as a potentially confounding factor [46]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [47].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [48, 49].

*3.2.9 **Summary of evidence and guidelines for epidemiology and risk factors***

Summary of evidence	**LE**
Worldwide, bladder cancer is the 11th most commonly diagnosed cancer.	2a
Several risk factors associated with bladder cancer diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy, or a combination of EBRT and brachytherapy, must be considered during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3

Recommendations	**Strength rating**
Council patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

3.3 Pathology

*3.3.1 **Handling of transurethral resection and cystectomy specimens***

During transurethral resection (TUR), a specimen from the tumour and normal looking bladder wall should be taken, if possible. Specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random

biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be submitted separately [50].

In RC, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen. In a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [51].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [52, 53]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [54]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) have to be documented by the pathologist.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipose differentiation of the LN, the entire specimen is to be included. Lymph nodes should be counted and measured on slides, capsular extension and percentage of LN invasion should be reported as well as vascular embols [55, 56]. In the case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Potentially positive soft tissue margins should be inked by the pathologist for evaluation [57]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [58].

*3.3.2 **Pathology of muscle-invasive bladder cancer***

All MIBC cases are high-grade UCs. For this reason, no prognostic information can be provided by grading MIBC [59]. However, identification of morphological subtypes is important for prognostic reasons and treatment decisions [60-62].

An update of the World Health Organization (WHO) grading was published in 2016 [63], however, the data presented in these guidelines are based on the 2004 WHO classification [64].

Currently the following differentiations are used [60, 65]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary and microcystic UC;
4. nested variant (including large nested variant);
5. lymphoepithelioma-like;
6. plasmocytoid, signet ring, diffuse;
7. some UCs with small-cell carcinomas;
8. sarcomatoid carcinomas;
9. poorly differentiated.

Other, extremely rare, variants exist, which are not listed above.

*3.3.3 **Guidelines for the assessment of tumour specimens***

Recommendations	Strength rating
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4b).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, uterus and vaginal top.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphatic or blood vessel invasion.	
Record the presence of carcinoma *in situ*.	

3.3.4 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer* [5, 6]*

Consensus statement
Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive small cell neuroendocrine variant of bladder urothelial carcinoma should not receive preventive brain irradiation to avoid brain recurrence.
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8th edition) is recommended [66]. Blood and lymphatic vessel invasion have an independent prognostic significance [67, 68].

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [66] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [66]

T - Primary Tumour		
Tx	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: “flat tumour”	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:	
	T3a	microscopically
	T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in a common iliac lymph node(s)	
M - Distant Metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

Painless haematuria is the most common presenting complaint. Other clinical signs include urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR of the bladder (TURB), to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [69, 70]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination [71].

5.1.3 Bladder imaging

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging.

5.1.4 Urinary cytology

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is a useful indicator in cases of high-grade malignancy or CIS.

However, positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [72, 73] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [74].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories was published in 2016 [75]:

- adequacy of urine specimens (Adequacy);
- negative for high-grade UC (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade UC (Suspicious);
- high-grade UC (HGUC);
- low-grade urothelial neoplasia (LGUN).

5.1.5 Cystoscopy

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. If a bladder tumour has been visualised unequivocally by imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted, and the patient can proceed directly to TURB for histological diagnosis and resection. Currently, there is no evidence for the role of photodynamic diagnosis (PDD) in the standard diagnosis of invasive BC.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of any mucosal abnormalities [76]. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present, to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS and in experienced hands the rate of false-positive results may be similar to that with regular white-light cystoscopy [68, 77].

5.1.6 Transurethral resection of invasive bladder tumours

The goal of TURB is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection specimen.

In case MIBC is suspected tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable them to make a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [78].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, with concomitant bladder CIS, and in the case of multiple tumours [79-81] (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative-predictive value and is more accurate [82-84].

*5.1.7 **Second resection***

In the case of high-grade non-muscle-invasive tumour, residual disease is observed in 33-53% of patients [85-91]. In order to reduce the risk of understaging [86, 87], a second TURB resection is often required to determine subsequent treatment strategy.

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which is a contraindication to a neobladder reconstruction.

In case the initial TUR did not include biopsies of the paracollicular (males) or bladder neck (females), frozen sections should be sent separately to the pathologist during the second resection.

*5.1.8 **Concomitant prostate cancer***

Prostate cancer is found in 21-50% of male patients undergoing RC for BC [92-95]. Incidentally discovered clinically significant prostatic adenocarcinoma did not alter survival [94, 95]. Pathological reporting of the specimens should follow the recommendations as presented in the EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer [96].

*5.1.9 **Summary of evidence and guidelines for the primary assessment of presumably invasive bladder tumours***

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]).

*5.1.10 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*** [5, 6]*****

Consensus statement
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [97, 98]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure

that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

- extent of local tumour invasion;
- tumour spread to LNs;
- tumour spread to the UUT and other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

5.2.1 ***Local staging of MIBC***

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [99]. The principal aim of CT and MRI is to detect T3b disease, or higher.

5.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). A meta-analysis of 17 studies showed a 91% sensitivity and 96% specificity for 3.0-T device MRI combined with diffusion-weighted imaging (DWI) to differentiate ≤ T1 tumours from ≥ T2 tumours before surgery [100]. These values were 10-33% (mean 19%) higher than those obtained with CT [101]. Dynamic contrast-enhanced-MRI may help to differentiate bladder tumour from surrounding tissues, in particular in patients where organ-preserving cystectomy is considered. Magnetic resonance imaging may evaluate post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [101-103].

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Contrast-enhanced CT using iodinated contrast media can be considered as an alternative [104] (LE: 4).

5.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [105] and increases with more advanced disease [106].

5.2.2 ***Imaging of lymph nodes in MIBC***

Assessment of LN metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally-enlarged nodes. The sensitivity for detection of LN metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [101, 107-111]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [112, 113].

Positron emission tomography (PET) combined with CT is increasingly being used in clinical practice and its exact role continues to be evaluated [114].

5.2.3 ***Upper urinary tract urothelial carcinoma***

5.2.3.1 Computed tomography urography

Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques [115]. The sensitivity of CT urography for UTUC is 0.67-1.0 and specificity is 0.93-0.99 [116].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial “flat lesions” without mass effect or urothelial thickening are generally not visible with CT.

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [117, 118]. The presence of enlarged LNs is highly predictive of metastases in UTUC [119].

5.2.3.2 Magnetic resonance urography

Magnetic resonance urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [120]. The sensitivity of MR urography is 0.75 after

contrast injection for tumours < 2 cm [120]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of NSF. Computed tomography urography is generally preferred to MR urography for diagnosing and staging UTUC.

*5.2.4 **Distant metastases at sites other than lymph nodes***

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [121] and liver metastases [122], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [123, 124]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [125, 126] (LE: 2b).

*5.2.5 **Future developments***

Evidence is accruing in the literature suggesting that ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential clinical use for staging metastatic BC [127, 128], but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made. Recently, the first study was published showing the superior feasibility of DWI over T2-weighted and DCE-MRI for assessing the therapeutic response to induction chemotherapy against MIBC [129]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

*5.2.6 **Summary of evidence and guidelines for staging in muscle-invasive bladder cancer***

Summary of evidence	**LE**
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of diffusion-weighted imaging (DWI) and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in MIBC to allow for a recommendation to be made.	
The diagnosis of upper tract urothelial carcinoma depends on CT urography and ureteroscopy.	2

Recommendations	**Strength rating**
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging.	Strong
Perform a CT urography for upper tract evaluation and for staging.	Strong
For upper tract evaluation, use diagnostic ureteroscopy and biopsy only in cases where additional information will impact treatment decisions.	Strong
Use magnetic resonance urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	Strong
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	Strong
Use CT to diagnose pulmonary metastases. Computed tomography and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	Strong

5.3 MIBC and comorbidity

Complications related to RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC, although chronological age is less important than biological age [130-132]. Controversy remains regarding age, RC and the type of urinary diversion. Radical cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years [133].

The largest retrospective study on RC in septuagenarians and octogenarians based on data from the National Surgical Quality Improvement Program database (n = 1,710) showed no significant difference for wound, cardiac, or pulmonary complications. However, the risk of mortality in octogenarians compared to septuagenarians is higher (4.3% vs. 2.3%) [134]. Although some octogenarians successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion. It is important to evaluate functioning and quality of life (QoL) of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation [135].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing RC for BC [136]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [137]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [138]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence-free and OS after RC [139, 140]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

*5.3.1 **Evaluation of comorbidity***

Rochon *et al*. have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [141]. Evaluation of comorbidity helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [142].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman *et al*., who have demonstrated an association between comorbidity and adverse pathological and survival outcomes following RC [143]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [144]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help selecting patients most likely to benefit from radical surgery and to optimise treatment outcomes [145]. Unfortunately, most published series evaluating RC do not include indices of comorbidity in their patient evaluation.

*5.3.2 **Comorbidity scales, anaesthetic risk classification and geriatric assessment***

A range of comorbidity scales has been developed [146], six of which have been validated [147-152] (LE: 3). The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [153, 154], overall mortality [155], and CSM [133, 156-158]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [159]. The age-adjusted CCI (Table 5.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [160].

Table 5.1: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1	50-60 years
	Myocardial infarction
	Heart failure
	Peripheral vascular insufficiency
	Cerebrovascular disease
	Dementia
	Chronic lung disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	61-70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3	71-80 years
	Moderate to severe liver disease
4	81-90 years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation:
1. Calculate Charlson Comorbidity Score or Index = i
    a. Add comorbidity score to age score
    b. Total denoted as 'i' in the Charlson Probability calculation (see below).
        i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality = Y)
    a. Calculate $Y = 10^{(i \times 0.9)}$
    b. Calculate $\bar{z} = 0.983^{Y}$ (where $\bar{z}$ is the 10-year survival)

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann *et al*. have shown that there is no correlation between morbidity and competitive activity level [161]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [162] (LE: 3). Performance score is correlated with patient OS after RC [157] and palliative chemotherapy [163-165].

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of elderly people, to catalogue their resources and strengths, to assess individual service needs, and to develop a coordinated plan of care. The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [166] which is tailored to the care of cancer patients [167]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [168].

*5.3.3 **Summary of evidence and guidelines for comorbidity scales***

Summary of evidence	LE
Chronological age is of limited relevance.	3
A comorbidity score developed in particular for the assessment of patients diagnosed with bladder cancer would be helpful.	3

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in elderly/frail patients with invasive bladder cancer on tumour stage and comorbidity.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting (see Section 5.3.2).	Strong

6. MARKERS

6.1 Introduction

Both patient and tumour characteristics guide treatment decisions and prognosis of patients with MIBC.

6.2 Prognostic markers

*6.2.1 **Histopathological and clinical markers***

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [169]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [170]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and cancer mortality, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [171].

In a systematic review and meta-analysis including 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher odds ratio (OR) of ureteral involvement (pooled OR: 4.51, 2.59-7.84). Concomitant CIS was not independently associated with OS,

recurrence-free survival (RFS) and DSS survival in all patients, but in patients with organ-confined disease concomitant CIS was associated with worse RFS (pooled HR: 1.57, 1.12-2.21) and CSM (pooled HR: 1.51, 1.001-2.280) [171].

Tumour location has been associated with prognosis. Tumours located at the bladder neck or trigone of the bladder appear to have an increased likelihood of nodal metastasis (OR: 1.83 95% CI: 1.11-2.99) and have been associated with decreased survival [97, 169, 172, 173].

Prostatic urethral involvement at the time of RC was also found to be associated with worse survival outcomes. In a series of 995 patients, prostatic involvement was recorded in 31% of patients. The 5-year CSS in patients with CIS of the prostatic urethra was 40%, whilst the prognosis of patients with UC invading the prostatic stroma was worse with a 5-year CSS of only 12% [174].

Recently neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and disease-free survival (DFS) in both localised and metastatic disease [175]. In contrast, a secondary analysis of the SWOG 8710 trial, a randomised phase III trial assessing cystectomy ± neoadjuvant chemotherapy (NAC) in patients with MIBC, suggests that NLR is neither a prognostic nor predictive biomarker for OS in MIBC, nor could an OS benefit from NAC be demonstrated [176].

In patients with LN-positive disease, the AJCC-TNM staging system provides 3 subcategories. In addition, several other prognostic LN-related parameters have been reported. These include, but are not limited to, the number of positive LNs, the number of LNs removed, LN density (the ratio of positive LNs to the number of LNs removed) and extranodal extension. In a systematic review and meta-analysis, it was reported that LN density was independently associated with OS (HR: 1.45; 95%, CI: 1.11-1.90) [177]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [178]. However, in spite of these studies supporting the use of LN density, LN density relies on the number of LNs removed which, in turn, is subject to surgical and pathological factors. This makes the concept of LN density difficult to apply uniformly [179].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [179, 180]. Whilst conclusion was that the AJCC-TNM staging system for LN status did not perform well, none of the other tested variables outperformed the AJCC system.

*6.2.2 **Molecular markers***

6.2.2.1 Molecular groups based on the Cancer Genome Atlas (TCGA) cohort

It has been attempted to classify UC from a molecular point of view. Four major subtypes have been described:

- basal BC with the basal and claudin low-type group;
- luminal BC with luminal and p53-like subtype.

The basal group shows an over-expression of epidermal growth factor receptor 3 (EGFR3) and is chemosensitive. The luminal type can display an over-expression of fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptors (*ERBB2*↑ and *ERBB3*), and is chemotherapy resistant [61, 62, 181].

Warrick *et al*. found that intratumoural molecular heterogeneity and great somatic mutation burden could also be related to therapeutic response [182].

Recently a consensus on molecular classification reported [183]. The authors analysed 1,750 MIBC transcriptomic profiles from 18 datasets and identified six MIBC molecular classes that reconcile all previously published classification schemes. The molecular subgroup classes include luminal papillary (LumP), luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like). Each class has distinct differentiation patterns, oncogenic mechanisms, tumour micro-environments and histological and clinical associations. However, the authors stressed that consensus was reached for biological rather than clinical classes. Therefore, at this moment in time, this classification should be considered as a research tool for retrospective and prospective studies until future studies will establish how these molecular subgroups can be used best in a clinical setting.

Molecular classification of MIBC is still evolving and treatment tailored to molecular subtype is not a standard yet. In the coming years, new insights into BC carcinogenesis may change our management of the disease.

6.3 *Predictive markers*

*6.3.1 **Clinical and histopathological markers***

Based on retrospective data only, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [184]. Pietzak *et al*. retrospectively analysed clinicopathologic outcomes comparing

245 patients with clinical T2-4aN0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC. They found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (univariable: 26% vs. 45%, multivariable: OR: 0.4 [95% CI: 0.18-0.84, p = 0.02]). They also found that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone (p = 0.002).

Variant histologies and non-UC have also been linked to worse outcomes after NAC, but there is, as yet, insufficient data to conclude that they can be considered as predictive markers [185].

*6.3.2 **Molecular markers***

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor [186], urinary (wild-type and mutant) and FGFR3, somatic genomic alterations (i.e. ERCC2); DDR and RB1 gene alterations and circulating tumour cells [184, 187-189]. Although promising, there are currently no predictive molecular markers that are routinely used in clinical practice. Further validation studies are awaited.

Recently, data of the PURE-01 study was published [190]. This study was designed to assess the efficacy and obtain biomarker results of single-agent, neoadjuvant pembrolizumab administration in patients with MIBC. The primary endpoint in the intention-to-treat (ITT) population was pathologic complete response (pT0). Biomarker analyses included programmed death-ligand 1 (PD-L1) expression using the combined positive score (CPS; Dako 22C3 pharmDx assay), genomic sequencing (FoundationONEassay), and an immune gene expression assay. Fifty patients were enrolled and pathological response was observed in 42% (95% CI: 28.2% to 56.8%). It was concluded that tumour mutational burden (TMB) and PDL-1-positive status was associated with a higher ratio of pT0 disease at RC [190].

An update of this PURE-01 study focusing on a subgroup of patients with variant histology reported that those patients presenting with SCC or a lymphoepithelioma-like variant feature had major pathological responses compared with those with other predominant variant histologies. And again, in this subset of patients, the expression of PDL-1 and TMB were predictive of pathological response to pembrolizumab [191]. Even though these data are promising, they are too preliminary for application in daily clinical practice.

6.4 Conclusion

Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but large phase III randomised controlled trials (RCTs) with long-term follow-up will be needed to clarify the many questions currently still remaining. The increasing use of next-generation sequencing, in combination with predictive gene expression signatures and algorithms may also alter future treatment approaches.

6.5 *Summary of evidence for urothelial markers*

Summary of evidence	**LE**
Currently, treatment decisions cannot be based on molecular markers.	3

*6.5.1 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*** [5, 6]*****

Consensus statement
In patients with metastatic disease, genetic profiling should always be done.
Before prescribing a checkpoint inhibitor, tumour mutation burden does not need to be assessed.
In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy must be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy).
In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy should be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy).
Before prescribing checkpoint inhibitor therapy, ribonucleic acid subtypes need not be identified.
Before radical cystectomy or chemotherapy, the neutrophil-to-lymphocyte ratio does not need to be assessed.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle invasive bladder cancer

7.1.1 High-risk non-muscle-invasive urothelial carcinoma

In 2015 the European Organisation for Research and Treatment of Cancer (EORTC) group presented new nomograms based on two large phase III trials with a median follow-up of 7.4 years. These showed that with one to three years of maintenance bacillus Calmette-Guerin (BCG), the risk for progression at 5 years was 19.3% for T1G3 tumours [192]. Meta-analyses have demonstrated that BCG therapy prevents the risk of tumour recurrence [193] and the risk of tumour progression [194, 195], but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [194-196]. The EAU NMIBC Guidelines present data supporting cystectomy in selected patients with NMIBC [2].

Large cystectomy series show a risk of an understaging error in TaT1 tumours of 35-62%. This may be caused by the presence of persisting or recurrent tumours due to omission of a second TURB or re-TURB, and the absence of neoadjuvant therapy [197-199]. Second TURB identifies upstaging to > T2 tumours in 10-20% of patients [200, 201]. Residual T1 disease in second TURB is associated with higher recurrence and progression rates, as well as with a higher CSM [202].

Progression to MIBC has been shown to significantly decrease CSS. In a review of nineteen trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. Although all studies reflect these findings, a large retrospective Canadian study showed that even progressing patients had a slightly better outcome [203].

High-grade T1 disease remains a dangerous disease, which underlines the need to recommend early radical treatment, such as RC, in case of intravesical therapy failure [2, 204]. Based on retrospective data only, so far patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [184].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate RC to patients with non-muscle-invasive tumours who are at highest risk of progression [205-209]. Risk factors are any of the following:

- T1 tumours;
- G3 (high grade) tumours;
- CIS;
- multiple, recurrent and large (> 3 cm) TaG1G2/low-grade tumours (all features must be present).

Subgroup of highest-risk tumours:

- T1G3/high-grade associated with concurrent bladder CIS;
- multiple and/or large T1G3/high grade and/or recurrent T1G3/high-grade;
- T1G3/high-grade with CIS in the prostatic urethra;
- some forms of variant histology of UC;
- lymphovascular invasion.

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the 10-year RFS rate is 80% and similar to that of TURB and BCG maintenance therapy [2, 198, 210, 211].

Radical cystectomy is also strongly recommended in patients with a muscle-invasive tumour detected during follow up, in BCG-refractory tumours, BCG relapse and BCG-unresponsive tumours, which are defined in the NMIBC guidelines [2]:

BCG-refractory tumour	
1.	if T1G3/high-grade tumour is present at 3 months [212]. Further conservative treatment with BCG is associated with an increased risk of progression [213, 214];
2.	If TaG3/high-grade tumour is present after 3 months or at 6 months, after either re-induction or first course of maintenance [215];
3.	If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [215-217].
4.	If high-grade tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour	
Recurrence of G3/high-grade (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response) [204].	

BCG-unresponsive tumour
BCG-refractory or T1Ta/high-grade BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure [218].
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [219].

**Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

Patients with disease recurrence within two years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease [220].

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy and combination therapy [221]. At the present time, treatments other than RC must, however, be considered oncologically inferior in such patients with BCG-unresponsive disease [212-214].

7.1.2 Guidelines for treatment failure of non-muscle-invasive bladder cancer

Recommendations	Strength rating
Discuss immediate radical treatment (radical cystectomy [RC]) with patients at the highest risk of tumour progression (i.e. high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	Strong
Offer RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

7.1.3 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma *in situ*.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
TURBT = transurethral resection of bladder tumour.

7.2 Neoadjuvant therapy

7.2.1 Introduction

The standard treatment for patients with urothelial MIBC and MIBC with variant histologies is RC. However, RC only provides 5-year survival in about 50% of patients [199, 222-225]. To improve these results, cisplatin-based NAC has been used since the 1980s [199, 222-227].

7.2.2 Role of cisplatin-based chemotherapy

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive UC of the bladder and cN0M0 disease:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [228, 229], although published studies on the negative effect of delayed cystectomy only include chemo-naïve patients. There are no trials indicating that delayed surgery due to NAC has a negative impact on survival.

- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 post-operative complications was seen in both treatment arms [230]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm with 71% of patients receiving all three chemotherapy cycles [231].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [71]. Overtreatment is a possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [230, 232-240].

7.2.2.1 Summary of available data

Several randomised phase III trials addressed the potential survival benefit of NAC administration [230, 232-237, 241-245]. The main differences in trial designs were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [238-240]. In a meta-analysis, published in 2005 [240] with updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC. The most recent meta-analysis included four additional randomised trials, and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials, consisting of information for 427 new patients and updated information for 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a number needed-to-treat of 12.5 [246]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [238, 240]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin and methotrexate (CM), cisplatin/adriamycin, and cisplatin/5-fluorouracil (5-FU) [247].

The updated analysis of a large randomised phase III trial [232] with a median follow-up of eight years confirmed previous results and provided additional findings:

- 16% reduction in mortality risk;
- improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;
- no benefit for locoregional control and locoregional DFS, with the addition of neoadjuvant CMV independent of the definitive treatment.

More modern chemotherapeutic regimens such as cisplatin/gemcitabine have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses, but have not been assessed in RCTs [247-250]. Modified dose-dense MVAC (ddMVAC) was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission [251, 252]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for ddMVAC [253]. Another dose-dense regimen using cisplatin/gemcitabine reported in two small phase II trials [254, 255]. While pathological response rates (< pT2) in the range of 45%-57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [254]. This approach is therefore not recommended outside of clinical trials.

There seem to be differences in the outcomes of patients treated with NAC for primary or secondary MIBC. However, in the absence of prospective data, patients with secondary MIBC should be treated similarly to those presenting with primary MIBC [184].

It is unclear, if patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved OS and lower rates of non-organ-confined disease when receiving NAC. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC [256].

A retrospective analysis assessed the use of NAC in MIBC based on data from the U.S. National Cancer Database [257]. Only 19% of all patients received NAC before RC (1,619 of 8,732 patients) and no clear survival advantage for NAC following propensity score adjustment was found despite efforts to include patients based on SWOG 8710 study criteria [230]. These results have to be interpreted with caution, especially since no information was available for the type of NAC applied. Such analyses emphasise the importance of pragmatically designed studies that reflect real-life practice.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m^2 on day 1, split-dose modifications regimens are often used with 35 mg/m^2 on days 1+8 or days 1+2. In a retrospective analysis the standard schedule was compared to a split-dose schedule in terms of complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [258].

7.2.3 The role of imaging and predictive biomarkers

Data from small imaging studies aiming to identify responders in patients treated with NAC suggest that response after two cycles of treatment is related to outcome. Although multiparametric (mp) MRI has the advantage of better resolution of the bladder wall tissue planes as compared to CT, it is not ready yet for standard patient care. However, bladder mpMRI may be useful to inform on tumour stage after TURB and response to NAC [259]. So far neither PET-CT, conventional MRI nor DCE-MRI can accurately assess treatment response [260-263]. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [264]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. Molecular tumour profiling might guide the use of NAC in the future but, as yet, this is not applicable in routine practice [265, 266] (see Section 6 - Prognosis).

7.2.4 Role of neoadjuvant immunotherapy

Inhibition of PD-1/PD-L1 checkpoint has demonstrated significant benefit in patients with unresectable and metastatic BC in the second-line setting and in platinum-ineligible PD-L1+ patients as first-line treatment using different agents. Checkpoint inhibitors are increasingly tested in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Preliminary data from several phase II trials has been presented with encouraging results. So far only the results of one phase II trial using the PD-1 inhibitor pembrolizumab has been published [190]. In this preliminary report complete pathological remission (pT0) was achieved in 42% and pathological response (< pT2) in 54% of patients. While immunotherapy is not yet approved in the neoadjuvant setting, enrolment of patients in clinical trials is encouraged.

7.2.5 Summary of evidence and guidelines for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently immunotherapy with checkpoint inhibitors as monotherapy, or in different combinations, is being tested in phase II and III trials. Initial results are promising.	
There are still no tools available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

7.3 Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

7.3.1 Post-operative radiotherapy

Data on adjuvant RT after RC are very limited and old. However, advances in targeting and reducing the damage to surrounding tissue, may yield better results in the future [267]. An RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [268]. Approximately half of these patients had UC, while the other half had SCC. In locally advanced BC (T3-T4, N0/N1, M0), the local recurrence rate seems to decrease with post-operative RT [269].

7.3.2 ***Pre-operative radiotherapy***

7.3.2.1 Retrospective studies

Older data and retrospective studies alone cannot provide an evidence base for modern guideline recommendations due to major study limitations, which include concomitant chemotherapy and differences between surgery and RT. This conclusion was supported by a 2003 systematic review [270]. A retrospective study from 2015 showed decreased cause-specific mortality and overall mortality for pre-operative RT in clinical T2b and T3 patients only [271]. Another retrospective study with pre-operative RT in clinical T1-3 tumours showed that down-staging to T0 tumours occurs in > 50% of the irradiated patients, as compared to < 10% of patients who did not receive pre-operative RT [272]. Additionally, down-staging resulted in a longer progression-free survival (PFS).

7.3.2.2 Randomised studies

To date, six RCTs have been published, investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used in patients with muscle-invasive tumours resulting in a significant increase in pathological complete response (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [273]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in ≥ T3 tumours [274, 275]. Two other small trials confirmed down-staging after pre-operative RT [276, 277].

A meta-analysis of the five RCTs showed a difference in 5-year survival (OR: 0.71; 95% CI: 0.48-1.06) in favour of pre-operative RT [278]. However, the meta-analysis was potentially biased by data from the largest trial in which patients were not given the planned treatment. When the largest trial was excluded from the analysis, the OR became 0.94 (95% CI: 0.57-1.55), which was not significant.

7.3.3 ***Summary of evidence and guidelines for pre- and post-operative radiotherapy***

Summary of evidence	LE
No data exist to support that pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer (MIBC) increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in down-staging after 4 to 6 weeks.	2
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after radical cystectomy.	3

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

7.3.4 ***EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*** [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional.

7.4 Radical surgery and urinary diversion

7.4.1 ***Removal of the tumour-bearing bladder***

7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [199, 279]. Recent interest in patients' QoL has promoted the trend toward bladder-preserving treatment modalities, such as

radio- and/or chemotherapy (see Section 7.6). Performance status and life expectancy influence the choice of primary management, as well as the type of urinary diversion, with cystectomy being reserved for patients with a longer life expectancy without concomitant disease and a better PS. The value of assessing overall health before proceeding with surgery was emphasised in a multivariate analysis [133]. The analysis found an association between comorbidity and adverse pathological- and survival outcomes following RC [133].

Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [161].

7.4.1.2 Radical cystectomy: timing

An analysis of the Netherlands Cancer Registry showed that a delay of RC > 3 months was not associated with a worse clinical outcome [280]. Previously, Ayres *et al*. also found that in the United Kingdom cystectomy within 90 days of diagnosis had no effect on OS for MIBC (n = 955). However, analysis of T2 tumours showed a statistically significant survival benefit if patients had surgery within 90 days of diagnosis (n = 543; HR: 1.40; 95% CI: 1.10-1.79) [281]. A population-based study from the U.S. SEER database analysed patients who underwent a cystectomy between 1992 and 2001 and concluded that a delay of more than twelve weeks has a negative impact on outcome and should be avoided [282]. Moreover, the SEER analysis did not show any significant utilisation and timing differences between men and women.

*7.4.2 **Radical cystectomy: indications***

Traditionally, RC was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [279]. Other indications include high risk and recurrent non-muscle-invasive tumours, BCG-refractory, BCG-relapsing and BCG-unresponsive, T1G3 tumours (see Section 7.1), as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-UC (these tumours respond poorly to chemotherapy and RT). It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (see Section 7.5.1 - Palliative cystectomy).

When there are positive LNs, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [283].

*7.4.3 **Radical cystectomy: technique and extent***

Different approaches have been described to improve voiding and sexual function in patients undergoing RC for BC. No consensus exists regarding which approach preserves function best. Concern remains regarding the impact of “sparing-techniques” on oncological outcomes.

To determine the effect of sexual function-preserving cystectomy (SPC) on functional and oncological outcomes the Panel undertook two systematic reviews addressing sparing techniques in men and women [284, 285].

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [286].

7.4.3.1 Radical cystectomy in men

Four main types of sexual-preserving techniques have been described:

1. **Prostate sparing cystectomy:** part of or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. **Capsule sparing cystectomy:** the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or *en bloc* with the bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.
3. **Seminal sparing cystectomy:** seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. **Nerve-sparing cystectomy:** the neurovascular bundles are the only tissue left in place.

Twelve studies recruiting a total of 1,098 patients were identified, including nine comparative studies [287-297] and three single-arm case series [298-300]. In the majority of cases, the open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results with a median follow-up longer than five years.

The majority of the studies included patients who were potent pre-operatively with organ-confined disease without tumour in the bladder neck and/or prostatic urethra. Prostate cancer was ruled out in all of the SPC techniques, except in nerve-sparing cystectomy.

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years. Local recurrence after SPC was commonly defined as any UC recurrence below the iliac bifurcation within the pelvic soft tissue and ranged from 1.2-61.1% vs. 16-55% in the control group. Metastatic recurrence ranged from 0-33.3%.

For techniques preserving prostatic tissue (prostate- or capsule-sparing), rates of incidental prostate cancer in the intervention group ranged from 0-15%. In no case was incidental prostate cancer with ISUP grade ≥ 4 reported.

Post-operative potency was significantly better in patients who underwent any type of sexual-preserving technique compared to conventional RC ($p < 0.05$), ranging from 80-90%, 50-100% and 29-78% for prostate-, capsule- or nerve-sparing techniques, respectively. Data did not show superiority of any sexual-preserving technique.

Urinary continence, defined as the use of no pads in the majority of studies, ranged from 88-100% (day-time continence) and from 31-96% (night-time continence) in the prostate-sparing cystectomy patients. No major impact was shown with regard to continence rates for any of the three approaches.

The evidence base suggests that these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes. However, the overall quality of the evidence was moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored.

7.4.3.1.1 Summary of evidence and recommendations for sexual-preserving techniques in men

Summary of evidence	**LE**
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2a
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve-sparing) have shown to be superior, and no particular technique can be recommended.	3

Recommendations	**Strength rating**
Do not offer sexual-preserving radical cystectomy to men as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

7.4.3.2 Radical cystectomy in women

Pelvic floor disorders, sexual and voiding dysfunction in female patients are prevalent after RC [301]. As part of the pre-operative evaluation a gynaecological history should be obtained and patients should be counselled on the potential negative impact of RC on sexual function and/or vaginal prolapse. Most importantly, a history of cervical cancer screening, abnormal vaginal bleeding and a family history of breast and/or ovarian cancer should be recorded, as well as ruling out possible pelvic organ prolapse. Equally important is screening for sexual and urinary function and prolapse post-operatively. Better imaging modalities, increased knowledge of the function of the pelvic structures and improved surgical techniques have enabled less destructive methods for treating high-risk BC.

Pelvic organ-preserving techniques involve preserving the neurovascular bundle, vagina, uterus, ovaries or variations of any of the stated techniques. From an oncological point of view, concomitant malignancy in gynaecological organs is rare and local recurrences reported after RC are infrequent [302, 303]. In premenopausal women, by preserving ovaries, hormonal homeostasis will be preserved, decreasing risk of cognitive impairment, cardiovascular diseases and loss of bone density. In case of an increased risk of hereditary breast or ovarian cancer (i.e. *BRCA1/2* mutation carriers, patients with Lynch syndrome), salpingo-oophorectomy should be advised after childbearing and to all women over 40 years of age [304]. On the other hand, preservation of the uterus and vagina will provide the necessary support for the neobladder thereby reducing the risk of urinary retention. It also helps to avoid post-operative prolapse. If there are no signs of tumour infiltration into the anterior vaginal wall, preservation should be considered, provided there is no

existing prolapse, in which case removing the uterus also treats the prolapse. It is noteworthy that by resecting the vaginal wall, the vagina shortens which could potentially impair sexual satisfaction and function.

Based on retrospective, low quality, data only, a systematic review evaluating the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder in female patients concluded that in well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes [285].

Pelvic organ-preserving RC could be considered also in elderly and fragile patients having abdominal diversions. By reducing excision range, it might be beneficial from the point of reduced operating time, estimated blood loss and quicker bowel recovery [305].

7.4.3.2.1 Summary of evidence and recommendations for sexual-preserving techniques in women

Summary of evidence	LE
Data regarding pelvic organ-preserving radical cystectomy for female patients remain immature.	3

Recommendations	Strength rating
Do not offer pelvic organ-preserving radical cystectomy to women as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select patients based on: • organ-confined disease; • absence of tumour in bladder neck or urethra.	Strong

*7.4.4 **Lymphadenectomy: role and extent***

Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy studies for RC have been performed so far. The first study showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal LNs. There was also a significant correlation between nodal metastases and concomitant distant metastases ($p < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [306].

The second autopsy study focused on the nodal yield when super-extended pelvic LN dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [307]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta [308-312]. Mapping studies also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located LN metastases, is rare [312, 313].

The optimal extent of LND has not been established to date. Standard lymphadenectomy in BC patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [314]. Extended lymphadenectomy includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet, as well as the area described for standard lymphadenectomy [314-318]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [319, 320].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [321]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [314-318, 320, 322-334]. All five studies comparing LND vs. no LND reported a better oncological outcome for the LND group. Seven out of twelve studies comparing (super)extended with limited or standard LND reported a beneficial outcome for (super) extended LND in at least a subset of patients which is in concordance with the findings of several other meta-analyses [335, 336]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [320, 332]. A prospective phase III RCT including 401 patients with

a median follow-up of 43 months recently reported [337]. Extended LND failed to show a significant advantage (the trial was designed to show an absolute improvement of 15% in 5-year RFS by extended LND) over limited LND in RFS, CSS, and OS. Results from another large RCT on the therapeutic impact of the extent of lymphadenectomy are expected shortly.

It has been suggested that PFS as well as OS might be correlated with the number of LNs removed during surgery. Although there are no data from RCTs on the minimum number of LNs that should be removed, survival rates increase with the number of dissected LNs [338]. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS in retrospective studies [339-341]. Submitting separate nodal packets instead of *en bloc* has shown significant increased total LN yield, but did not result in an increased number of positive LNs, making LN density an inaccurate prognosticator [342]. In conclusion, extended LND might have a therapeutic benefit compared to less extensive LND, but due to study bias no firm conclusions can be drawn [139, 321].

7.4.5 ***Laparoscopic/robotic-assisted laparoscopic cystectomy***

Further publications on robotic-assisted laparoscopic RC (RARC) have become available, including a new RCT [343] with a separate publication of oncological results [344] and a Cochrane review summarising the five published RCTs [345].

Novara *et al*. published a systematic review including 105 studies on RARC in 2015 [346]. With the exception of three papers which had a higher level of evidence (2b) all other publications (n = 102) only presented expert opinion (LE: 4). For RARC with urinary diversion, the mean operative time was six to seven hours which seemed to decrease over time, although it remained longer than for open RC (ORC). The mean length of hospital stay for RARC also decreased with time and experience, and was 1 to 1.5 days shorter when compared to ORC. Blood loss and transfusion rate favour RARC. Intra-operative, 30-day complication rate and mortality were similar for RARC and ORC, but 90-day complication rates of any-grade and 90-day grade 3 complication rates favoured RARC.

Although the low level of evidence of the included studies remains a major limitation of this review, most of the authors' findings are supported by a recent Cochrane review which includes data from all five published RCT's [345]. Time to recurrence, positive surgical margin rate, grade 3-5 complications and QoL was comparable for RARC and ORC, whilst transfusion rate was likely lower after RARC. For other endpoints outcomes were uncertain due to study limitations.

The Pasadena Consensus Panel (a group of experts on RC, lymphadenectomy and urinary reconstruction) reached similar conclusions as the Novara review based on the same methodology and literature [347]. Additionally, they reported that RARC was associated with increased costs, although there are ergonomic advantages for the surgeon, as compared to laparoscopic RC (LRC). For both techniques, surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20-250 cases. However, the Pasadena Consensus Panel performed statistical modelling and came to the conclusion that 30 cases should be enough to achieve proficiency in RARC, but they also concluded that challenging cases (high BMI, post chemotherapy or RT, pelvic surgery, T4 or bulky tumours, or positive nodes) should be performed by experienced robotic surgeons only. Safety after RT was confirmed by a small (n = 46) retrospective study [348]. In experienced hands the percentage of 90-day (major) complications after robotic cystectomy was independent of previous RT.

Oncological results of the first sufficiently powered RCT, comparing ORC (n = 58) vs. RARC (n = 60) and open diversion, were published in 2018 [344]. Overall recurrence rate, CSS and OS were comparable between the two procedures. For ORC an increase in metastatic sites at first recurrence was reported (HR 2.2, CI: 0.96-5.12) but more local/abdominal recurrences were associated with RARC (HR: 0.34, CI: 0.12-0.93). The Bochner *et al*. trial, however, was not powered to detect differences in recurrence. Jancke *et al*. reported on 8 patients with port-site metastasis (in addition to other metastatic sites) suggesting underreporting of metastatic sites after RARC, which is less common for open surgery [349].

The largest RCT to date is the RAZOR trial [343]. This study showed RARC to be non-inferior to ORC in terms of 2-year PFS (72.3% vs. 71.6%), adverse events (67% vs. 69%) and QoL. Most reviewed series, including the RAZOR trial, offer extracorporeal reconstruction. Hussein *et al*. retrospectively compared extracorporeal reconstruction (n = 1,031) to intracorporeal reconstruction (n = 1,094) and the latter was associated with a shorter operative time, fewer blood transfusions but more high-grade complications, which, again, decreased over time [350].

It is important to note that, although an intracorporeal neobladder is a very complex robotic procedure [351], the choice for neobladder or cutaneous diversion should not depend on the surgical approach.

For LRC, a review came to similar conclusions as described for RARC [351]. The review included sixteen eligible studies on LRC. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, blood transfusions and analgesic use, less blood loss and a shorter length of hospital stay. However, the review was limited by the inherent limitations of the included studies. Although this review also showed better oncological outcomes, these appeared comparable to ORC series in a large LRC multicentre study [351].

The CORAL study was a small single-centre RCT comparing open (n = 20) vs. robotic (n = 20) vs. laparoscopic (n = 19) cystectomy [352]. The 30-day complication rate was significantly higher in the open arm (70%) compared to the laparoscopic arm (26%). There was no difference between the 90-day Clavien complication rates in the three study arms. Limitations of this study include the small sample size, three different, although experienced, surgeons, and cross over between arms.

7.4.5.1 Summary of evidence and guidelines for laparoscopic/robotic-assisted laparoscopic cystectomy

Summary of evidence	**LE**
Robot-assisted radical cystectomy (RARC) has longer operative time (1-1.5 hours) and major costs, but shorter length of hospital stay (1-1.5 days) and less blood loss compared to open radical cystectomy (ORC).	1
Retrospective RARC series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-day complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and quality of life, are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied.	4

Recommendations	**Strength rating**
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

*7.4.6 **Urinary diversion after radical cystectomy***

From an anatomical standpoint, three alternatives are currently used after cystectomy:

- abdominal diversion, such as an uretero-cutaneostomy, ileal or colonic conduit, and various forms of a continent pouch;
- urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution);
- rectosigmoid diversions, such as uretero-(ileo-)rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [353]. Several studies have compared certain aspects of health-related quality of life (HRQoL) such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socio-economic status, and time interval to primary surgery.

7.4.6.1 Patient selection and preparations for surgery

The ASA score has been validated to assess the risk of post-operative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [139, 354], particularly those related to the type of urinary diversion (Table 7.4) [355]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [356, 357]

ASA	
1	No organic pathology, or patients in whom the pathological process is localised and does not cause any systemic disturbance or abnormality.
2	A moderate but definite systemic disturbance caused either by the condition that is to be treated or surgical intervention, or which is caused by other existing pathological processes.
3	Severe systemic disturbance from any cause or causes. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgment.
4	Extreme systemic disorders that have already become an imminent threat to life, regardless of the type of treatment. Because of their duration or nature, there has already been damage to the organism that is irreversible.
5	Moribund patients not expected to survive 24 hours, with or without surgery.

In consultation with the patient, both an orthotopic neobladder and ileal conduit should be considered in case reconstructive surgery exposes the patient to excessive risk (as determined by comorbidity and age).

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated; in males, in case of CIS and extension of the tumour in the prostatic urethra, in females, urethral frozen section has to be performed on the cystoprostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck. Non-muscle-invasive BC in prostatic urethra or bladder neck biopsies does not necessarily preclude orthotopic neobladder substitution, provided that patients undergo regular follow-up cystoscopy and urinary cytology [358].

When there are positive LNs, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [283].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared to those with conduits or continent cutaneous diversions [359].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [360]. Despite the necessary interruption and re-anastomosis of bowel, formal bowel preparation may not be necessary [361]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [362]. Patients treated according to the “fast tract”/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [363].

A cornerstone of the ERAS protocol is post-operative pain management which involves significantly reducing the use of opioids; offering opioids mainly as breakthrough pain medication. Instead of patient-controlled analgesia and epidural opioids, most patients receive high-dose acetaminophen and/or ketorolac, starting intra-operatively. Patients on ERAS experience more pain as compared to patients on a traditional protocol (Visual Analogue Scale 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [364].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ-opioid receptor antagonist, experienced quicker bowel recovery compared to patients receiving placebo [365]. However, this drug is, as yet, not approved in Europe.

Venous thromboembolism (VTE) prophylaxis may be implemented as part of an ERAS protocol. A single-centre non-RCT showed a significant lower 30-day VTE incidence rate in patients treated for 28 days with enoxaparin compared to patients without prophylaxis [366]. Data from the Ontario Cancer Registry including 4,205 cystectomy patients, of whom 1,084 received NAC, showed that VTE rates are higher in patients treated with NAC as compared to patients treated with cystectomy only (12% vs. 8%; $p = 0.002$) [367, 368].

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- impaired liver or renal function;
- transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative RT, complex urethral stricture disease, and severe urethral sphincter-related incontinence [369].

7.4.6.2 Different types of urinary diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports complications of RC, while ignoring the fact that most complications are diversion related [370]. Age alone is not a criterion for offering continent diversion [369, 371]. Comorbidity, cardiac- and pulmonary function, and cognitive function, are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% in men and 50% in women [372-375]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60-89 mL/min/1.73 m^2) or 3a (eGFR 45-59 mL/min/1.73 m^2) [376]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.4.6.2.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, stay at intensive care and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit [377]. Therefore, in older, or otherwise compromised, patients who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure [378, 379]. Quality of life, which was assessed using the Bladder Cancer Index (BCI), showed equal urinary bother and function for patients treated with ileal conduit and uretero-cutaneostomy [377]. However, others have demonstrated that in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [380].

Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (trans-uretero-cutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [378].

In a retrospective multicentre study peri-operative morbidity was evaluated for urinary diversion using bowel as compared to uretero-cutaneostomy. Patients selected for a uretero-cutaneostomy were older and had a higher ASA score, while their mean Charlson score was lower (4.2 vs. 5.6, $p < 0.001$) [381].

Despite the limited comparative data available, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in uretero-cutaneostomy compared to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [382].

7.4.6.2.2 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [382]. The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the UUT in up to 30% [383-385]. An increase in complications was seen with longer follow-up in the Berne series of 131 patients who were followed for a minimum of five years (median follow-up 98 months) [386]; the rate of complications increased from 45% at five years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.6.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [387-389]. Different anti-reflux techniques can be used [390]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [391]. In a retrospective study of > 800 patients, stomal stenosis was seen in 23.5% of patients with an appendix stoma and 15% of those with an efferent intussuscepted ileal nipple [391]. Stone formation in the pouch occurred in 10% of patients [390-392]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [393].

7.4.6.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an anti-refluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [394, 395]. Most indications for this procedure have become obsolete due to a high incidence of upper UTIs and the long-term risk of developing colon cancer [359, 396]. Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent these problems by interposing a segment of ileum between the ureters and rectum or sigmoid in order to augment capacity and avoid direct contact between the urothelium and colonic mucosa, as well as faeces and urine [397].

7.4.6.2.5 Orthotopic neobladder

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [222, 279, 369]. However, in elderly patients (> 80 years), it is rarely performed, even in high-volume expert centres [398, 399]. The terminal ileum is the gastrointestinal segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [279]. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis, and sphincter relaxation. Early and late morbidity in up to 22% of patients is reported [400, 401]. In two studies with 1,054 and 1,300 patients [369, 402], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. A study comparing cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit showed no difference in CSS between the two groups when adjusting for pathological stage [403]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [369, 404]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether neobladder is better for QoL compared to non-continent urinary diversion [405, 406].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [390, 401]. According to the long-term results, the UUT is protected sufficiently by either method.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [407]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [408]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Additionally, the tumours were at higher risk of advanced stage and nodal involvement [409].

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits, based on clinical experience [410, 411]. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to RC and urinary diversions are listed in Section 7.5.

*7.4.7 **Morbidity and mortality***

In three long-term studies, and one population-based cohort study, the peri-operative mortality was reported as 1.2-3.2% at 30 days and 2.3-8.0% at 90 days [222, 370, 372, 412, 413]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [370]. Late morbidity was usually linked to the type of urinary diversion (see also above) [373, 414]. Early morbidity associated with RC for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [415]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [412, 416-420].

Table 7.6: Management of neobladder morbidity (30-64%) [421]

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	**Immediate complications:**	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics (ATB), no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase dieresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion[1,2]
		Pulmonary embolism	Heparinotherapy[3]
		Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Indwelling leader to raise the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intra-operative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/ intensive care unit management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and CT scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non-obstructive renal failure	Bicarbonate/aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and ATB
Grade V	Death of a patient		
Suffix 'd'	*If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.*		

[1] A systematic review showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. The foreign antigens in transfused blood induce immune suppression, which may lead to tumour cell spread, tumour growth and reduced survival in already immunosuppressed cancer patients. As other possible causes for this finding increased post-operative infections and blood incompatibility were mentioned [422]. Buchner and co-workers showed similar results in a retrospective study. The 5-year CSS decreased in cases where intra-operative blood transfusion (CSS decreased from 67% to 48%) or post-operative blood transfusion (CSS decreased from 63% to 48%) were given [423].

[2] Intra-operative tranexamin acid infusion reduces peri-operative blood transfusion rates from 57.7% to 31.1%. There was no increase seen in peri-operative venous thromboembolism [424].

[3] Hammond and co-workers reviewed 20,762 cases of venous thromboembolism (VTE) after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [425]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [426].

7.4.8 ***Survival***

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the 5-year RFS rate was 58% and CSS was 66% [427]. External validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [428].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at five years and 60% and 43%, at ten years, respectively [199]. However, the 5-year RFS in node-positive patients who underwent cystectomy was considerably less at 34-43% [198, 429]. In a surgery-only study, the 5-year RFS was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [199].

A trend analysis according to the 5-year survival and mortality rates of BC in the U.S. between 1973 and 2009 with a total of 148,315 BC patients, revealed increased stage-specific 5-year survival rates for all stages, except for metastatic disease [430].

7.4.9 ***Impact of hospital and surgeon volume on treatment outcomes***

Recently, a systemic review was performed to assess the impact of hospital and/or surgeon volume on peri-operative outcomes of RC [431]. In total, 40 studies including over 560,000 patients were included. All studies were retrospective cohort studies. Twenty-two studies reported on hospital volume only, six studies on surgeon volume only and twelve studies reported on both. The results of the systematic review suggests that a higher hospital volume is likely associated with lower in-hospital, 30-day and 90-day mortality rates. Also, higher volume hospitals are likely to have lower positive surgical margins, higher LND and neobladder rates and lower complication rates. For surgeon volume, less evidence is available and it seems that outcome after RC is mainly hospital-driven. In spite of the lower quality, the available evidence suggests that performing more than 10 RCs per year per hospital reduces 30- and 90-day mortality. Performing more than 20 RCs per hospital per year might even further reduce these mortality rates.

7.4.10 *Summary of evidence and guidelines for radical cystectomy and urinary diversion*

Summary of evidence	LE
For MIBC, radical cystectomy (RC) is the curative treatment of choice.	3
Higher hospital volume likely improves quality of care and reduction in peri-operative mortality and morbidity.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended lymph node dissection (LND) (vs. standard or limited LND) improves survival after RC.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open RC.	3
The use of extended prophylaxis significantly decreases the incidence of venous thromboembolism after RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted grading system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

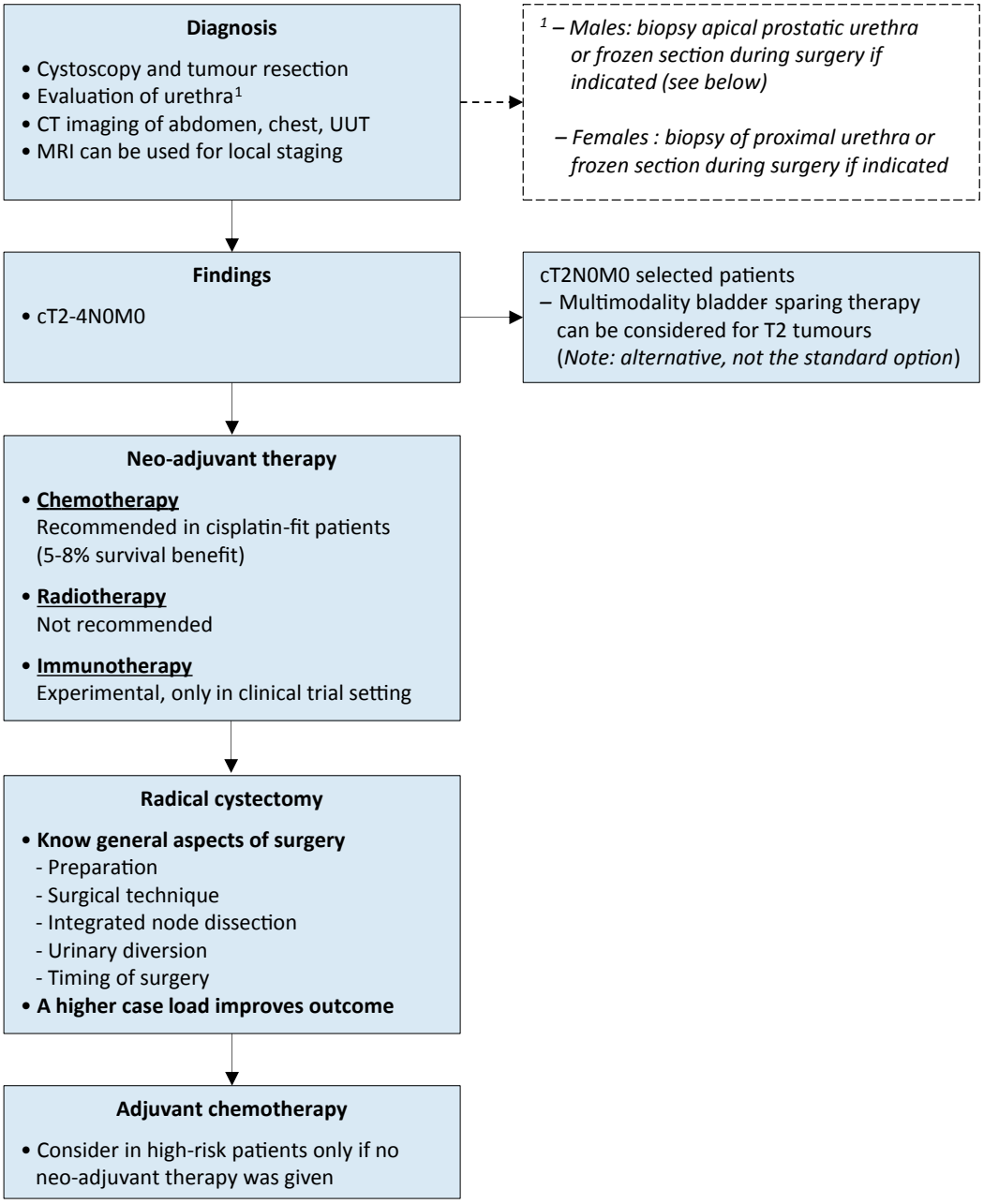
Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Pre-operative bowel preparation is not mandatory. “Fast track” measurements may reduce the time to bowel recovery.	Strong
Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong
Offer RC in T2-T4a, N0M0, and high-risk non-muscle-invasive BC.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

7.4.11 ***EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*** [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral healthcare professional such as a specialist nurse.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
TURBT = transurethral resection of bladder tumour.

Figure 7.1: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

7.5 Unresectable tumours

7.5.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [432-434].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, RC was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [435]. Another ten patients underwent palliative cystectomy, but local pelvic recurrence occurred in all ten patients within the first year of follow-up. Another small study (n = 20) showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [436].

7.5.1.1 Guidelines for unresectable tumours

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms.	Weak

*7.5.1.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours.
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

*7.5.2 **Supportive care***

7.5.2.1 Obstruction of the upper urinary tract

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve. Stents must be regularly replaced and there is the risk of stent obstruction or displacement. Another possible solution is a urinary diversion with, or without, a palliative cystectomy.

7.5.2.2 Bleeding and pain

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [437]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [437]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy to control bleeding and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [438]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [437]. Radical surgery is a last resort and includes cystectomy and diversion (see above Section 7.5.1).

7.6 Bladder-sparing treatments for localised disease

*7.6.1 **Transurethral resection of bladder tumour***

Transurethral resection of bladder tumour alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [439]. In general, approximately 50% of patients will still have to undergo RC for recurrent MIBC with a disease-specific mortality rate of up to 47% within this group [440]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [441, 442]. A prospective study by Solsona *et al*., which included 133 patients with radical TURB and re-staging negative biopsies, reported a 15-year follow-up [442]. Thirty per cent had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten, and fifteen years, the results showed CSS rates of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy, or refuses open surgery, or as part of a multimodality bladder-preserving approach.

7.6.1.1 *Guideline for transurethral resection of bladder tumour*

Recommendation	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

7.6.1.2 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma *in situ*.
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional.

7.6.2 ***External beam radiotherapy***

Current RT techniques with soft-tissue matching result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target dose for curative EBRT in BC is 64-66 Gy [443], with a subsequent boost using external RT or interstitial RT. In a phase II study including 55 patients (median age 86) unfit for cystectomy or even daily RT, BC was treated with 6-weekly doses of 6 Gy [444]. Forty-eight patients completed EBRT with acceptable toxicity and 17% had showed local progression after two years demonstrating good local control with this hypofractionated schedule.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [445]. Acute diarrhoea is reduced even more with intensity-modulated RT [446]. Important prognostic factors for outcome include response to EBRT, tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors reported were age and stage [447].

With the use of modern EBRT techniques, efficacy and safely results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [432], although this was not the case in a 2014 retrospective review using a propensity score analysis [433]. In a 2017 retrospective cohort study of U.S. National Cancer Data Base data, patients over 80 were identified with cT2-4, N0-3, M0 BC, who were treated with curative EBRT (60-70 Gy, n = 739) or concurrent chemoradiotherapy (n = 630) between 2004 and 2013 [448]. The 2-year OS was 42% for EBRT vs. 56% for chemoradiotherapy ($p < 0.001$). For EBRT a higher RT dose and a low stage were associated with improved OS.

In conclusion, although EBRT results seem to improve over time, EBRT alone does not seem to be as effective as surgery or combination therapy (see Section 7.6.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery, as it can be used to control bleeding.

7.6.2.1 *Summary of evidence and guideline for external beam radiotherapy*

Summary of evidence	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or as part of a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendation	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

*7.6.2.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
Radiotherapy alone (single block) is not the preferred radiotherapeutic schedule.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

7.6.3 Chemotherapy

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical complete response rate of up to 56% is reported in some series, which must be weighed against a staging error of > 60% [449, 450]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [451].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [230, 245, 452, 453]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a down-staging of the primary tumour in various prospective series [230, 245, 452].

A bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly selected patient population [451].

A recent large retrospective analysis of a National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [454]. The two and 5-year OS for all patients was 49% and 32.9% and for cT2 patients it was 52.6% and 36.2%, respectively. While these data show that long-term survival with intact bladder can be achieved in a subset of patients it is not recommended for routine use.

7.6.3.1 Summary of evidence and guideline for chemotherapy

Summary of evidence	LE
Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients.	2b

Recommendation	Strength rating
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong

7.6.4 Multimodality bladder-preserving treatment

Multimodality treatment (MMT) or trimodality treatment combines TURB, chemotherapy and RT. The rationale to combine TURB with RT is to achieve local tumour control in the bladder and adjacent nodes. The addition of systemic chemotherapy or other radiosensitisers (mentioned below) is aimed at the potentiation of RT. Micrometastases are targeted by platinum-based combination chemotherapy (for details see Section 7.2). The aim of MMT is to preserve the bladder and QoL without compromising oncological outcome.

There are no completed RCTs comparing the outcome of MMT with RC, but MMT has been shown to be superior to RT alone [455, 456]. Many of the reported series have differing characteristics as compared to the larger surgical series, which typically have median ages in the mid-to-late 60s compared to mid-70s for some large RT series (reviewed by James, *et al*. [455]). In the case of MMT, two distinct patterns of care emerge: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit, patients. For the former category, MMT presents selective bladder preservation and in this case, the initial step is a radical TURB, where as much tumour as possible should be resected. In this case appropriate patient selection (T2 tumours, no CIS) is critical [457]. Even in case of an initial presumed complete resection, a second TUR reveals tumour in > 50% of patients and subsequently improves 5-year OS in case of MMT [458]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, but extensive CIS and poor bladder function should both be regarded as strong contraindications.

A collaborative review has described the principles of MMT [459]. For radiation, two schedules are most commonly used: a split-dose format with interim cystoscopy is used in the U.S. [456], whilst single-phase treatment is more commonly used elsewhere [455]. A standard radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40 Gy, with a boost to the whole bladder of 54 Gy and a further tumour boost, with a total dose of 64 Gy. In a small RCT, however, it was reported that leaving out elective pelvic nodal irradiation did not compromise pelvic control rate, but significantly decreased the acute radiation toxicity [460].

Different chemotherapy regimens have been used, but most evidence exists for cisplatin [357] and mitomycin C plus 5-FU [455]. In addition to these agents, other schedules have also been used, such as hypoxic cell sensitisation with nicotinamide, carbogen and gemcitabine, without clear preference for a specific radiosensitizer [5, 6]. In a recently published phase II RCT, twice-a-day radiation plus fluorouracil/cisplatin was compered to once-daily radiation plus gemcitabine [461]. Both arms were found to result in a >75% freedom of distant metastases at 3 years (78% and 84%, respectively). However, patients in the fluorouracil/cisplatin arm experienced more grade 4 bone marrow toxicity (7 vs. 2 respectively).

To detect non-responders, which should be offered salvage cystectomy, bladder biopsies should be performed after MMT.

Five-year CSS and OS rates vary between 50% to 82% and 36% to 74%, respectively, with salvage cystectomy rates of 10-30% [357, 455, 459, 462]. The Boston group reported on their experience in 66 patients with variant histologies treated with MMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [463]. Compared to RC, the impact of MMT on long-term OS remains undefined. Two retrospective analyses of the National Cancer Database from 2004-2013, with propensity score matching, compared RC to MMT. Ritch *et al*. identified 6,606 RC and 1,773 MMT patients [464]. Worse survival was linked to higher age, comorbidity and tumour stage. After modelling, MMT resulted in a lower mortality at one year (HR: 0.84, 95% CI: 0.74-0.96, $p = 0.01$). However, in years 2 and onwards, there was a significant and persistent higher mortality after MMT (year 2: HR: 1.4, 95% CI: 1.2-1.6, $p < 0.001$; and year 3 onwards: HR: 1.5, 95% CI: 1.2-1.8, $p < 0.001$). The second analysis was based on a larger cohort, with 22,680 patients undergoing RC; 2,540 patients received definitive EBRT and 1,489 MMT [465]. Survival after modelling was significantly better for RC compared to any EBRT, definitive EBRT and MMT (HR: 1.4 [95% CI: 1.2-1.6]) at any time point. In older patients, potentially less ideal candidates for radical surgery, Williams *et al*. found a significantly lower OS (HR :1.49, 1.31-1.69) and CSS (1.55, 1.32-1.83) for MMT as compared to surgery as well as increased costs [466]. This was a retrospective SEER database study which, however, included 687 propensity-matched patients in each arm. On the other hand, a systematic review including 57 studies and over 30,000 patients comparing RC and MMT, found improved 10-year OS and DSS for MMT, but for the entire cohort OS and DSS did not significantly differ between RC and MMT [467]. Complete response after MMT resulted in significantly better survival, as did down-staging after TURB or NAC in case of RC.

Current data show that major complication rates are similar for salvage and primary cystectomy [468]. One option to reduce side effects after MMT is the use of IMRT and image-guided radiotherapy (IGRT) [5, 6].The majority of recurrences post-MMT are non-invasive and can be managed conservatively [455]. A retrospective study showed QoL to be good after MMT and in most domains better than after cystectomy, although prospective validations are needed [469].

A collaborative review came to the conclusion that data are accumulating, suggesting that bladder preservation with MMT leads to acceptable outcomes and therefore MMT may be considered a reasonable treatment option in well-selected patients as compared to RC [459]. Multimodality bladder-preserving treatment should also be considered in all patients with a contraindication for surgery, either a relative or absolute contraindication since the factors that determine fitness for surgery and chemoradiotherapy differ.

There are no definitive data supporting the benefit of using neoadjuvant or adjuvant chemotherapy. Patient selection is critical in achieving good outcomes [459]. Whether a node dissection should be performed before MMT, as in RC, remains unclear [5, 6].

A bladder-preserving multimodality strategy requires very close multidisciplinary cooperation [5, 6]. This was also highlighted by a Canadian group [470]. In Ontario between 1994 and 2008 only 10% (370/3,759) of patients with cystectomy had a pre-operative radiation oncology consultation, with high geographical variations. Independent factors associated with this consultation included advanced age ($p < 0.001$), greater comorbidity ($p < 0.001$) and earlier year of diagnosis ($p < 0.001$). A bladder-preserving multimodality strategy also requires a high level of patient compliance. Even if a patient has shown a clinical response to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term bladder monitoring is essential and patients should be counselled that this will be required.

A sub-analysis of two RTOG trials looked at complete response (T0) and near complete response (Ta or Tis) after MMT [471]. After a median follow-up of 5.9 years 41/119 (35%) of patients experienced a bladder recurrence, and fourteen required salvage cystectomy. There was no difference between complete and near-complete responders. Non-muscle-invasive BC recurrences after complete response to MMT were reported in 25% of patients by the Boston group, sometimes over a decade after initial treatment [472]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

7.6.4.1 Summary of evidence and guidelines for multimodality treatment

Summary of evidence	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	2b

Recommendations	Strength rating
Offer surgical intervention or multimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option.	Strong

*7.6.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma *in situ*.
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).
Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or by brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

7.7 Adjuvant therapy

*7.7.1 **Role of adjuvant platinum-based chemotherapy***

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate [468, 473].

The general benefits of adjuvant chemotherapy include:

- chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided;
- no delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- assessment of *in vivo* chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- delay or intolerability of chemotherapy, due to post-operative morbidity [474].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [473, 475-480]. An individual patient data meta-analysis [475] of survival data from six RCTs of adjuvant chemotherapy [462, 481-484] included 491 patients (unpublished data from Otto *et al*., were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [473]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and Adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [485], and one trial used cisplatin monotherapy [483]. The data were not convincing to give an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [477-479] resulting in the inclusion of 945 patients from nine trials [476]. None of the trials had fully accrued and individual patient data were not used in the analysis [476]. For one trial only an abstract was available at the time of the meta-analysis [478], and none of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine/cisplatin) [477, 478]. The HR for OS was 0.77 (95% CI: 0.59-0.99, p = 0.049) and for DFS 0.66 (95% CI: 0.45-0.91, p = 0.014) with a stronger impact on DFS in case of nodal positivity.

A retrospective cohort analysis including 3,974 patients after cystectomy and LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (HR: 0.75; CI: 0.62-0.90) [486]. A recent publication of the largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin-based chemotherapy (HR: 0.54; 95% CI: 0.4-0.73, p < 0.0001), but there was no significant OS benefit [487].

Furthermore, a large observational study including 5,653 patients with pathological T3-4 and/or pathological node-positive BC, treated between 2003 and 2006 compared the effectiveness of adjuvant chemotherapy vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a 5-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70; 95% CI: 0.64-0.76) in the observation group [488].

Another large retrospective analysis based on National Cancer Data Base including 15,397 patients with locally advanced (pT3/4) or LN-positive disease also demonstrated an OS benefit in patients with UC histology [489]. In patients with concomitant variant or pure variant histology, however, no benefit was found.

From the currently available evidence it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. The most recent meta-analysis from 2014 showed a therapeutic benefit of adjuvant chemotherapy, but the level of evidence of this review is still very low, with significant heterogeneity and methodological flaws in the only nine included trials [476]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

*7.7.2 **Role of adjuvant immunotherapy***

To evaluate the benefit of PD-1/PD-L1 checkpoint inhibitors, a number of randomised phase III trials comparing checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab have been performed but no data have been presented so far.

*7.7.3 **Guidelines for adjuvant therapy***

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Only offer immunotherapy with a checkpoint inhibitor in a clinical trial setting.	Strong

*7.7.4 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*** [5, 6]*

Consensus statement
When adjuvant chemotherapy is offered, patients should be selected based on the result of PLND (if done).

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
PLND = pelvic lymph node dissection.

7.8 Metastatic disease

7.8.1 ***Introduction***

Approximately 50% of patients with muscle-invasive UC relapse after RC, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis [490]. Before the development of effective chemotherapy, patients with metastatic UC had a median survival rarely exceeding three to six months [491].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [492, 493]. In a multivariate analysis, Karnofsky PS of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [493]. These prognostic factors have also been validated for newer combination chemotherapy regimens [494-496].

For patients refractory to, or progressing shortly after, platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that have developed in patients treated with vinflunine, and that have been validated in an independent data set: Hb < 10 g/dL; presence of liver metastases and ECOG PS ≥ 1 [497].

7.8.1.2 Comorbidity in metastatic disease

Comorbidity is defined as "the presence of one or more disease(s) in addition to an index disease" (see Section 5.3). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Different evaluation systems are being used to screen patients as potentially fit or unfit for chemotherapy, but age alone should not be used to base treatment selection on [498].

7.8.1.3 Definition - Not eligible for cisplatin (unfit)

The EORTC conducted the first randomised phase II/III trial for UC patients who were unfit for cisplatin chemotherapy [499]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [500] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss; peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [501]. More than 50% of patients with UC are not eligible for cisplatin-based chemotherapy [502-505]. Renal function assessment in UC is of utmost importance for treatment selection [502, 506]. In case of doubt, measuring GFR with radioisotopes (^{99m}Tc DTPA or ^{51}Cr-EDTA) is recommended. Cisplatin has also been administered in patients with lower GFR (40-60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [507-510]. However, no prospective randomised trial has compared split-dose cisplatin with conventional dosing.

7.8.2 ***First line systemic therapy for metastatic disease***

7.8.2.1 Standard first-line chemotherapy for fit patients

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s demonstrating an OS of twelve to fourteen months in different series (for a review see [511]). Methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) and GC prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older chemotherapy combinations. Neither of the two combinations is superior to the other but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the efficacy of the two regimens [512]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [164] has resulted in it becoming a new standard regimen [513]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [513, 514].

High-dose intensity MVAC (HD-MVAC) combined with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response (CR), and 2-year survival rate. However, there is no significant difference in median survival between the two regimens [515, 516]. In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal LNs vs. 29% and 33% at extranodal sites [515]. The disease sites also have an impact on long-term survival. In LN-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [512].

Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the ITT population of a large randomised phase III trial, comparing PCG triple regimen to GC [517]. However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%, p = 0.0031), and the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR = 0.85, p = 0.075) became significant in the eligible population.

7.8.2.1.1 Carboplatin-containing chemotherapy

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [518].

7.8.2.2 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [501]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity was 13.6% in patients treated with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [499]. The ORR and severe acute toxicity were both 26% for the former group, and 20% and 24%, respectively, for the latter group [499]. Phase III data have confirmed these results [496].

A randomised, multinational phase II trial (JASINT1) assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine-gemcitabine vs. vinflunine-carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination vinflunine-gemcitabine [519].

7.8.2.2.1 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in RCTs; therefore, it is not recommended for first-line use in cisplatin-eligible patients [520-527].

7.8.2.2.2 Single-agent chemotherapy

Response rates to single-agent first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials [528, 529]. Responses with single agents are usually short-lived, complete responses are rare, and no long-term DFS has been reported. The median survival in such patients is only six to nine months.

7.8.2.3 Immunotherapy in first-line treatment

Several randomised phase III trials are currently investigating the use of checkpoint inhibitors in the first-line setting for cisplatin-eligible and ineligible patients using combinations with chemotherapy or CTLA-4 inhibitors as well as monotherapy. At the moment published data from two single-arm phase II trials in cisplatin-ineligible patients are available to inform treatment decisions.

The PD-1 inhibitor pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29%, and complete remission in 7% of patients [530]. The PD-L1 inhibitor atezolizumab was also evaluated in the same patient population in a phase II trial including 119 patients. The ORR was 23%; 9% of patients presented with a complete remission and the median OS was 15.9 months [531]. The results are difficult to interpret due to the missing control arm and the heterogeneity of the study population with regards to PD-L1 status. The toxicity profile was favourable for pembrolizumab as well as for atezolizumab.

Both drugs are approved by the FDA and the EMA for first-line treatment in cisplatin-ineligible patients in case of positive PD-L1 status based on unpublished results from ongoing phase III trials only. Patients with negative PD-L1 should be treated with chemotherapy-based combinations.

7.8.3 ***Second-line systemic therapy for metastatic disease***

7.8.3.1 Second-line chemotherapy

Second-line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from a single randomised phase III study which for the first time established prognostic factors (see Section 7.8.1.1) [497]. A reasonable strategy has been to re-challenge former cisplatin-sensitive patients if progression occurred at least six to twelve months after first-line cisplatin-based combination chemotherapy. Second-line response rates of single agent treatment with paclitaxel (weekly), docetaxel, nab-paclitaxel [532] oxaliplatin,

ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [528, 533, 534]. Gemcitabine has also shown good response rates in second-line use but most patients receive this drug as part of their first-line treatment [527].

The paclitaxel/gemcitabine combination has shown response rates of 38-60% in small single-arm studies. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination [491, 525, 535].

Vinflunine, a novel third-generation vinca alkaloid, was tested in a randomised phase III trial and compared against best supportive care in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [536]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit in favour of vinflunine, which was, however, only statistically significant in the eligible patient population (not in the ITT population).

Vinflunine was approved as second-line treatment in Europe (not in the U.S.). More recently, second-line therapy with PD-1/PD-L1 checkpoint inhibitors has been established as standard second-line therapy and vinflunine is reserved for patients with contraindications to immunotherapy and may be considered as third- or later-line treatment option although no randomised data for these indications exist.

A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.07 vs. 2.76 months) and higher response rates (24.5% vs. 14%), respectively [537]. While the primary endpoint of PFS prolongation was reached, the clinical benefit appears small and OS data have not yet been reported [537].

7.8.3.2 Second-line immunotherapy for platinum-pre-treated patients

Trials investigated and still investigate different immunotherapeutic agents either as monotherapy or in combination with other immune-enhancing agents or chemotherapy in a range of different disease settings. Pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, standard platinum-based chemotherapy in phase I, II and III trials.

Pembrolizumab, a PD-1 inhibitor, has been tested in patients progressing during or after platinum-based first-line chemotherapy in a randomised phase III trial and demonstrated significant OS benefit leading to approval. In the trial, patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS in the pembrolizumab arm was 10.3 months (95% CI: 8.0-11.8) vs. 7.4 months (95% CI: 6.1-8.3) for the chemotherapy arm (HR for death, 0.73; 95% CI: 0.59-0.91, p = 0.002) independent of PD-L1 expression levels [538]. This trial was recently updated with a longer follow-up of 27.7 months with consistent improvement of OS [539]. In addition, HRQoL analysis showed that patients on pembrolizumab experience stable or improved HRQoL whereas it deteriorated on chemotherapy [540].

Atezolizumab, a PD-L1 inhibitor, tested in patients progressing during, or after, previous platinum-based chemotherapy in phase I, phase II and phase III trials, was the first checkpoint inhibitor approved for BC [541-543]. The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (either paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression (IC score 2/3) with 11.1 months vs. 10. 6 months (0.87, 95% CI: 0.63-1.21, p = 0.41) but OS was numerically improved in the ITT population in an exploratory analysis (8.6 months vs. 8.0 months, HR: 0.85, 95% CI: 0.73-0.99). A phase IV single-arm safety study was conducted with atezolizumab including 1,004 patients confirming the efficacy and tolerability profile [544].

The PD-1 inhibitor nivolumab was approved based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The first endpoint was ORR. Objective response rate was 19.6%, and OS was 8.74 months for the entire group [545]. Based on results of phase I/II and phase IB trials, two additional PD-L1 inhibitors, durvalumab and avelumab, are currently only approved for this indication in the U.S. [546-548].

7.8.3.3 Novel agents for second or later-line therapy

The results of a single-arm phase II trial using the FGFR inhibitor erdafitinib demonstrated encouraging response rates in patients with pre-specified FGFR alterations [549]. Moreover, a phase I trial investigated the FGFR inhibitor rogaratinib in patients with over-expression of FGFR mRNA including patients with UC resulting in clinical responses [550]. It is expected that both testing for molecular subtype, as well as identification of FGFR mutations and amplifications, will become an important basis for treatment decisions in localised and advanced UC [5, 6].

Another promising drug is enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, which is highly expressed in UC. A published phase-II single-arm study (n = 125) in patients previously treated with platinum

chemotherapy and checkpoint inhibition showed objective response rates of 44%, including 12% of complete responses with a tolerable safety profile. A phase III randomised trial comparing enfortumab vedotin with single-agent chemotherapy is ongoing [551].

*7.8.4 **Post-chemotherapy surgery and oligometastatic disease***

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with LN metastases only, good PS and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term DFS [512, 516, 552, 553]. The role of surgery of residual LNs after chemotherapy is still unclear. Although some studies suggest a survival benefit and QoL improvement, the level of evidence supporting this practice is mainly anecdotal [554-568]. Retrospective studies of post-chemotherapy surgery after partial or complete remission have indicated that surgery may contribute to long-term DFS in selected patients [569-572]. These findings have been confirmed in a recent systematic review including 28 studies [572].

In the absence of data from RCTs, patients should be evaluated on an individual basis and discussed by an interdisciplinary tumour board [572].

*7.8.4.1 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
In a minority of patients with one metastatic lesion, cure is possible after radical treatment.
In patients with more than two metastatic sites, cure is not possible.
In metachronous OMD, time to relapse is an important prognostic indicator.
Liver is an unfavourable OMD site for curative therapy.
Bone is a unfavourable OMD site for curative therapy.
PET-CT scanning should be included in OMD staging when considering radical treatment.
Radical treatment of OMD should be accompanied by adjuvant or neoadjuvant systemic therapy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
OMD = oligometastatic disease; PET-CT = positron emission tomography-computed tomography.

*7.8.5 **Treatment of patients with bone metastases***

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30-40% [573]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [574]. Bisphosphonates such as zoledronic acid (ZA) reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study [575]. Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor κB ligand), was shown to be non-inferior to ZA in preventing or delaying SREs in patients with solid tumours and advanced MBD, including patients with UC [576]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [574].

Patients treated with ZA or denosumab should be informed about possible side effects including osteonecrosis of the jaw and hypocalcaemia. Supplementation with calcium and vitamin D is mandatory. Dosing regimens of ZA should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [577]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.6 *Summary of evidence and guidelines for metastatic disease*

Summary of evidence	LE
In a first-line setting, performance status (PS) and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival (DFS) reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer (UC).	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, because they reduce and delay skeletal related events.	1b
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1-positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1-positive patients.	2a

Recommendations	Strength rating
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to PD-L1-positive patients.	Strong
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer zoledronic acid or denosumab for supportive treatment in case of bone metastases.	Weak
Only offer vinflunine to patients for metastatic disease as subsequent-line treatment if immunotherapy, or combination chemotherapy, or FGFR3-inhibitor therapy, or inclusion in a clinical trial is not feasible.	Weak

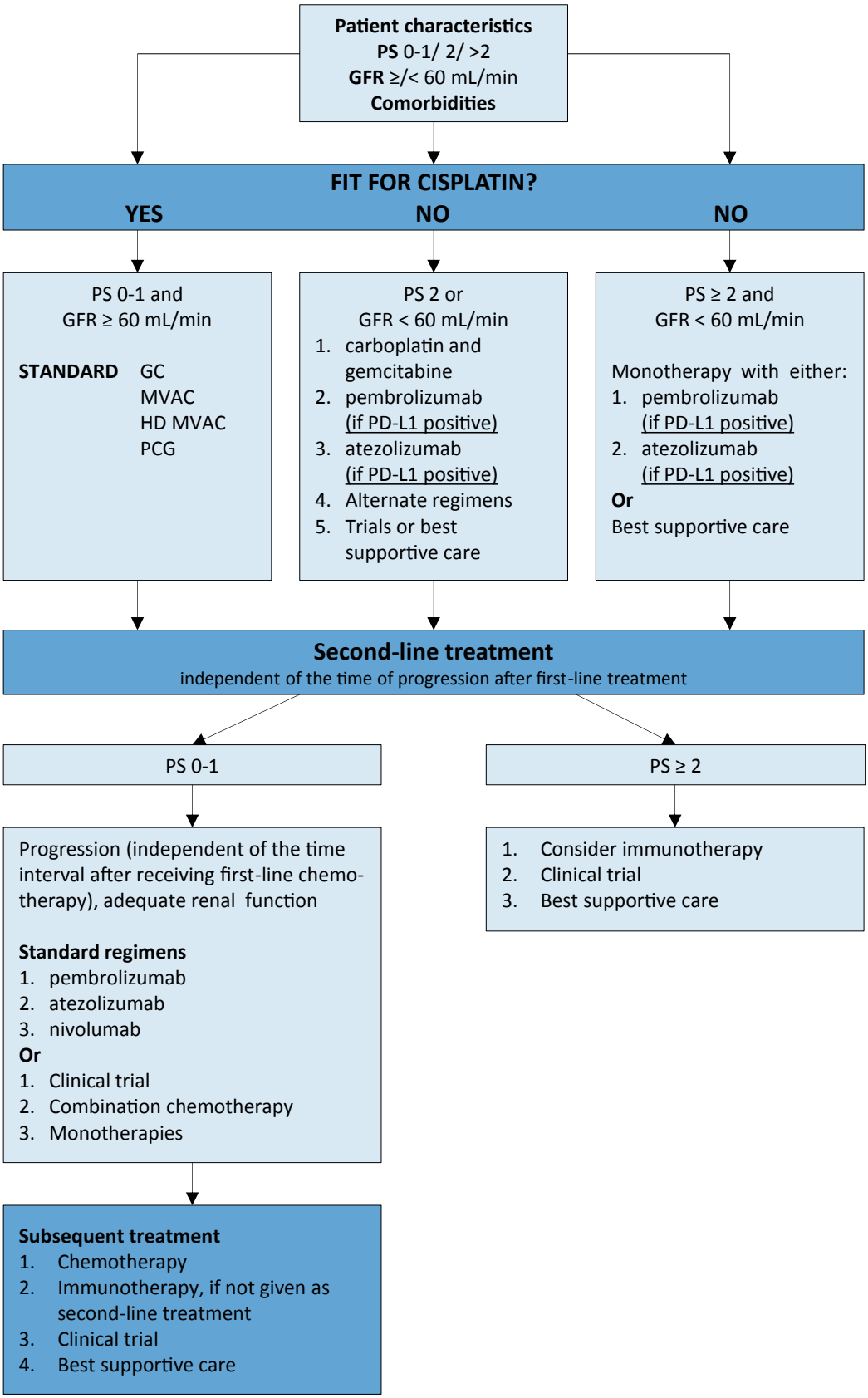
GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine.

7.8.7 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer* [5, 6]*

Consensus statement
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.
Pseudo-progression has not been demonstrated in urothelial cancer.
In patients with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy but with high PDL1 expression (as per approved drug specific methodology), both treatment with an ICI and chemotherapy can be offered.
Since no data exist for cisplatin-ineligible PDL1-positive patients in order to differentiate between different ICIs (atezolizumab and pembrolizumab), either agent can be administered.
Enrolment in a clinical trial remains the preferred option for patients with cisplatin-eligible advanced/ metastatic urothelial cancer until ongoing randomised trials report in this population.
Treatment with an ICI should be offered to patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy. This includes tumours which have progressed within a year or following peri-operative (cystectomy) chemotherapy.
Once initiated, ICI therapy should be continued until progression of disease in patients with advanced/ metastatic urothelial cancer.
In contrast to the first-line setting, the PD-L1 biomarker is not useful for selecting patients for immunotherapy in platinum-refractory metastatic urothelial cancer.
Carboplatin-based chemotherapy remains a viable first-line treatment option in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma until data from randomised phase 3 trials of ICIs are available.
Cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma should be considered for chemotherapy instead of sequencing of immunotherapy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups) are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
ICI = immune checkpoint inhibitor; PD-L1 = programmed death-ligand 1.

Figure 7.2: Flow chart for the management of metastatic urothelial cancer



GC = gemcitabine plus cisplatin; GFR = glomular filtration rate; HD-MVAC = (high-dose) methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine; PS = performance status.

7.9 Quality of life

7.9.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. The impact of BC on HRQoL was recently reported in a population-based study using the SEER registry, including a total of 535 BC patients (458 with non-invasive disease and 77 with invasive disease) older than 65 years and 2,770 matched non-cancer controls. The authors concluded that BC patients experienced statistically significant declined HRQoL in all domains. In invasive BC, particularly physical and social functioning were affected [578].

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [579], EORTC QLQ-C30 [580], EORTC QLQ-BLM (MIBC module) [581], and SF (Short Form)-36 [582, 583] and recently the BCI questionnaire specifically designed and validated for BC patients [584].

A psychometric test, such as the FACT-BL, should be used for recording BC morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences [585].

7.9.2 Neoadjuvant chemotherapy

The impact of NAC on patient-reported outcomes (using EORTC QLQ questionnaires) was investigated by Feuerstein *et al*. [586]. A propensity-matched analysis of 101 patients who completed NAC and 54 patients who did not undergo NAC, did not demonstrate a negative effect of NAC on patient-reported outcomes.

7.9.3 Radical cystectomy and urinary diversion

Two recent systematic reviews focused on HRQoL after RC [587, 588] and one systematic review, based on 18 studies (n = 1,553), showed a slight, but not significant, improvement of QoL in patients with an orthotopic diversion [587]. However, analysing only the studies comparing exclusively ileal conduit vs. ileal orthotopic neobladder, the advantage in QoL of the latter group was significant. Another systematic review, based on 29 studies (n = 3,754), showed no difference in overall QoL between continent and incontinent diversion [588]. Subgroup analysis demonstrated greater improvement in physical health for incontinent compared to continent diversions (p = 0.002), but no differences in mental health (p = 0.35) or social health (p = 0.81). However, patients with a neobladder demonstrated superior emotional function and body image [588-590].

Clifford and co-workers prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [591]. Day-time continence increased from 59% at less than three months post-operatively to 92% after 12 to 18 months. Night-time continence increased from 28% at less than three months post-operatively to 51% after 18 to 36 months. Also of interest is the urinary bother in female neobladder. Bartsch and co-workers found in 56 female patients day-time and night-time continence rates of 70.4% and 64.8%, respectively. Thirty-five patients (62.5%) performed clean intermittent catheterisation, which is much worse when compared to male neobladder patients. Moreover, patients with non-organ-confined disease (p = 0.04) and patients with a college degree (p = 0.001) showed worse outcomes on HRQoL scores [592].

Altogether, HRQoL outcomes are most likely a result of good patient selection. An older, more isolated, patient is probably better served with an ileal conduit, whereas a younger patient with a likely higher level of interest in body image and sexuality is better off with an orthotopic diversion. The patient's choice is the key to the selection of reconstruction method [588].

7.9.4 Bladder sparing trimodality therapy

A cross-sectional bi-institutional study found in multivariable analysis that patients who received trimodality therapy (n = 64) had higher physical-, social-, emotional- and cognitive functioning, better general QoL, sexual function and body image than patients after RC (n = 109). However, urinary symptom scores were similar [469]. To draw valid conclusions, prospective studies are needed.

7.9.5 Non-curative or metastatic bladder cancer

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [593]. There is limited literature describing HRQoL in BC patients receiving palliative care [594], but there are reports of bladder-related symptoms relieved by palliative surgery [436], RT [595], and/or chemotherapy [596]. Recently, a HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [540]. It was reported that patients treated with pembrolizumab had stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [540].

7.9.6 Summary of evidence and recommendations for health-related quality of life

Summary of evidence	LE
Compared to non-cancer controls, the diagnosis and treatment of bladder cancer has a negative impact on HRQoL.	2a
There is no difference in overall QoL between patients with continent or incontinent diversion.	1a
In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used.	2b
Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.	3
In patients with platinum-refractory advanced urothelial carcinoma, pembrolizumab may be superior in terms of HRQoL compared to another line of chemotherapy.	1b

Recommendations	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with MIBC.	Strong
Offer a continent urinary diversion unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications.	Strong
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	Strong
Provide clear and exhaustive information on all potential benefits and side-effects, allowing patients to make informed decisions. Encourage patients to actively participate in the decision-making process.	Strong

8. FOLLOW-UP

8.1 Follow-up in muscle invasive bladder cancer

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options [597].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [598, 599].

Current surveillance protocols are based on patterns of recurrence drawn from retrospective series only. Combining this data is not possible since most retrospective studies use different follow-up regimens and imaging techniques. Additionally, reports of asymptomatic recurrences diagnosed during routine oncological follow-up, and results from retrospective studies are contradictory [600-602]. From the Volkmer B, *et al*. series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [601]. Conversely, in the Giannarini, *et al*. series of 479 patients; those with recurrences detected during routine follow-up (especially in the lungs) and with secondary urothelial tumours as the site of recurrence, had a slightly higher survival [600]. Boorjian, *et al*. included 1,599 RC patients in their series, with 77% symptomatic recurrences. On multivariate analysis, patients who were symptomatic at recurrence had a 60% increased risk of death as compared to asymptomatic patients [602].

However, at this time, no data from prospective trials demonstrating the potential benefit of early detection of recurrent disease, and its impact on OS, are available [603]. For details see Section 7.6.4.

8.2 Site of recurrence

8.2.1 Local recurrence

Local recurrence takes place in the soft tissues of the original surgical site or in LNs. Contemporary cystectomy has a 5-15% probability of pelvic recurrence which usually occurs during the first 24 months, most often within 6 to 18 months after surgery. However, late recurrences can occur up to five years after RC. Risk factors described are pathological stage, LNs, positive margins, extent of LND and peri-operative chemotherapy [604].

Patients generally have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Multimodality management generally involves a combination of chemotherapy, radiation and surgery [603].

*8.2.2 **Distant recurrence***

Distant recurrence is seen in up to 50% of patients treated with RC for MIBC. As with local recurrence, pathological stage and nodal involvement are risk factors [605]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52-70%) [606].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrences appear within the first three years after RC, mainly in the first two years, although late recurrence has been described after more than 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [607-609]. However, longer survival (28-33% at 5 years) has been reported in patients with minimal metastatic disease undergoing multimodality management, including metastasectomy [555, 563].

*8.2.3 **Urothelial recurrences***

After RC, the incidence of new urethral tumours was 4.4% (1.3-13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [610].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [603]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [611]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease; in case of distant disease, systemic chemotherapy is indicated [3].

Upper urinary tract UCs occur in 4-10% of cases and represent the most common sites of late recurrence (3-year DFS following RC) [612]. Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [603]. A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigations, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used during surveillance, the rate of primary detection was 7% vs. 29.6% with UUT imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [613]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephro-ureterectomy can prolong survival [614].

8.3 Time schedule for surveillance

Although, based on low level evidence only, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [613].

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualised recommendations and may increase recurrence detection. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally advanced disease or LN involvement are at a higher risk of recurrence for more than 20 years [615]. However, this model has not been validated and does not incorporate several risk factors related to non-BC mortality. Furthermore, the prognostic implications of the different sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease will not influence survival [616]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Since data for follow-up strategies are sparse, a number of key questions were included in a recently held consensus project [5, 6]. Outcomes for all statements for which consensus was achieved are listed in Section 8.6.

8.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. This rate increases over time, and exceeds 54% after 15 years of follow-up. Therefore, long-term follow-up of functional outcomes is desirable [603].

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [603]. Especially in women approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [592]. Recently a 21% increased risk of fractures was also described as compared to no RC, due to chronic metabolic acidosis and subsequent long-term bone loss [616].

Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually [5, 6, 382].

8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	LE	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease (NMIBC/CIS or positive ureteral margins).		See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
After radical cystectomy with curative intent, regular follow-up is needed.
After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended.
After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g. multifocality, carcinoma *in situ* and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 mos initially; then after 3 yrs, every 6 mos in the majority of patients.
After trimodality treatment with curative intent, regular follow-up for the detection of relapse is needed in the majority of patients.
After trimodality treatment with curative intent, follow-up imaging to assess distant recurrence or recurrence outside the bladder is needed.
After trimodality treatment with curative intent, assessment of the urothelium to detect recurrence is recommended every 6 mos in the majority of patients.
After trimodality treatment with curative intent, in addition to a CT scan, other investigations of the bladder are recommended.
In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 yrs in the majority of patients.
In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value.
To detect relapse after radical cystectomy with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 yrs in the majority of patients.

To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
Levels of LDH and CEA are not essential in the follow-up of patients with urothelial cancer to detect recurrence.
Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
CEA = carcinoembryonic antigen; CT = computed tomography; LDH = lactate dehydrigenase; mos = months; yrs = years.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Working Group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel.

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11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Primary Urethral Carcinoma

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1. INTRODUCTION

1.1 Aims and scope

The aim of these guidelines is to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma. When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary urethral carcinoma, in contrast to secondary urethral carcinoma, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary urethral carcinoma is reported after radical cystectomy for bladder cancer [1, 2] (see Chapter 7.4 of the European Association of Urology (EAU) Guidelines on Muscle-invasive and Metastatic Bladder Cancer [MIBC] [2]).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on MIBC is responsible for this publication. This is an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of suffering from urethral carcinoma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: https://uroweb.org/guideline/primary-urethral-carcinoma/.

1.3 Publication history and summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013 [3]. This is the seventh update of this document.

*1.3.1 **Summary of changes***

The literature for the complete document has been assessed and updated, where relevant. In particular for:

- Section 3.1 - Epidemiology and 3.2 Aetiology;
- Section 4.3 - Handling of tumour specimens, a new table has been included;
- Section 6.2 - Predictors of survival in primary urethral carcinoma;
- Chapter 7 - An algorithm presenting an overview of the management of primary urethral carcinoma has been included.

2. METHODS

2.1 Data identification

For the 2020 Primary Urethral Carcinoma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between June 30th, 2018 and July 3rd, 2019. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 114 unique records were identified, retrieved and screened for relevance. Eleven new references were included in this 2020 publication. A detailed search strategy is available online: https://uroweb.org/guideline/primary-urethral-carcinoma/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, based on a modified GRADE methodology [4, 5]. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

This document was peer-reviewed prior to publication in 2015.

2.3 Future goals

The MIBC Guidelines Panel aims to systematically address the following key clinical topics in future updates of the Primary Urethral Carcinoma Guidelines:

- assessment of the accuracy of computed tomography [CT] and magnetic resonance imaging [MRI] for local staging of primary urethral carcinoma and their predictive value on clinical decision-making;
- the (long-term) efficacy of urethral-sparing surgery and chemoradiotherapy for genital preservation in localised and locally advanced tumours;
- the prognostic impact of neoadjuvant and adjuvant treatment modalities in locally advanced disease;
- the prognostic impact of the extent of transurethral resection of the prostate prior to bacillus Calmette-Guérin (BCG) treatment in urothelial malignancies of the prostatic urethra and ducts;
- the therapeutic benefit and clinical safety of programmed cell death (ligand)-1 inhibitors for the treatment of advanced primary urethral carcinoma;
- the extent and prognostic benefit of regional Lymph node (LN) dissection at primary treatment.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary urethral carcinoma is considered a rare cancer, accounting for < 1% of all genitourinary malignancies [8] (ICD-O3 topography code: C68.0) [9]. In 2013, the prevalence of urethral carcinoma in the 28 European Union countries was 3,986 cases with an estimated annual incidence of 1,504 new cases, with a male/female prevalence of 2.9: 1 [10]. Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary urethral carcinoma peaked in the > 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women, and was almost negligible in those aged < 55 years (0.2/million) [11].

3.2 Aetiology

For male primary urethral carcinoma, various predisposing factors have been reported, including urethral strictures [12, 13], chronic irritation after intermittent catheterisation/urethroplasty [14-16], external beam irradiation therapy (EBRT) [17], radioactive seed implantation [18], chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [19, 20] and lichen sclerosus [13]. In female urethral carcinoma, urethral diverticula [21-23] and recurrent urinary tract infections [24] have been associated with primary urethral carcinoma. Mid-urethral sling meshes have not been associated with an increased risk of primary urethral carcinoma [25]. Clear-cell adenocarcinoma (AC) may also have a congenital origin [26, 27].

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma (UC) of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC) (16-22%) and AC (10-16%) [10, 28]. A SEER analysis of 2,065 men with primary urethral carcinoma (mean age: 73 years) found that UC was most common (78%), and SCC (12%) and AC (5%) were significantly less frequent [29]. In women, AC is the more frequent histology (38-46.7%) followed by SCC (25.4-28%), UC (24.9-28%) and other histological entities (6%) [30, 31].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis (UICC/TNM) staging system

In men and women, urethral carcinoma is classified according to the 8th edition of the TNM classification [9] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [9]. Of note, for cancers occurring in the urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [32].

Table 4.1: TNM classification (8th edition) for urethral carcinoma [9]

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma *in situ,* involvement of prostatic urethra
Tis pd	Carcinoma *in situ,* involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus sponsiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

The former World Health Organization (WHO) grading system of 1973, which differentiated urothelial carcinomas into three different grades (G1-G3), has been replaced by the grading system in 2004 [33]. Non-urothelial urethral carcinoma is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [33]. The 2004 classification corresponds to the new 2016 WHO classification [34].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary urethral carcinoma [33]

Urothelial urethral carcinoma	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial urethral carcinoma	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

4.3 Handling of tumour specimens

Specimen handling should follow the general rules as published by the International Collaboration on Cancer Reporting [35].

Table 4.3: Required and recommended elements for pathology reporting of carcinoma of the urethra in urethrectomy specimens [9, 35]

Required		Recommended	
Operative procedure		Clinical information	Previous history of urinary tract disease or distant metastasis
Additional specimens submitted			Previous therapy
Maximum tumour dimension	Cannot be assessed		Other clinical information
	No macroscopically visible tumour	Tumour focality	
	Maximum tumour dimension (largest tumour)	Other tumour dimensions (than maximum dimension) of the largest tumour	
Macroscopic tumour site		Block identification key	
Macroscopic extent of invasion		Associated epithelial lesions	
Histological tumour type	Histological subtype/ variant (urothelial carcinoma)	Extranodal spread for involved regional lymph node(s)	
Non-invasive carcinoma		Coexistent pathology	
Histological tumour grade		Ancillary studies	
Microscopic extent of invasion			
Lymphovascular invasion			
Margin status			
Regional lymph node status	No regional lymph nodes submitted		

4.4 Guideline for staging and classification systems

Recommendation	LE	Strength rating
Use the 2017 TNM classification and 2004/2016 WHO grading systems for pathological staging and grading of primary urethral carcinoma.	3	Strong

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45-57%) with primary urethral carcinoma present with symptoms associated with locally advanced disease (T3/T4) [36]. At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include; an extra-urethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [36].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [37]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged LNs, describing location, size and mobility [38].

5.3 Urinary cytology

Cytological assessment of urine specimens in suspect cases of primary urethral carcinoma should be conducted according to the Paris system [39]. The role of urinary cytology in primary urethral carcinoma is limited since its sensitivity ranges between 55% and 59% [40]. Detection rates depend on the underlying histological entity. In male patients, the sensitivity for UC and SCC was reported to be 80% and 50%, respectively, whereas in female patients, sensitivity was found to be 77% for SCC and 50% for UC [40].

5.4 Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology [37]. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist. To obtain all relevant information, the collection, handling, and evaluation of biopsy specimen should follow the recommendations provided by the International Collaboration on Cancer Reporting (see table 4.3) [35].

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [41]. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis [42]. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (between the five and seven o'clock position from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [43].

5.5 Radiological imaging

Radiological imaging of urethral carcinoma aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. MRI can be used to evaluate local tumour extent and presence of regional LN metastases, focusing in particular on inguinal and pelvic LNs [44-46]. Computed tomography can be used for distant staging and concentrate on chest, abdomen and pelvis, with CT of the thorax and abdomen in all patients with invasive disease (> cT1N0M0) [47]. If imaging of the remainder of the urothelium is required, CT urography should be performed [48].

5.6 Regional lymph nodes

In contrast to penile cancer (41%) [49], enlarged LNs in urethral carcinoma often represent metastatic disease (84%) [50-52]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal LNs and, subsequently, to the pelvic (external, obturator and internal iliac) LNs. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic LNs. In women, the lymph of the proximal third drains into the pelvic LN chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [53, 54].

5.7 Summary of evidence and guidelines for diagnostic evaluation and staging

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic LNs often exhibit pathological LN metastasis.	3

Recommendations	LE	Strength rating
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	3	Strong
Assess the presence of distant metastases by computed tomography of the thorax and abdomen/pelvis.	3	Strong
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour and regional lymph node enlargement.	3	Strong

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the one- and 5-year relative overall survival (OS) rates in patients with urethral carcinoma in Europe are 71% and 54%, respectively [10]. With longer follow-up, a SEER analysis of 2,651 cases with common and 257 cases of rare PUC reported 10-year OS rates of 42.4 and 31.9%, respectively [55]. Cancer-specific survival (CSS) rates at five and ten years are 68% and 60%, respectively [11].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, 5-year OS rate does not substantially differ between the sexes [10, 31]. Prognostic factors of decreased survival in patients with primary urethral carcinoma are:

- advanced age (> 65 years) and black race [10, 31, 56];
- stage, grade, nodal involvement [51] and metastasis [29];
- tumour size and proximal tumour location [29];
- extent of surgical treatment and treatment modality [29, 56];
- underlying histology [10, 29, 56, 57];
- presence of concomitant bladder cancer [41];
- location of recurrence (urethral vs. non-urethral) [58].

Some limitations have to be taken into when interpreting these results. In the Dutch study, the numbers were low (n = 91) [57]. A study based on the SEER database compared prognostic factors in rare pathological types of PUC (n = 257) and common pathological groups (n = 2,651). Age (> 60 years), race (others vs. whites), T-stage (T3/T4 vs. Ta-T2) and M-stage (M1 vs. M0) were independent prognostic risk factors for OS and CSS in rare pathological variants [55].

6.3 Summary of evidence for prognosis

Summary of evidence	LE
Prognostic factors for survival in primary urethral carcinoma are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7. DISEASE MANAGEMENT

7.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male distal urethral carcinoma followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [37]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [59]. Therefore, optimising treatment of distal urethral carcinoma has become the focus of clinicians to improve functional outcome and quality of life,

while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 distal urethral carcinoma treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected LN disease [60]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have also been reported in recent series [61, 62]. However, a series on patients treated with penis-preserving surgery for distal urethral cancer reported a higher risk of progression in patients with positive proximal margins, which was also more frequently present in cases of lymphovascular and peri-neural invasion of the primary tumour [63].

*7.1.1 **Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in males***

Summary of evidence	LE
In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence.	3

Recommendations	LE	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if surgical margins are negative.	3	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penis-preserving surgery is intended.	3	Strong

7.2 Treatment of localised urethral carcinoma in females

*7.2.1 **Urethrectomy and urethra-sparing surgery***

In women with localised urethral carcinoma, to provide the highest chance of local cure, primary radical urethrectomy should remove all the peri-urethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and appendicovesicostomy for primary distal urethral lesions has been shown to provide satisfactory functional results in women [37].

Previous series have reported outcomes in women with mainly distal urethral tumours undergoing primary treatment with urethra-sparing surgery with or without additional radiotherapy (RT) compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [64, 65]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who subsequently required additional reconstructive surgery [64, 65].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal urethral tumours, have also resulted in considerable local failure rates of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral carcinoma to prevent local and systemic progression [64].

*7.2.2 **Radiotherapy***

In women RT was investigated in several older long-term series with a medium follow up of 91-105 months [66]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year CSS was 49% [66]. Most local failures (95%) occurred within the first two years after primary treatment [66]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of RT (EBRT vs. interstitial brachytherapy) was not [66]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [67]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [66].

*7.2.3 **Summary of evidence and guidelines for the treatment of localised urethral carcinoma in females***

Summary of evidence	LE
In distal tumours, urethra-sparing surgery and local RT represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	LE	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to women with distal urethral tumours, if negative surgical margins can be achieved intraoperatively.	3	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to women with localized urethral tumours, but discuss local toxicity.	3	Weak

7.3 Multimodal treatment in locally advanced urethral carcinoma in both genders

7.3.1 Introduction

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with the option of additional RT [68]. Multimodal therapy is often underutilised (16%) in locally advanced disease notwithstanding promising results [68]. It confers an OS benefit in primary urethral carcinoma of urothelial origin [69-71]. A large retrospective cohort study in patients with locally advanced urethral carcinoma treated with adjuvant RT and surgery vs. surgery alone demonstrated that the addition of RT improved OS [72].

7.3.2 Preoperative cisplatin-based chemotherapy

For local staging, there is increasing evidence that MRI is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [73].

Retrospective studies have reported that modern cisplatin-based combination chemotherapy regimens can be effective in advanced primary urethral carcinoma, providing prolonged survival even in LN-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally advanced urethral carcinoma.

In a series of 124 patients, 39 (31%) were treated with peri-operative platinum-based chemotherapy for advanced primary urethral carcinoma (twelve patients received neoadjuvant chemotherapy, six received neoadjuvant chemoradiotherapy and 21 adjuvant chemotherapy). Patients who received neoadjuvant chemotherapy or chemoradiotherapy for locally advanced primary urethral carcinoma (≥ cT3 and/or cN+) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [74]. Another retrospective series including 44 patients with advanced primary urethral carcinoma, reported outcomes on 21 patients who had preoperatively received cisplatin-based combination chemotherapy according to the underlying histologic subtype. The overall response rate for the various regimens was 72% and the median OS 32 months [50].

7.3.3 Chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of local RT with concurrent chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several series. This approach offers a potential for genital preservation [75-79]. The largest, and recently updated, retrospective series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent EBRT. A complete response to primary chemoradiotherapy was observed in ~80%. The 5-year OS and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery initiated only in non-responders or in case of local failure, was not reported to be associated with improved survival [75].

7.3.4 Salvage treatment in recurrent primary urethral carcinoma after surgery for primary treatment

A multicentre study reported that patients who were treated with surgery for primary therapy, and underwent surgery or RT-based salvage treatment for recurrent solitary or concomitant urethral disease, demonstrated similar survival rates compared to patients who never developed recurrence after primary treatment [58].

7.3.5 Treatment of regional lymph nodes

Nodal control in urethral carcinoma can be achieved either by regional LN dissection [37], RT [66] or chemotherapy [50]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral carcinoma [52]. However, in patients with clinically enlarged inguinal/pelvic LNs or invasive tumours, regional lymphadenectomy should be considered as initial treatment since cure might still be achievable with limited disease [37].

7.3.6 *Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both genders*

Summary of evidence	LE
In locally advanced urethral carcinoma, cisplatin-based chemotherapy with curative intent prior to surgery might improve survival compared to chemotherapy alone, or surgery followed by chemotherapy.	3
In locally advanced SCC of the urethra, treatment with chemoradiotherapy might be an alternative to surgery.	3

Recommendations	LE	Strength rating
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radio-oncologists and oncologists.	3	Strong
In locally advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	3	Weak
In locally advanced squamous cell carcinoma of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	3	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	3	Weak

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent BCG instillation is effective in patients with Ta or Tis prostatic urethral carcinoma [80]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) [81]. Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement [82]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57% and 75% [80, 83]. Some earlier series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement [84, 85]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a LN mapping study found that twelve patients had positive LNs, with an increased proportion located above the iliac bifurcation [86].

7.4.1 *Summary of evidence and guidelines for the treatment of urothelial carcinoma of the prostate*

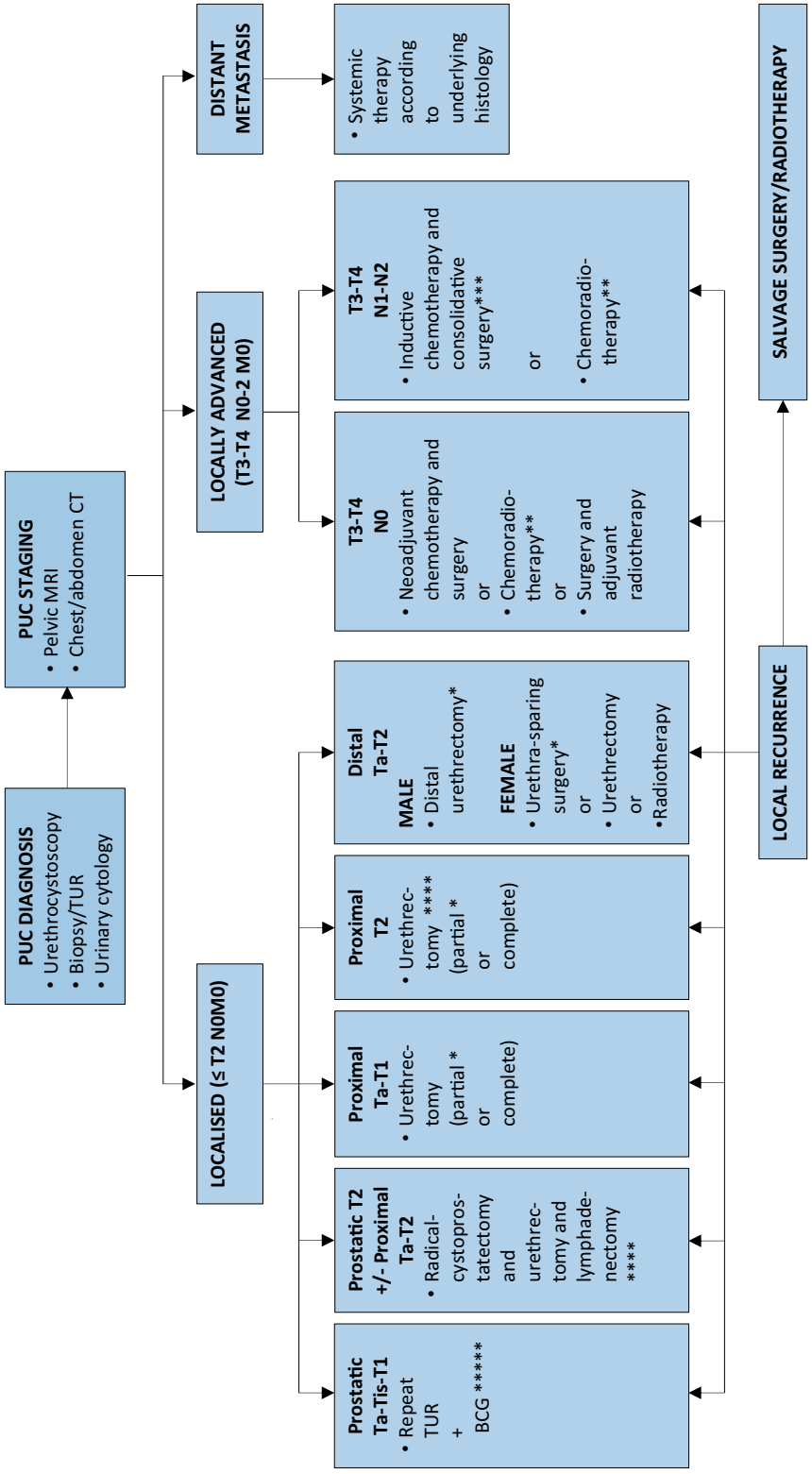
Summary of evidence	LE
Patients undergoing TUR of the prostate for prostatic urothelial carcinoma prior to BCG treatment show superior complete response rates compared to those who do not.	3

Recommendations	LE	Strength rating
Offer a urethra-sparing approach with transurethral resection (TUR) and bacillus-Calmette Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	3	Strong
Perform a TUR of the prostate prior to treatment with BCG to improve response to BCG.	3	Weak
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	3	Strong

7.5 Metastatic disease

There is no separate data addressing management of metastatic disease in primary urethral carcinoma patients. Systemic therapy in metastatic disease should be selected based on the histology of the tumour. The EAU Guidelines on Metastatic Bladder Cancer can be followed if UC is the predominant histology [2]. Even though urethral carcinoma patients have been included in large clinical trials on immunotherapy, so far, in terms of response rates, no subgroup analyses are available [87].

Figure 7.1: Management of primary urethral carcinoma



* Ensure complete circumferential assessment if penis-preserving/urethra-sparing surgery or partial urethrectomy is intended.

** Squamous cell carcinoma.

*** Regional lymphadenectomy should be considered in clinically enlarged lymph nodes.

**** Consider neoadjuvant chemotherapy.

***** In extensive or BCG-unresponsive disease: consider (primary) cystoprostatectomy +/- urethrectomy + lymphadenectomy.

BCG = bacillus Calmette-Guérin; CT = computed tomography; MRI = magnetic resonance imaging; PUC = primary urethral carcinoma; TUR = transurethral resection.

8. FOLLOW-UP

Given the low incidence of primary urethral carcinoma, follow-up has not been systematically investigated. Therefore, it seems reasonable to tailor surveillance regimens according to patients' individual risk factors (see Section 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocystoscopy and cross-sectional imaging despite the lack of specific data.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/primary-urethral-carcinoma/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU - EANM - ESTRO - ESUR - SIOG Guidelines on

Prostate Cancer

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European Association of Urology

European Society of Urogenital Radiology

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

SIOG INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

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1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, a pathologist and a patient representative.

All imaging sections in the text have been developed jointly with the European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM). Representatives of the ESUR and the EANM in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. S. Fanti, Prof.Dr. O Rouvière and Dr. I.G. Schoots.

All radiotherapy sections have been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/prostatecancer/?type=panel.

1.2.1 Acknowledgement

The PCa Guidelines Panel gratefully acknowledges the assistance and general guidance provided by Prof.Dr. M. Bolla, honorary member of the PCa Guidelines Panel.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the PCa Guidelines.
All documents can be accessed on the EAU website: http://uroweb.org/guideline/prostate-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU PCa Guidelines were first published in 2001. This 2020 document presents a limited update of the 2019 PCa Guidelines publication.

1.4.2 Summary of changes

The literature for the complete document has been assessed and updated based upon a review of all recommendations and creation of appropriate GRADE forms. Evidence summaries and recommendations have been amended throughout the current document and several new sections have been added.

The following sections have been revised, or were added:

- Section 3.2.1 - Family history/genetics, has been updated resulting in a new recommendation.

5.1.3 Guidelines for screening and early detection

Recommendation for all patients	LE	Strength rating
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men carrying *BRCA2* mutations > 40 years of age.	2b	Strong

- Chapter 4 - Classification and staging systems, including two recommendations.

4.4 Guideline for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 system for grading of PCa.	Strong

- Section 5.2.4.2.7.3 - The role of risk-stratification, has been revised with the inclusion of a new table (Table 5.2.4.2: Impact of the PSA density on csPCa detection rates in patients with negative mpMRI findings) and amended recommendations.

5.2.4.4 Guidelines for imaging in PCa detection

Introductory statement	LE
Systematic biopsy is an acceptable approach in case mpMRI is unavailable.	3

Recommendations for all patients	LE	Strength rating
Do not use mpMRI as an initial screening tool.	3	Strong
Adhere to PI-RADS guidelines for multiparametric magnetic resonance imaging (mpMRI) acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	3	Strong

- Section 5.3.2.3 - Prostate-specific membrane antigen-based PET/CT, has been completely revised.

- Section - 5.2.7.3 Tissue-based prognostic biomarker testing, includes the findings of a recently published multidisciplinary Guideline, resulting in one recommendation to be changed from ‘Strong’to ‘Weak’.

5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination and a prostate-specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • an additional serum or urine-based test.	Weak

- Chapter 5.2 - Clinical diagnosis, in particular Section 5.2.6 - Prostate biopsy procedure, was amended resulting in an changed recommendation.

5.2.8 Guidelines for the clinical diagnosis of prostate cancer

Recommendation for all patients	LE	Strength rating
Do not offer non-targeted transition zone sampling at initial biopsies due to low detection rates.	2b	Weak

- Section 6.1.2 - Radical prostatectomy, has been completely revised.

- Section 6.1.3.1.3 - Hypofractionation, was revised, also including a new table (Table 6.1.8: Selected trials on hypofractionation for intact localised PCa).

- Section 6.1.4 - Hormonal therapy, new Section 6.1.4.1.1.6.4 - Darolutamide, has been added.

- Section 6.2.1 - Treatment of low-risk disease; the findings of an international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised have been incorporated, resulting in several changes to the recommendations for this section.

  New sections 6.2.1.1.3 - Imaging for treatment selection, 6.2.1.1.4 - Monitoring during active surveillance, and 6.2.1.1.5 - Active surveillance, when to change strategy, have been added. Due to the inclusion of new data, new sections and the findings of the international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised PCa, a number of recommendations were changed, and new recommendations have been added.

6.2.1.4 Guidelines for the treatment of low-risk disease

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
If required perform mpMRI before a confirmatory biopsy.	Strong
Take both targeted biopsy (of any PI-RADS > 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
Perform digital rectal examination (DRE) every 12 months.	Strong
Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
Counsel patients about the possibility of needing further treatment in the future.	Strong
Other therapeutic options	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

- 6.2.2.4 - Other options for the primary treatment of intermediate-risk PCa (experimental therapies), has been revised.

- Section 6.2.3 - Treatment of high-risk localised disease; due to the inclusion of new data, a recommendation was revised.

6.2.4.4 Guidelines for radical treatment of high-risk localised disease

Recommendation	Strength rating
Radical Prostatectomy (RP)	
Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong

- Section 6.2.4 - Treatment of locally-advanced prostate cancer, has been revised, also including a new section on the treatment of cN1 disease, resulting in a new recommendation:

6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendations	Strength rating
Radiotherapeutic treatments	
Offer long-term ADT for at least two years.	Weak
Therapeutic options outside surgery and radiotherapy	
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
Offer patients with cN1 disease a local treatment (either RP or external beam radiation therapy) plus long-term ADT.	Weak

- Section 6.2.5 - Adjuvant treatment after radical prostatectomy, due to the inclusion of new data, two recommendations were revised.

6.2.5.6 Guidelines for adjuvant treatment options after radical prostatectomy

Recommendations	Strength rating
Offer adjuvant external-beam radiation therapy to the surgical field to highly selected patients.	Strong
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional radiotherapy; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

- Section 6.3.4 - The role of imaging in PSA-only recurrence, has been completely revised.

- Due to the inclusion of new data in the second-line treatment modalities, two recommendations have been added.

6.3.9 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence after radical prostatectomy	
Offer PSA monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak

- Section 6.4 - Treatment of metastatic prostate cancer, has been considerably revised with additional data (including new Section - 6.4.4.2.2 - Combination with the new hormonal treatments [abiraterone, ezalutamide]) and the inclusion of a new table (Table 6.4.5: Results from the ENZAMET and TITAN studies), necessitating changes to the recommendations.

6.4.9 Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

- Section 6.5 - Treatment; Castration-resistant PCa, has been updated, also including additional information general aspects (Section 6.5.1.2) and sequencing of drugs. New section 6.5.8 - Prostate-specific membrane antigen (PSMA) therapy, has been included. Recommendations were changed in sections:

6.5.13 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease

Recommendation	Strength rating
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong

6.5.15 Guidelines for supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

Recommendation	Strength rating
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong

6.5.16 Guidelines for non-metastatic castrate-resistant disease

Recommendations	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases.	Strong

- Chapter 7 - Follow-up, aside from revised data, includes new section 7.2.6 - Disease progression during androgen deprivation therapy.

- Due to the inclusion of new publications, new recommendations were added to Chapter 8 - Quality of life outcomes in prostate cancer:

8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments

Recommendation	Strength rating
Advise men on androgen deprivation therapy to maintain a healthy weight and diet, to stop smoking and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong

8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer men starting on long-term androgen deprivation therapy dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Use the WHO FRAX tool to guide monitoring and treatment of bone mineral density in men on long term ADT.	Strong

2. METHODS

2.1 Data identification

For the 2020 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a comprehensive review of the GRADE forms [see definition below) and associated recommendation. Changes in recommendations were only considered on the basis of high level evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. A total of 223 additional references were added to the 2020 PCa Guidelines. Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [3, 4]. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [6]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

The results of an international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised PCa have been incorporated in the 2020 EAU-EANM-ESTRO-ESUR-SIOG PCa Guidelines update. The methodology used is presented in detail in the scientific publication [7].

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In addition, the International Society of Geriatric Oncology (SIOG), the European Society for Radiotherapy & Oncology (ESTRO), the European Society for Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM) have endorsed the PCa Guidelines.

2.2 Review

Publications ensuing from systematic reviews have all been peer-reviewed.

2.3 Future goals

Results of ongoing and new SRs will be included in the 2021 update of the PCa Guidelines:

- A SR on the deferred treatment with curative intent for localised PCa, explore heterogeneity of definitions, thresholds and criteria [8];
- A SR on progression criteria and quality of life (QoL) of patients diagnosed with PCa;
- A SR on the definition and the prognostic value of PSA persistence after radical prostatectomy (RP) for PCa;
- Care pathways for the various stages of PCa management are being developed. These pathways will, in due time, inform treatment flowcharts and an interactive app;
- A SR on surgeon/hospital volume for RP in non-metastatic PCa;
- A SR comparing oncological outcomes for nerve-sparing RP vs. non-nerve-sparing surgery in non-metastatic PCa;
- A SR on patient- and tumour-related characteristics as prognostic factors for post-RP incontinence in non-metastatic PCa.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [9]. The frequency of autopsy-detected PCa is roughly the same worldwide [10]. A systematic review of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% confidence interval [CI]: 3-8%), increasing by an odds ratio (OR) of 1.7 (1.6-1.8) per decade, to a prevalence of 59% (48-71%) by age > 79 years [11].

The incidence of PCa diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [9, 10].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (Caribbean: ASR of 29 and Sub-Saharan Africa: ASRs ranging between 19 and 14), intermediate in the USA and very low in Asia (South-Central Asia: ASR of 2.9) [9].

3.2 Aetiology

3.2.1 Family history/genetics

Family history and racial/ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [12, 13]. Only a small subpopulation of men with PCa (~9%) has true hereditary disease. This is defined as three or more affected relatives or at least two relatives who have developed early-onset PCa (< 55 years) [13]. Hereditary PCa is associated with a 6 to 7-year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [13, 14]. The probability of high-risk PCa at age 65 in men with their father and two brothers affected was 11.4% (vs. a population risk of 1.4%) in a Swedish population-based study [15].

Men with one first-degree relative diagnosed with PCa still suffer an increased risk (relative risk [RR]: 1.8) of developing PCa, and this increases further in men with a father and brother (RR: 5.51) or two brothers (RR: 7.71) diagnosed with PCa [16]. Ancestry-specific risk loci have been identified [17] and genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for PCa [18-20]. Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. However, it is accepted that men of African descent show a higher incidence of PCa and generally have a more aggressive course of disease [21].

Germline mutations have also been increasingly identified amongst men with non-hereditary PCa. In metastatic PCa patients an incidence of 11.8% germline mutations was found in genes mediating DNA-repair processes [22]. Mutations were most commonly seen in *BRCA2* (5.35%), *ATM* (1.6%), *CHEK2* (1.9%), *BRCA1* (0.9%), and *PALB2* (0.4%). In 3,607 unselected PCa patients, 620 (17.2%) were found to have a pathogenic germline variant [23]. The percentage of *BRCA1/2* mutations in this study was 5.99%. Germline mutations in genes such as *BRCA1/2* and *HOXB13* have been associated with an increased risk of PCa and targeted genomic analysis of these genes could offer options to identify families at high risk [24, 25].

A prospective cohort study of male *BRCA1* and *BRCA2* carriers confirmed the association between *BRCA2* and aggressive PCa [26]. *BRCA* mutation carriers were reported to have a worse outcome when compared to non-carriers after local therapy [27]. The IMPACT study evaluates targeted PCa screening (annually, biopsy recommended if PSA > 3.0 ng/mL) using PSA in men aged 40-69 years with germline *BRCA1/2* mutations [28]. The authors found that after 3 years of screening, *BRCA2* mutation carriers were associated with a higher incidence of PCa, a younger age of diagnosis, and more clinically significant tumours compared with non-carriers. The influence of *BRCA1* mutations on PCa remains unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. Limitations of the IMPACT study include the lack of mpMRI data and targeted biopsies as it was initiated before that era.

3.2.2 Risk factors

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression from latent to clinical PCa [29]. Japanese men have a lower PCa risk compared to men from the Western world. However, as Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men, implying a role of environmental or dietary factors [30]. However, currently there are no known effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome (MetS)

The single components of MetS hypertension ($p = 0.035$) and waist circumference > 102 cm ($p = 0.007$) have been associated with a significantly greater risk of PCa, but in contrast, having ≥ 3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60-0.82) [31, 32].

3.2.2.1.1 Diabetes/metformin

On a population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never-users (adjusted OR: 0.84; 95% CI: 0.74-0.96) [33]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa and therefore not advised as a preventive measure (OR: 1.19, $p = 0.50$) [34]. The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial assesses metformin use in advanced PCa [35].

3.2.2.1.2 Cholesterol/statins

A meta-analysis of 14 large prospective studies did not show an association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of either overall PCa or high-grade PCa [36]. Results from the REDUCE study also did not show a preventive effect of statins on PCa risk [34].

3.2.2.1.3 Obesity

Within the REDUCE study, obesity was associated with lower risk of low-grade PCa in multivariable analyses (OR: 0.79, $p = 0.01$), but increased risk of high-grade PCa (OR: 1.28, $p = 0.042$) [37]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [38].

3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied (Table 3.1).

Table 3.1: Dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [39]. A meta-analysis shows a dose-response relationship with PCa [40].
Dairy	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [41].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [42]. A relation between intake of fried foods and risk of PCa may exist [43].
Tomatoes (lycopenes/ carotenes)	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [44, 45]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [46].
Meat	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [47].
Phytoestrogens	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [48].
Soy (phytoestrogens [isoflavones/ coumestans])	Total soy food intake has been associated with reduced risk of PCa, but also with increased risk of advanced disease [49, 50].
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [51, 52].
Vitamin E/Selenium	Inverse associations of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [53, 54]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [55].

3.2.2.3 Hormonally active medication

3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)

Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (~25%, for ISUP grade 1 cancer only), this must be weighed against treatment-related side-effects as well as the potential small increased risk of high-grade PCa [56-58]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.3.2 Testosterone

Hypogonadal men receiving testosterone supplements do not have an increased risk of PCa [59]. A pooled analysis showed that men with very low concentrations of free testosterone (lowest 10%) have a below average risk (OR: 0.77) of PCa [60].

3.2.2.4 Other potential risk factors

Balding was associated with a higher risk of PCa death [61]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31; 95% CI: 1.14-1.52) [62]. Occupational exposure may also play a role, based on a meta-analysis which revealed that night-shift work is associated with an increased risk (2.8%, p = 0.030) of PCa [63]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24; 95% CI: 1.18-1.31) [64]. A meta-analysis on Cadmium (Cd) found a positive association (magnitude of risk unknown due to heterogeneity) between high Cd exposure and risk of PCa for occupational exposure, but not for non-occupational exposure, potentially due to higher Cd levels during occupational exposure [65]. Men positive for human papillomavirus-16 may be at increased risk [66].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [67] and self-reported acne [68]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa and mortality [69, 70].

Ultraviolet radiation exposure decreased the risk of PCa (hazard ratio [HR]: 0.91; 95% CI: 0.88-0.95) [71]. A review found a small but protective association of circumcision status with PCa [72]. Higher ejaculation frequency (≥ 21 times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [73].

The associations with PCa identified to date lack evidence for causality. As a consequence there is no data to suggest effective preventative strategies.

3.2.3 Summary of evidence and guidelines for epidemiology and aetiology

Summary of evidence
Prostate cancer is a major health concern in men, with incidence mainly dependent on age.
Genetic factors are associated with risk of (aggressive) PCa.
A variety of exogenous/environmental factors may have an impact on PCa incidence and the risk of progression.
Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.
In hypogonadal men, testosterone supplements do not increase the risk of PCa.

Recommendation	Strength rating
No specific preventive or dietary measures are recommended to reduce the risk of developing prostate cancer.	Weak

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the development of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [74] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.3) [75]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence after radical prostatectomy (RP) or external beam radiotherapy (EBRT).

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [74]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional (pelvic) Lymph Nodes[1]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis[2]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

[1] Metastasis no larger than 0.2 cm can be designated pNmi.

[2] When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Clinical T stage only refers to DRE findings; imaging findings are not considered in the TNM classification. Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after RP are pathological stage T2 and the current Union for International Cancer Control (UICC) no longer recognises pT2 substages [74].

4.2 Gleason score and International Society of Urological Pathology 2014 grade

The 2005 International Society of Urological Pathology (ISUP) modified Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If one pattern is present, it needs to be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the GS. A GS ≤ 5 should not be given based on prostate biopsies [76, 77]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the extent of each grade from all prostate biopsies. The 2014 ISUP endorsed grading system [77, 78] limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2), in order to:

1. align the PCa grading with the grading of other carcinomas;
2. eliminate the anomaly that the most highly differentiated PCas have a GS 6;
3. to further define the clinically highly significant distinction between GS 7(3+4) and 7(4+3) PCa [79].

Table 4.2: International Society of Urological Pathology 2014 grades

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Table 4.3 EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

4.3 Prognostic relevance of stratification

A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management. The adoption of the current ISUP grading system, defining the split-up of GS 7 cancers into ISUP grade 2 (primary Gleason grade 3) and ISUP grade 3 (primary Gleason grade 4) because of their distinct prognostic impact strengthens such a separation of the intermediate-risk group into a low-intermediate (ISUP grade 2) and high intermediate-risk (ISUP grade 3) group [78] (see Section 5.2.7.4.3).

Emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [79, 80].

4.4 Guideline for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 system for grading of PCa.	Strong

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection

5.1.1 Screening

Population or mass screening is defined as the 'systematic examination of asymptomatic men (at risk)' and is usually initiated by health authorities. The co-primary objectives are:

- reduction in mortality due to PCa;
- a maintained QoL as expressed by QoL-adjusted gain in life years (QALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [81]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries. Currently, screening for PCa still remains one of the most controversial topics in the urological literature [82].

Initial widespread aggressive screening in USA was associated with a decrease in mortality [83]. In 2012 the US Preventive Services Task Force (USPSTF) released a recommendation against non-selective PSA screening [84], which was adopted in the 2013 AUA Guidelines [85] and resulted in a reduction in the use

of PSA for early detection [86]. While PCa mortality had decreased for two decades since the introduction of PSA [87], the incidence of advanced disease and, possibly, cancer-related mortality began to rise after 2012 [88]. Similarly, the reduction in the use of PSA testing was associated with higher rates of advanced disease at diagnosis (e.g., a 6% increase in the number of patients with metastatic PCa) [89-93]. Moreover, additional evidence suggests a long-term benefit of PSA in terms of reduction of cancer-specific mortality [94, 95].

In 2017 the USPSTF issued an updated statement suggesting that men aged 55-69 should be informed about the benefits and harms of PSA-based screening as this might be associated with a small survival benefit. The USPSTF has now upgraded this recommendation to a grade C [96], from a previous grade of 'D' [96-98]. The grade D recommendation remains in place for men over 70 years old. This represents a major switch from discouraging PSA-based screening (grade D) to offering screening to selected patients depending on individual circumstances.

A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with a marginal survival benefit, at best, in the opportunistic screening regimen [99].

A Cochrane review published in 2013 [100], which has since been updated [101], presents the main overview to date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2009 review:

- Screening is associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).
- Screening is associated with detection of more localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80, 95% CI: 0.73-0.87).
- From the results of 5 RCTs, randomising more than 341,000 men, no PCa-specific survival benefit was observed (RR: 1.00, 95% CI: 0.86-1.17). This was the main endpoint in all trials.
- From the results of four available RCTs, no overall survival (OS) benefit was observed (RR: 1.00, 95% CI: 0.96-1.03).

The diagnostic tool (i.e. biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [57, 58]. Increased diagnosis has historically led to over-treatment with associated side-effects. However, despite this, the impact on the patient's overall QoL is still unclear. At a population level screening has never been shown to be detrimental [102-104]. Nevertheless, all these findings have led to strong advice against systematic population-based screening in most countries, including those in Europe.

In case screening is considered, a single PSA test is not enough based on the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial. The CAP trial evaluated a single PSA screening vs. controls not undergoing PSA screening on PCa detection in men aged 50 to 69 years old. The single PSA screening intervention detected more low-risk PCa cases but had no significant effect on PCa mortality after a median follow-up of 10 years [105].

Since 2013, the European Randomized Study of Screening for Prostate Cancer (ERSPC) data have been updated with 16 years of follow up (see Table 5.1) [106]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen (NNS) and to treat is decreasing, and is now below the NNS observed in breast cancer trials [106, 107].

Table 5.1: Follow-up data from the ERSPC study [106]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27
16	570	18

5.1.2 Early detection

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it [12, 108].

Men at elevated risk of having PCa are those > 50 years [109] or at age > 45 years with a family history of PCa (either paternal or maternal [110]) or of African descent [111, 112]. Men of African descent are more likely to be diagnosed with more advanced disease [113] and upgrade was more frequent after prostatectomy as compared to Caucasian men (49% vs. 26%) [114]. In 2014, as for breast cancer, a genetic abnormality associated with an increased risk has been shown prospectively i.e. *BRCA2* [115, 116]. Prostate-specific antigen screening in male *BRCA2* carriers detected more significant cancers at a younger age compared to non-mutation carriers [28].

In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years are also at increased risk of PCa metastasis or death from PCa several decades later [117, 118]. The long-term survival and QoL benefits of such an approach remain to be proven at a population level.

The use of DRE alone in the primary care setting had a sensitivity and specificity below 60%, possibly due to inexperience, and can therefore not be recommended to exclude PCa [119]. Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [120]. The optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective trials. A single PSA test in men between 50 and 69 years did not improve 10-year PCa-specific survival compared to standard care in a large RCT in a primary care setting [105]. A risk-adapted strategy might be a consideration, based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 to 10 years in those not at risk with an initial PSA < 1 ng/mL at 40 years and a PSA < 2 ng/mL at 60 years of age and a negative family history [121]. An analysis of ERSPC data supports a recommendation for an 8-year screening interval in men with an initial PSA concentration < 1 µg/L; fewer than 1% of men with an initial PSA concentration < 1 µg/L were found to have a concentration above the biopsy threshold of 3 µg/L at 4-year follow-up; the cancer detection rate by 8 years was close to 1% [122]. Data from the Goteborg arm of the ERSPC trial suggest that the age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a 15-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy; comorbidity is at least as important as age. A detailed review can be found in Section 5.4 'Evaluating health status and life expectancy' and in the SIOG Guidelines [123, 360].

Multiple tools are now available to determine the need for a biopsy to establish the diagnosis of a PCa, including imaging by MRI, if available (see Section 5.2.4). New biological markers such as *TMPRSS2-ERG* fusion, PCA3 [124, 125] or kallikreins as incorporated in the Phi or 4Kscore tests [126, 127] have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and lowering over-diagnosis (see Section 5.2.2.4). At this time there is too limited data to implement these markers into routine screening programmes.

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including:

- the PCPT cohort: PCPTRC 2.0 http://myprostatecancerrisk.com/;
- the ERSPC cohort: http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators; An updated version was presented in 2017 including prediction of low and high risk now also based on the ISUP grading system and presence of cribriform growth in histology [128].
- a local Canadian cohort: https://sunnybrook.ca/content/?page=asure-calc (among others).

Since none of these risk calculators has clearly shown superiority, it remains a personal decision as to which one to use [129].

5.1.3 Guidelines for screening and early detection

Recommendations	LE	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	3	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men > 50 years of age; • men > 45 years of age and a family history of PCa; • men of African descent > 45 years of age; • men carrying *BRCA*2 mutations > 40 years of age.	2b	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	3	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	3	Strong

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores.

5.2.1 Digital rectal examination

Most PCas are located in the peripheral zone and may be detected by DRE when the volume is ≥ 0.2 mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [130]. A suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value (PPV) of 5-30% [131]. An abnormal DRE is associated with an increased risk of a higher ISUP grade and is an indication for biopsy [132, 133].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [134]. Prostate-specific antigen is organ but not cancer specific; therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS) [135].

There are no agreed standards defined for measuring PSA [136]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [137]. Table 5.2.1 demonstrates the occurrence of GS ≥ 7 (or ISUP ≥ grade 2) PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant (cs) PCa. The use of nomograms may help in predicting indolent PCa [138].

Table 5.2.1: Risk of PCa in relation to low PSA values [137]

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade ≥ 2 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

5.2.2.1 PSA density

Prostate-specific antigen density is the level of serum PSA divided by the prostate volume. The higher the PSA density, the more likely it is that the PCa is clinically significant (see Section 6.2.1 - Treatment of low-risk disease).

5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [139];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [140].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treating PCa but have limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time [141]. These measurements do not provide additional information compared with PSA alone [142-145].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA must be used cautiously because it may be adversely affected by several pre-analytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [146]. Prostate cancer was detected in men with a PSA 4-10 ng/mL by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng/mL [147]. A systematic review including 14 studies found a pooled sensitivity of 70% in men with a PSA of 4-10 ng/mL [148]. Free/total PSA is of no clinical use if the total serum PSA is > 10 ng/mL or during follow up of known PCa. The clinical value of f/t PSA is limited in the light of novel serum tests.

5.2.2.4 Additional serum testing

Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the U.S. Food and Drug Administration (FDA) approved Prostate Health Index (PHI) test, (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2] in addition to age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multicentre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa in men with a PSA between 2-10 ng/mL [127, 149-151]. In a head-to-head comparison both tests performed equally [152].

5.2.2.5 Urine tests: PCA3 marker/SelectMDX/Mi Prostate score (MiPS)/ExoDX

Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding microRNA (mRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for PCA3 is superior to total and percent-free PSA for the detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve (AUC) for positive biopsies [153-156].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts the ISUP grade [157]. Currently, the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [158]. Wei *et al.* showed 42% sensitivity at a cut-off of 60 in the primary biopsy setting with a high specificity (91%) and a PPV of 80% suggesting that the assay may be used in the primary setting [159].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of *HOXC6* and *DLX1* mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [160].

TMPRSS2-ERG fusion, a fusion of the trans-membrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCas [161]. When detection of *TMPRSS2-ERG* in urine was added to PCA3 expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [162]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [163, 164]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care. However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In 6 head-to-head comparison studies of PCA3 and PHI, only Seisen *et al.* found a significant difference; PCA3 detected more cancers, but for the detection of significant disease, defined as ISUP grade ≥ 2, more than three positive cores, or > 50% cancer involvement in any core, PHI proved superior [165]. Russo *et al.* suggested in their systematic review that, based on moderate quality data, PHI and the 4K panel had a high diagnostic accuracy and showed similar performance in predicting the detection of significant disease [166]. However, in the screening population of the ERSPC study the use of both PCA3 and 4K panel when added to the risk calculator led to an improvement in AUC of less than 0.03 [124]. Based on the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [167]. However, upfront multiparametric magnetic resonance imaging (mpMRI) is also likely to affect the utility of above-mentioned

biomarkers (see Section 5.2.4).

5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination and a prostate-specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • risk-calculator; • imaging;	Strong
• an additional serum or urine-based test.	Weak

5.2.3 Baseline biopsy

The need for prostate biopsy is based on PSA level and/or suspicious DRE and/or imaging (see Section 5.2.4). Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [168]. Risk stratification is a potential tool for reducing unnecessary biopsies [168].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate specific antigen level should be verified after a few weeks, in the same laboratory, using the same assay under standardised conditions (i.e. no ejaculation, manipulations, and urinary tract infections [UTIs]) [169, 170]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [171].

Ultrasound (US)-guided biopsy is now the standard of care. Prostate biopsy is performed by either the transrectal or transperineal approach. Cancer detection rates, when performed without prior imaging with MRI, are comparable between the two approaches [172], however some evidence suggests reduced infection risk with the transperineal route (see Section 5.2.6.4). Rectal disinfection with povidone-iodine may be considered [173, 174].

Transurethral resection of the prostate should not be used as a tool for cancer detection [175].

5.2.4 The role of imaging in clinical diagnosis

5.2.4.1 Transrectal ultrasound and ultrasound-based techniques

Grey-scale TRUS is not reliable at detecting PCa [176] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [177]. Prostate HistoScanning™ provided inconsistent results across studies [178]. New sonographic modalities such as sonoelastography, contrast-enhanced US or high-resolution micro-ultrasound have given promising preliminary findings; either alone or combined in the so-called 'multiparametric US'. However, these techniques are still limited by lack of standardisation, lack of large-scale evaluation and unclear results in transition zones [179-184].

5.2.4.2 Multiparametric magnetic resonance imaging

5.2.4.2.1 Multiparametric magnetic resonance imaging performance in detecting ISUP grade ≥ 2 PCa

Correlation with RP specimens shows that mpMRI has good sensitivity for the detection and localisation of ISUP grade ≥ 2 cancers [185-187]. This was further confirmed in patients who underwent template biopsies. In a recent Cochrane meta-analysis which compared mpMRI to template biopsies (≥ 20 cores) in biopsy-naïve and repeat-biopsy settings, mpMRI had a pooled sensitivity of 0.91 (95% CI: 0.83-0.95) and a pooled specificity of 0.37 (95% CI: 0.29-0.46) for ISUP grade ≥ 2 cancers [188]. For ISUP grade ≥ 3 cancers, mpMRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87-0.99) and 0.35 (95% CI: 0.26-0.46), respectively.

5.2.4.2.2 Multiparametric magnetic resonance imaging performance in detecting ISUP grade 1 PCa

Multiparametric MRI is less sensitive in identifying ISUP grade 1 PCa. It identifies less than 30% of ISUP grade 1 cancers smaller than 0.5 cc identified on RP specimens by histopathology analysis [185]. In series using template biopsy findings as the reference standard, mpMRI has a pooled sensitivity of 0.70 (95% CI: 0.59-0.80) and a pooled specificity of 0.27 (95% CI: 0.19-0.37) for identifying ISUP grade 1 cancers [188].

5.2.4.2.3 Does targeted biopsy improve the detection of ISUP grade ≥ 2 as compared to systematic biopsy?

In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores, 8-15) and MRI-targeted biopsies (MRI-TBx; median number of cores, 2-7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-TBx alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02-1.23) for ISUP grade ≥ 2 cancers and 1.20 (95% CI: 1.06-1.36) for ISUP grade ≥ 3 cancers, and therefore in favour of MRI-TBx [188]. However, the pooled detection ratios for ISUP grade ≥ 2 cancers and ISUP grade ≥ 3 cancers were 1.44 (95% CI: 1.19-1.75) and 1.64 (95% CI: 1.27-2.11), respectively, in patients with prior negative systematic biopsies, and only 1.05 (95% CI: 0.95-1.16) and 1.09 (95% CI: 0.94-

1.26) in biopsy-naïve patients.

Three prospective multicentre trials evaluated MRI-TBx in biopsy-naïve patients. In the PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial, 500 biopsy-naïve patients were randomised to either MRI-TBx only or TRUS-guided systematic biopsy only. The detection rate of ISUP grade ≥ 2 cancers was significantly higher in men assigned to MRI-TBx (38%) than in those assigned to SBx (26%, p = 0.005, detection ratio 1.46) [189]. In the Assessment of Prostate MRI Before Prostate Biopsies (MRI-FIRST) trial, 251 biopsy-naïve patients underwent TRUS-guided systematic biopsy by an operator who was blinded to mpMRI findings, and MRI-TBx by another operator. MRI-TBx detected ISUP grade ≥ 2 cancers in a higher percentage of patients but the difference was not significant (32.3% vs. 29.9%, p = 0.38; detection ratio: 1.08) [177]. However, MRI-TBx detected significantly more ISUP grade ≥ 3 cancers than systematic biopsy (19.9% vs. 15.1%, p = 0.0095; detection ratio: 1.32). A similar trend for improved detection of ISUP grade ≥ 3 cancers by MRI-TBx was observed in the Cochrane analysis, however, it was not statistically significant (detection ratio 1.11 [0.88-1.40]) [188]. The Met Prostaat MRI Meer Mans (4M) study included 626 biopsy-naïve patients; all patients underwent systematic biopsy, and those with a positive mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] 3-5, 51%) underwent additional in-bore MRI-TBx. The results were close to those of the MRI-FIRST trial with a detection ratio for ISUP grade ≥ 2 cancers of 1.09 (detection rate: 25% for MRI-TBx vs. 23% for systematic biopsy) [190]. However, in this study, MRI-TBx and systematic biopsy detected an equal number of ISUP grade ≥ 3 cancers (11% vs. 12%; detection ratio: 0.92).

Thus, MRI-TBx significantly out-performs systematic biopsy for the detection of ISUP grade ≥ 2 in the repeat-biopsy setting. In biopsy-naïve patients, the difference appears to be less marked and not significant in all series, but it remains in favour of MRI-TBx in most studies.

5.2.4.2.4 Does MRI-TBx reduce the detection of ISUP grade 1 PCa as compared to systematic biopsy?

In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy and MRI-TBx, the detection ratio for ISUP grade 1 cancers was 0.62 (95% CI: 0.44-0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54-0.74) in biopsy-naïve patients [188]. In the PRECISION and 4M trials, the detection rate of ISUP grade 1 patients was significantly lower in the MRI-TBx group as compared to systematic biopsy (9% vs. 22%, p < 0.001, detection ratio of 0.41 for PRECISION; 14% vs. 25%, p < 0.001, detection ratio of 0.56 for 4M) [189, 190]. In the MRI-FIRST trial, MRI-TBx detected significantly fewer patients with clinically insignificant PCa (defined as ISUP grade 1 and maximum cancer core length < 6 mm) than systematic biopsy (5.6% vs. 19.5%, p < 0.0001, detection ratio of 0.29) [177]. Consequently, MRI-TBx significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy.

5.2.4.2.5 The added value of systematic and targeted biopsy

Magnetic resonance imaging-targeted biopsies can be used in two different diagnostic pathways: 1) the ‘combined pathway’, in which patients with a positive mpMRI undergo combined systematic and targeted biopsy, and patients with a negative mpMRI undergo systematic biopsy; 2) the ‘MRI pathway’, in which patients with a positive mpMRI undergo only MRI-TBx, and patients with a negative mpMRI are not biopsied at all.

Many studies evaluated combined systematic and targeted biopsy in the same patients and could therefore assess the absolute added value of each technique (i.e. the percentage of patients diagnosed by only one biopsy technique). Data from the Cochrane meta-analysis of these studies and from the MRI-FIRST and 4M trials suggest that the absolute added value of MRI-TBx for detecting ISUP grade ≥ 2 cancers is higher than that of systematic biopsy (see Table 5.2.4.1).

Table 5.2.4.1: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 cancer detection

		ISUP ≥ 2			ISUP ≥ 3		
ISUP grade		**Cochrane meta-analysis*** [188]	**MRI-FIRST trial*** [177]	**4M trial** [190]	**Cochrane meta-analysis*** [188]	**MRI-FIRST trial*** [177]	**4M trial** [190]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8-8.2)	7.6% (4.6-11.6)	7.0% (ND)	4.7% (3.5-6.3)	6.0% (3.4-9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6-6.9)	5.2% (2.8-8.7)	5.0% (ND)	2.8% (1.7-4.8)	1.2% (0.2-3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7-32.6)	37.5% (31.4-43.8)	30% (ND)	15.5% (12.6-19.5)	21.1% (16.2-26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7-11.8)	-	-	6.3% (5.2-7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2-4.5)	-	-	1.1% (0.5-2.6)	-	-
	Overall prevalence	22.8% (20.0-26.2)	-	-	12.6% (10.5-15.6)	-	-

** 95% CI.*
The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.
ISUP = International Society for Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

In Table 5.2.4.1 the absolute added values refer to the percentage of patients in the entire cohort; if the cancer prevalence is taken into account, the 'relative' percentage of additional detected PCa can be computed. Adding MRI-TBx to systematic biopsy in biopsy-naïve patients increases the number of ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-TBx increases detection of ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naïve patients would miss approximately 16% of ISUP grade ≥ 2 PCa and 18% of ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP grade ≥ 2 PCa and 9% of ISUP grade ≥ 3 PCa.

5.2.4.2.6 Number of biopsy procedures potentially avoided in the 'MR pathway'

The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' depends on the Likert/PI-RADS threshold used to define positive mpMRI. In pooled studies on biopsy-naïve patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of ≥ 3 would have avoided 30% (95% CI: 23-38) of all biopsy procedures while missing 11% (95% CI: 6-18) of all detected ISUP grade ≥ 2 cancers (relative percentage) [188]. Increasing the threshold to ≥ 4 would have avoided 59% (95% CI: 43-78) of all biopsy procedures while missing 28% (95% CI: 14-48) of all detected ISUP grade ≥ 2 cancers [188]. Of note, the percentages of negative mpMRI (Likert/PI-RADS score ≤ 2) in MRI-FIRST, PRECISION and 4M were 21.1%, 28.9% and 49%, respectively [177, 189, 190].

5.2.4.2.7 Other considerations

5.2.4.2.7.1 Multiparametric magnetic resonance imaging reproducibility

Despite the use of the PIRADSv2 scoring system [191], mpMRI inter-reader reproducibility remains moderate at best [192, 193] which currently limits its broad use by non-dedicated radiologists. However, significant improvement in the accuracy of mpMRI and MRI-TBx can be observed over time, both in academic and community hospitals, especially after implementation of PIRADSv2 scoring and multidisciplinary meetings using pathological correlation and feedback [194-197]. An updated version of the PIRADS score (PIRADSv2.1) has been recently published to improve reader reproducibility [198], but it has not yet been fully evaluated. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at mpMRI [199-201].

5.2.4.2.7.2 Targeted biopsy accuracy and reproducibility

Clinically significant PCa not detected by the 'MRI pathway' can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or undersampled by MRI-TBx). In two retrospective studies of 211 and 116 patients with a unilateral mpMRI lesion, targeted biopsy alone detected 73.5-85.5% of all csPCa (ISUP grade ≥ 2); combining MRI-TBx with systematic biopsy of the lobe with the MRI lesion detected 96-96.4% of all csPCas and combined targeted and systematic biopsy of the contralateral lobe only identified 81.6-92.7% of csPCas [202, 203]. The difference may reflect targeting errors leading to undersampling of the tumour. Increasing the number of cores taken per target may partially compensate for guiding imprecision. In a retrospective study of 479 patients who underwent MRI-TBx with 4 cores per target that were sequentially labelled, the first 3 cores detected 95.1% of the csPCas detected by the 4-core strategy [204]. In two other retrospective studies of 330 and 744 patients who underwent MRI-TBx with up to 5 cores per target, the one-core and 3-core sampling strategies detected respectively 63-75% and 90-93% of the ISUP grade ≥ 2 PCa detected by the 5-core strategy [205, 206]. These percentages are likely to be influenced by the lesion size and location, the prostate volume or the operator's experience, but no study has quantified the impact of these factors yet.

5.2.4.2.7.3 Role of risk-stratification

The negative predictive value (NPV) of a diagnostic test decreases when the disease prevalence increases, i.e. when the *a priori* risk of the patient increases. Therefore, the excellent NPV reported for mpMRI in the literature may not apply to patients with a higher risk of disease [207] and evaluating the individual risk of csPCa is essential for interpreting mpMRI results. Prostate-specific antigen density (PSAD) is one of the strongest predictors of csPCa in risk-models and several studies found that PSAD and the PIRADS score were significant independent predictors of csPCa at biopsy [208, 209]. In patients with negative mpMRI findings (PIRADS 1-2), the risk of finding csPCa at subsequent SBx is usually ≤ 10% if the PSAD is < 0.15 ng/mL/cc. In contrast, it is 27-40% if the PSAD is > 0.15-0.20 ng/mL/cc [190, 209-213] (Table 5.2.4.2).

Several groups have developed nomograms which combine mpMRI findings with simple clinical data as a tool to predict subsequent biopsy results. These nomograms require further validation, but in due time they may out-perform predictors such as the current risk calculators (e.g. ERSPC or PCPT) in the selection of patients who may benefit from systematic and/or MRI-TBx [214]. Combining mpMRI findings with the PCA3 score, the PHI density or the results of the Stockholm3 blood test may also improve risk stratification [215-217].

Table 5.2.4.2: Impact of the PSA density on csPCa detection rates in patients with negative mpMRI findings

Study	Study design	Population	Biopsy protocol	csPCa definition	csPCa detection rate
Washino (2017) [209]	Retrosp. Single centre	n = 288 Biopsy naive	SBx (14 cores) + cognitive TBx	ISUP ≥ 2 or MCCL ≥ 4 mm	**Whole cohort** (prevalence): 49% **PIRADS 1-2**: 0% if PSAD < 0.15, 20% if PSAD = 0.15-0.29, 30% if PSAD ≥ 0.3
Distler (2017) [208]	Retrosp. analysis of prospective database Single centre	n = 1,040 Biopsy naive + prior negative biopsy	TTP (24 cores) + fusion TBx	ISUP ≥ 2	**Whole cohort** (prevalence): 43% **PIRADS 1-2 / Whole cohort:** 11% if PSAD ≤ 0.15, 33% if PSAD > 0.15 **PIRADS 1-2 / prior negative biopsy:** 7% if PSAD ≤ 0.15, 27% if PSAD > 0.15
Hansen (2017) [210]	Retrosp. Single centre	n = 514 Prior negative biopsy or AS for ISUP 1 PCa	TTP (24 cores) + fusion TBx	ISUP ≥ 2	**Whole cohort** (prevalence): 31% **Likert 1-2:** 9% if PSAD ≤ 0.10, 9% if PSAD ≤ 0.2, 29% if PSAD > 0.2
Hansen (2018) [211]	Retrosp. Multicentre	n = 807 Biopsy naive	TTP + cognitive or fusion TBx	ISUP ≥ 2	**Whole cohort** (prevalence): 49% **PIRADS 1-2:** 10% if PSAD < 0.10, 21% if PSAD = 0.1-0.2, 33% if PSAD > 0.2
Oishi (2019) [212]	Retrosp. analysis of prospective database Single centre	n = 135 Biopsy naive + prior negative biopsy + AS + Restaging **Only pts with negative MRI (PIRADS < 2)**	SBx (12 cores)	ISUP ≥ 2	**Whole cohort** (prevalence): 18% **PSAD < 0.10:** 6% (overall pop), 15% (biopsy naïve), 0% (prior negative biopsy) **PSAD < 0.15:** 10% (overall pop), 20% (biopsy naïve), 0% (prior negative biopsy) **PSAD > 0.15:** 40% (overall pop), 29% (biopsy naïve), 29% (prior negative biopsy)
Boesen (2019) [213]	Retrosp. analysis of prospective database Single centre	n = 808 Biopsy-naive	SBx (10 cores) + fusion TBx	ISUP ≥ 2	**Whole cohort** (prevalence): 35% **PIRADS 1-2:** 3% if PSAD < 0.10, 5% < 0.15, 5% if PSAD < 0.2, 32% if PSAD ≥ 0.2

Van der Leest (2019) [190]	Prospective Multicentre	n = 626 Biopsy naive	TTP Bx (median 24 cores) + fusion TBx	ISUP ≥ 2	**Whole cohort** (prevalence): 30% **PIRADS 1-2:** 1.3% if PSAD < 0.10, 2% if PSAD < 0.15

Retrosp. = retrospective; n = number of patients; SBx = systematic transrectal biopsy; TBx = targeted biopsy; TTP = transperineal template biopsy; PSAD = PSA density; ISUP = international Society of Urological Pathology; MCCL = maximum cancer core length.

5.2.4.3 Summary of evidence and practical considerations on pre-biopsy mpMRI

Magnetic resonance imaging-targeted biopsies substantially improve the detection of ISUP grade ≥ 2 PCa. This improvement is most notable in the repeat-biopsy setting, with marginal added value for systematic biopsies. It is less marked in biopsy-naïve patients in whom systematic biopsy retain a higher added value, at least for the detection of ISUP grade 2 cancers. Magnetic resonance imaging-targeted biopsies also detect significantly less ISUP grade 1 cancers than systematic biopsies.

The 'MRI pathway' is appealing since it could decrease the number of biopsy procedures, reduce the detection of low-grade PCa while maintaining (or even improving) the detection of csPCa, as compared to systematic biopsy. However, mpMRI findings must be interpreted in the light of the *a priori* risk of csPCa. Risk calculators or PSAD may help identify patients that can safely avoid biopsy in case of a negative mpMRI. Furthermore, without standardisation of mpMRI interpretation and of MRI-TBx technique the 'MR pathway' may lead to suboptimal care outside large-volume (expert) centres. Indeed, limitations of the 'MR pathway' are the moderate inter-reader reproducibility of mpMRI and the lack of standardisation of MRI-TBx, as well as the fact that MRI-TBx inter-operator reproducibility has not been evaluated. These caveats also apply to the systematic biopsy procedure. A substantial proportion of csPCa missed by the 'MR pathway' may be due to the imprecision of current targeting methods, and 3 to 5 biopsy cores per target may be needed to reduce the risk of missing or undersampling the lesion, even with US/MR fusion systems.

Finally, it must be emphasised that the 'MR pathway' has only been evaluated in patients in whom the risk of csPCa was judged high enough to deserve biopsy. Pre-biopsy mpMRI must not be used in patients who do not have an indication for prostate biopsy based on their family history and clinical and biochemical data. Because of its low specificity, mpMRI in very low-risk patients would result in an inflation of false-positive findings and subsequent unnecessary biopsies.

5.2.4.4 Guidelines for imaging in PCa detection

Introductory statement	**LE**
Systematic biopsy is an acceptable approach in case mpMRI is unavailable.	3

Recommendations for all patients	**LE**	**Strength rating**
Do not use multiparametric magnetic resonance imaging (mpMRI) as an initial screening tool.	3	Strong
Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	3	Strong

Recommendations in biopsy naïve patients	**LE**	**Strength rating**
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	2a	Strong
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak

Recommendations in patients with prior negative biopsy	**LE**	**Strength rating**
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	2a	Weak
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared shared decision making with the patient.	2a	Strong

5.2.5 Repeat biopsy

5.2.5.1 Repeat biopsy after previously negative biopsy

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2.1 for risk estimates);
- suspicious DRE, 5-30% PCa risk [130, 131];
- atypical small acinar proliferation (i.e. atypical glands suspicious for cancer), 31-40% PCa risk on repeat biopsy [218, 219];
- extensive (multiple biopsy sites, i.e. ≥ 3) high-grade prostatic intraepithelial neoplasia (HGPIN), ~30% PCa risk [219, 220];
- a few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (i.e. PINATYP), ~50% PCa risk [221];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa [222];
- positive multiparametric MRI (mpMRI) findings (see Section 5.2.4.2).

5.2.5.1.1 Tests to select men for a repeat biopsy

In men with an elevated risk of PCa with a prior negative biopsy, additional information may be gained by the Progensa-PCA3 and SelectMDX DRE urine tests, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). The role of PHI, Progensa PCA3, and SelectMDX in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [158]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. In case PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes in benign prostatic tissue. A multicentre study found a NPV of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [223]. Given the limited available data and the fact that the role of mpMRI in tumour detection was not accounted for, no recommendation can be made regarding the routine application of ConfirmMDX, in particular in the light of current use of mpMRI before biopsy.

Table 5.2.5.1: Description of additional investigational tests after a negative prostate biopsy*

Name of test	Test substrate	Molecular	FDA approved
Progensa	DRE urine	lncRNA PCA3	Yes
SelectMDX	DRE urine	mRNA HOXC6, DLX1	No
PHI	Serum	Total, free and p2PSA	Yes
4Kscore Test	Serum/plasma	Total, free, intact PSA, hK2	No
ConfirmMDX	Benign prostate biopsy	Methylated APC, RASSF1 and GSTP1	No

**Isolated high-grade prostatic intraepithelial neoplasia (PIN) in one or two biopsy sites is no longer an indication for repeat biopsy [224].*

5.2.5.2 Saturation biopsy

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies [225]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention (10%) is a drawback [226].

5.2.6 Prostate biopsy procedure

5.2.6.1 Sampling sites and number of cores

On baseline biopsies, where no prior imaging with mpMRI has been performed, or where mpMRI has not shown any suspicious lesion, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas identified by DRE; suspect areas on TRUS might be consideration for additional biopsies. Sextant biopsy is no longer considered adequate. At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc [227]. Ten to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive [228, 229].

Where mpMRI has shown a suspicious lesion MR-TBx can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature does not show a clear superiority of one technique over another [230-233]. A minimum of 3 cores are taken from each lesion (see Section 5.2.4.2.7.2).

5.2.6.2 Antibiotics prior to biopsy

Oral or intravenous antibiotics are recommended. For transrectal biopsy, quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [234]. Antibiotic prophylaxis showed a significant reduction in UTIs post biopsy. A 3-day antibiotic prophylaxis regimen provided no benefit over single-dose prophylaxis [235]. Increased quinolone resistance is associated with a rise in severe post-biopsy infection [236, 237]. Norwegian registry data show an increase in antibiotic resistance for both TMP-SMX and ciprofloxacin in recent years with an associated increase in 30-day mortality [238]. Risk factors for quinolone resistance include previous TRUS biopsy, a current indwelling catheter, and any of: urogenital infection, international travel or hospital admission within the previous 6 months. To minimise risk of severe infection due to quinolone resistant rectal flora, patients with any of these risk factors should be offered either TRUS biopsy with prior rectal swab culture or targeted antibiotic prophylaxis [173]. Rectal disinfection with povidone-iodine may be considered [173]. For transperineal biopsy, which avoids rectal flora, a single dose of intravenous cephazolin only is sufficient [239, 240]. A 2017 systematic review [172] found no significant difference between transrectal and transperineal biopsies with respect to infection while a more recent meta-analysis including 7 comparative studies showed in twice the number of patients a RR of 0.26 (0.14-0.48) for the risk of fever after transperineal biopsies compared to transrectal biopsies [241].

5.2.6.3 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [242]. It is not important whether the depot is apical or basal. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [243]. Local anaesthesia can also be used effectively for mpMRI-targeted transperineal biopsy [244]. Patients are placed in the lithotomy position. Bupivacaine is injected into the perineal skin and subcutaneous tissues, followed two minutes later by a peri-prostatic block. A systematic review evaluating pain in 3 studies comparing transperineal vs. transrectal biopsies found that the transperineal approach significantly increased patient pain (RR: 1.83 [1.27-2.65]). [241]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [245]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [244, 246, 247].

5.2.6.4 Complications

Complications of TRUS biopsy are listed in Table 5.2.3 [248]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [249]. Low-dose aspirin is no longer an absolute contraindication [250]. A systematic review found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [251]. A meta-analysis of 4,280 men randomised between transperineal vs. TRUS biopsies in 13 studies found no significant differences in complication rates, however, data on sepsis compared only 497 men undergoing TRUS biopsy to 474 having transperineal biopsy. The transperineal approach required more (local) anaesthesia [172].

Table 5.2.6.1: Percentage of complications per TRUS biopsy session, irrespective of the number of cores

Complications	Percentage of patients affected
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/– surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

5.2.6.5 Seminal vesicle biopsy

Indications for seminal vesicle (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20-25% [252]. A seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent radiotherapy (RT). Its added value compared with mpMRI is questionable.

5.2.6.6 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to repeat biopsies [253].

5.2.7 Pathology of prostate needle biopsies

5.2.7.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [254]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [255, 256]. To optimise detection of small lesions, paraffin blocks should be cut at three levels and intervening unstained sections kept for immunohistochemistry [253].

5.2.7.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [257-259]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [257]. Table 5.2.7.1 lists the recommended terminology for reporting prostate biopsies [255].

Table 5.2.7.1: Recommended terminology for reporting prostate biopsies [255]

Recommended terminology	Strength rating
Benign/negative for malignancy; if appropriate, include a description	Strong
Active inflammation	
Granulomatous inflammation	
High-grade prostatic intraepithelial neoplasia (PIN)	
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)	
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer	
Adenocarcinoma	
Intraductal carcinoma	

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 grade [77]. A global ISUP grade comprising all biopsies is also reported (see Section 4.2). The global ISUP grade takes into account all biopsies positive for carcinoma, by estimating the total extent of each Gleason grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global ISUP grade would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worse grade would be ISUP grade 4 (i.e. GS 8[4+4]). Recent publications demonstrated that global ISUP grade is somewhat superior in predicting prostatectomy ISUP grade [260] and biochemical recurrence (BCR) [261].

Intraductal carcinoma, lymphovascular invasion (LVI) and extraprostatic extension (EPE) must each be reported, if identified. More recently, expansile cribriform pattern of PCa as well as intraductal carcinoma in biopsies were identified as independent prognosticators of metastatic disease [262] and PCa-specific survival [263].

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade, tumour volume, surgical margins and pathologic stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [264-266]. A pathology report should therefore provide both the proportion of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic

impact [267]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [268] triggering immediate treatment vs. AS in patients with ISUP grade 1.

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate. Mandatory elements to be reported for a carcinoma-positive prostate biopsy are:

- type of carcinoma;
- primary and secondary/worst Gleason grade (per biopsy site and global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (at least per biopsy site);
- if present: EPE, seminal vesicle invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- ISUP grade (global).

5.2.7.3 Tissue-based prognostic biomarker testing.

After a comprehensive literature review and several panel discussions an ASCO-EAU-AUA multidisciplinary expert panel made recommendations regarding the use of tissue-based PCa biomarkers. The recommendations were limited to 5 commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS and ProMark) with extensive validation in large retrospective studies and evidence that their test results might actually impact clinical decision-taking [269].

The selected commercially available tests significantly improved the prognostic accuracy of clinical multivariable models for identifying men who would benefit of AS and those with clinically significant PCa requiring curative treatment, as well as for guidance of patient management after RP. In addition, a few studies showed that tissue biomarker tests and MRI findings independently improved the detection of clinically significant cancer in an AS setting, but it remains unclear which men would benefit of both tests. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely, but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa at RP to decide on treatment intensification with hormonal therapy (HT).

5.2.7.4 Histopathology of radical prostatectomy specimens

5.2.7.4.1 Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded, to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate, and a single mid-anterior left and right section. Compared with total embedding, partial embedding detected 98% of PCa with an ISUP grade ≥ 2 with accurate staging in 96% of cases [270].

Ink the entire RP specimen upon receipt in the laboratory, to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 hours [271]. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [76]. The remainder of the specimen is cut in transverse, 3-4 mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with pre-operative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.7.4.1.1 Guidelines for processing prostatectomy specimens

Recommendations	LE	Strength rating
Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.	3	Strong
Ink the entire surface before cutting, to evaluate the surgical margin.	3	Strong
Examine the apex and base separately, using the cone method with sagittal or radial sectioning.	3	Strong

5.2.7.4.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.7.1). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.7.2). Synoptic reporting results in more transparent and complete pathology reporting [272].

Table 5.2.7.1: Mandatory elements provided by the pathology report

Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to ISUP grade (or not applicable if therapy-related changes).
Presence of intraductal carcinoma.
Tumour (sub)staging and surgical margin status: location and extent of EPE, presence of bladder neck invasion, laterality of EPE or seminal vesicle invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

Table 5.2.7.2: Example checklist: reporting of prostatectomy specimens

Histopathological type
Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade
Primary (predominant) Gleason grade Secondary Gleason grade Tertiary Gleason grade (if applicable) Global ISUP grade Approximate percentage of Gleason grade 4 or 5
Tumour quantitation (optional)
Percentage of prostate involved Size/volume of dominant tumour nodule
Pathological staging (pTNM)
If extraprostatic extension is present: indicate whether it is focal or extensive; specify sites; indicate whether there is seminal vesicle invasion. *If applicable, regional lymph nodes:* location; number of nodes retrieved; number of nodes involved.
Surgical margins
If carcinoma is present at the margin: specify sites.
Other
Presence of lymphovascular/angio-invasion Location of dominant tumour Presence of intraductal carcinoma/cribriform architecture

5.2.7.4.3 ISUP grade in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [77]. The ISUP grade is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [273].

The ISUP grade is based on the sum of the most and second-most dominant (in terms of volume) Gleason grade. ISUP grade 1 is any GS ≤ 6 (including < 5% Gleason grade 4). ISUP grades 2 and 3 represent carcinomas constituted of Gleason grade 3 and 4 components, with ISUP grade 2 when 50% of the carcinoma, or more, is Gleason grade 3 and ISUP grade 3 when the grade 4 component represents more than 50% of the carcinoma. ISUP grade 4 is largely composed of Gleason grade 4 and ISUP grade 5 of a combination of Gleason grade 4 and 5 or only Gleason grade 5. A global ISUP grade is given for multiple tumours, but a separate tumour focus with a higher ISUP grade should also be mentioned. Tertiary Gleason grade 5,

particularly if > 5% of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary Gleason grade and its approximate proportion of the cancer volume should also be reported in addition to the global ISUP grade (see Section 4.2) [274].

5.2.7.4.4 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with peri-prostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [275].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [276] or extension as < 1 per high-power field (HPF) [277], whereas others measure the depth of extent in millimetres [278].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence [279, 280] and should be recorded as EPE (pT3a). A positive margin at the bladder neck should be reported as EPE (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [281].

5.2.7.4.5 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [277, 282-285]. Nevertheless, a cut-off of 0.5 mL is traditionally used to distinguish insignificant from clinically relevant cancer [282]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [286].

5.2.7.4.6 Surgical margin status

Surgical margin is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [283] or at the surface of the tissue lacking ink. In tissues that have severe crush artefacts, it may not be possible to determine margin status [287].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [288]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [277]. However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [289], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate with outcome, and should be reported [245].

5.2.8 Guidelines for the clinical diagnosis of prostate cancer

Recommendations	LE	Strength rating
Perform transrectal prostate needle biopsies under antibiotic protection.	1b	Strong
Use a local anaesthetic by peri-prostatic infiltration for prostate needle biopsies.	1a	Strong
Do not offer non-targeted transition zone sampling at initial biopsies due to low detection rates.	2b	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	3	Strong

5.3 Diagnosis - Clinical Staging

The extent of PCa is evaluated by DRE and PSA, and may be supplemented with mpMRI, bone scanning and computed tomography (CT).

5.3.1 T-staging

The cT category used in the risk table only refers to the DRE finding. The imaging parameters and biopsy results for local staging are, so far, not part of the risk category stratification.

5.3.1.1 TRUS

Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [290]. Some single-

centre studies reported good results in local staging using 3D TRUS or colour Doppler but these good results were not confirmed by large-scale studies [291, 292].

5.3.1.2 mpMRI

T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5 Tesla, mpMRI has good specificity but low sensitivity for detecting T3 stages. Pooled data from a meta-analysis for EPE, SVI, and overall stage T3, showed a sensitivity and specificity of 0.57 (95% CI: 0.49-0.64) and 0.91 (95% CI: 0.88-0.93), 0.58 (95% CI: 0.47-0.68) and 0.96 (95% CI: 0.95-0.97), and 0.61 (95% CI: 0.54-0.67) and 0.88 (95% CI: 0.85-0.91), respectively [293]. Multiparametric MRI cannot detect microscopic EPE. Its sensitivity increases with the radius of extension within peri-prostatic fat. In one study, the EPE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [294]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage were 40%, 95% and 76%, respectively, for focal (i.e. microscopic) EPE, and 62%, 95% and 88% for extensive EPE [295].

The use of high field strength (3 Tesla) or functional imaging in addition to T2-weighted imaging improves sensitivity for EPE or SVI detection [293], but the experience of the reader remains of paramount importance [296] and the inter-reader agreement remains moderate with kappa values ranging from 0.41 to 0.68 [297]. Multiparametric MRI, although not perfect for local staging, may improve the prediction of the pathological stage when combined with clinical data [298, 299]. Other MRI-derived parameters such as the tumour volume or the contact length of the tumour with the capsule [300-302], or the ISUP grade obtained through MRI-TBx [303] could further improve the local staging [303].

Given its low sensitivity for focal (microscopic) EPE, mpMRI is not recommended for local staging in low-risk patients [298, 304, 305]. However, mpMRI can still be useful for treatment planning.

5.3.2 N-staging

5.3.2.1 Computed tomography (CT) and magnetic resonance imaging

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap the size of LN metastases. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [306, 307]. Computed tomography and MRI sensitivity is less than 40% [308, 309]. Among 4,264 patients, 654 (15.3%) of whom had positive LNs at LND, CT was positive in only 105 patients (2.5%) [306]. In a multicentre database of 1,091 patients who underwent pelvic LN dissection, CT sensitivity and specificity were 8.8% and 98%, respectively [310]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade < 4 cancer, PSA < 20 ng/mL, or localised disease [311-313].

Diffusion-weighted MRI may detect metastases in normal-sized nodes, but a negative diffusion-weighted MRI cannot rule out the presence of LN metastases [307, 314].

5.3.2.2 Choline PET/CT

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51-66%) and 92% (95% CI: 89-94%), respectively [315]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% at region-based analysis and 18.9% at patient-based analysis, which is too low to be of clinical value [316]. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk, in both cases out-performing contrast-enhanced CT [317]. However, comparisons between choline PET/CT and diffusion-weighted MRI yielded contradictory results, with PET/CT sensitivity found to be superior [318], similar [319, 320] or inferior [316] than that of diffusion-weighted MRI.

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms (see Section 6.3.4.1.2).

5.3.2.3 Prostate-specific membrane antigen-based PET/CT

^{68}Ga- or ^{18}F-labelled prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT is increasingly used, because it provides excellent contrast-to-noise ratio, thereby improving the detectability of lesions. Prostate-specific membrane antigen is also an attractive target because of its specificity for prostate tissue, even if expression of PSMA in other non-prostatic malignancies, sarcoidosis or benign bone diseases, may cause incidental false-positive findings [321-324].

Recent assessment of PSMA PET/CT showed promising sensitivity for LN involvement, also suggesting that this modality may impact clinical decision making. From a meta-analysis of 37 articles, a subgroup analysis of 13 studies was performed in PCa patients prior to definitive therapy, using histological correlation as reference standard. The predictive ability of PSMA-PET imaging for primary staging was derived

from 5 studies. On a per-LN analysis, the pooled sensitivity and specificity were 75% and 99%, respectively. On a per-patient analysis, the pooled sensitivity and specificity were 77% and 97%, respectively [325]. Another prospective, multicentre validation of ^{68}Ga PSMA PET/CT in patients with newly diagnosed PCa and negative bone scan findings was recently published. In 103 eligible patients at increased risk for metastatic LNs prior to surgery, 97 eLNDs were performed, resulting in the identification of 85 LN metastases in 41 patients (42.3%). Positron emission tomography was positive in 17 patients, resulting in a per-patient-based sensitivity and specificity of 41.5% (95% CI: 26.7-57.8) and 90.9% (95% CI: 79.3-96.6), respectively. A treatment change occurred in 12.6% of patients [326].

Prostate-specific antigen may be a predictor of a positive PSMA PET scan. In the primary staging cohort from the meta-analysis [325], however, only 4 studies reported PSMA PET-positivity based on the PSA value, offering no robust estimates of positivity. The tracer uptake is also influenced by the ISUP grade and the PSA level. In a series of 90 patients with primary PCa, tumours with an ISUP grade between 1 and 3 showed significantly lower tracer uptake than tumours with an ISUP grade ≥ 4. Similarly, patients with PSA levels ≥ 10 ng/mL showed significantly higher uptake than those with PSA levels < 10 ng/mL [327].

Comparison between PSMA PET/CT and mpMRI was recently performed in a systematic review and meta-analysis, including 13 studies (n = 1,597) [328]. ^{68}Ga- was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa. The pooled sensitivity and specificity of ^{68}Ga-PSMA PET were 0.65 (95% CI: 0.49-0.79) and 0.94 (95% CI: 0.88-0.97), respectively, while the corresponding values of MRI were 0.41 (95% CI: 0.26-0.57) and 0.92 (95% CI: 0.86-0.95). ^{68}Ga-PSMA PET was potentially a more effective and appropriate imaging modality to predict LN metastasis prior to surgery, as indicated by the area under the symmetric receiver-operating characteristic (SROC) curve. Another prospective trial reported superior sensitivity of PSMA PET/CT as compared to mpMRI for nodal staging of 36 high-risk PCa patients [329]. Therefore, PSMA PET/CT has higher sensitivity for LN metastases as compared to mpMRI, abdominal contrast-enhanced CT or choline PET/CT; however, small LN metastases, under the spatial resolution of PET (~5 mm), may still be missed.

5.3.3 M-staging

5.3.3.1 Bone scan

^{99m}Tc-Bone scan has been the most widely used method for evaluating bone metastases of PCa. A recent meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) at patient level and 59% (95% CI: 55-63%) and 75% (95% CI: 71-79%) at lesion level [330]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade and these three factors were the only independent predictors of bone scan positivity in a study of 853 patients [331]. The mean bone scan positivity rate in 23 different series was 2.3% in patients with PSA levels < 10 ng/ mL, 5.3% in patients with PSA levels between 10.1 and 19.9 ng/mL and 16.2% in patients with PSA levels of 20.0-49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for ISUP grade 2 and > 3, respectively [306]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive bone scan [332, 333].

Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade or clinical stage [306].

5.3.3.2 Fluoride PET and PET/CT, choline PET/CT and MRI

^{18}F-sodium fluoride (^{18}F-NaF) PET or PET/CT shows similar specificity and superior sensitivity to bone scan [334, 335]. However, unlike choline PET/CT, ^{18}F-NaF PET does not detect LN metastases, and is less cost-effective compared to bone scan [333]. A recent publication indicated that ^{18}F-NaF PET offers no added value over bone scintigraphy in patients with newly diagnosed PCa and negative bone scintigraphy results [336]. It remains unclear whether choline PET/CT is more sensitive than bone scan, but it has higher specificity, with fewer indeterminate bone lesions [315, 337, 338].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa [339, 340]. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [341]. A meta-analysis found that MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [330].

It is of note that choline PET/CT and diffusion-weighted MRI can also detect visceral metastases.

Bone scan and ^{18}F-NaF PET/CT only assess the presence of bone metastases.

5.3.3.3 Prostate-specific membrane antigen-based PET/CT

There is growing evidence on the performance of ^{68}Ga-PSMA PET/CT in initial staging. A recent systematic review including 12 studies and comprising a total of 322 patients reported high variation in sensitivity (range 33-99% median sensitivity on per-lesion analysis 33-92%, and on per-patient analysis 66-91%), with good

specificity (per-lesion 82-100%, and per-patient 67-99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [342]. Table 5.3.1 reports the data of the 5 studies including histopathologic correlation.

Table 5.3.1: PSMA PET/CT results in primary staging alone [342]

Study	Sensitivity (per lesion)	Specificity (per lesion)	PPV (per lesion)	NPV (per lesion)
Budaus	33%	100%	100%	69%
Herlemann	84%	82%	84%	82%
Van Leeuwen	58%	100%	94%	98%
Maurer	74%	99%	95%	94%
Rahbar	92%	92%	96%	85%

NPV = negative predictive value; PPV = positive predictive value.

One prospective multicentre study evaluated changes in planned management before and after PSMA PET/CT in 108 intermediate- and high-risk patients referred for primary staging. As compared to conventional staging, additional LNs and bone/visceral metastases were detected in 25% and 6% of patients, respectively [343]; management changes occurred in 21% of patients. A recent retrospective review investigated the risk of metastases identified by Ga-PSMA at initial staging in 1,253 patients (high-risk disease in 49.7%) [344]. Metastatic disease was identified by PSMA PET in 12.1% of men, including 8.2% with a PSA level of < 10 ng/mL and 43% with a PSA level of > 20 ng/mL. Lymph node metastases were suspected in 107 men, with 47.7% outside the boundaries of an extended pelvic LN dissection (eLND). Skeletal metastases were identified in 4.7%. In men with intermediate-risk PCa metastases were identified in 5.2%, compared to 19.9% with high-risk disease.

5.3.4 Summary of evidence and practical considerations on initial N/M staging

The field of non-invasive nodal and metastatic staging of PCa is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and MRI provide a more sensitive detection of LN and bone metastases than the classical work-up with bone scan and abdominopelvic CT. It could be tempting to conclude that bone scan and abdominopelvic CT must be replaced by more sensitive tests in all patients undergoing initial PCa staging. Yet, the clinical benefit of detecting metastases at an earlier time-point remains unclear [325]. In addition the prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases, detectable only with PET/CT or MRI, should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [345].

Results from RCTs evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, PSMA PET/CT and MRI are awaited, before a decision can be made to treat patients based on the results of these tests [346].

5.3.5 Guidelines for staging of prostate cancer

Any risk group staging	LE	Strength rating
Use pre-biopsy mpMRI for local staging information.	2a	Weak
Low-risk localised disease		
Do not use additional imaging for staging purposes.	2a	Strong
Intermediate-risk disease		
In ISUP grade ≥ 3, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	2a	Weak
High-risk localised disease/locally advanced disease		
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

5.4 Evaluating life expectancy and health status

5.4.1 Introduction

Evaluation of life expectancy and health status is important in clinical decision-making on screening, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [347, 348].

Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over 10 years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCa-specific mortality (PCSM) and life expectancy of surgery vs. active surveillance (AS) [349]. Although in a RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) among older men (RR: 0.68 and 0.60, respectively) [350]. External beam radiotherapy shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [351].

Older men with a high incidence of PCa may be under-treated despite the high overall mortality rates [352, 353]. Of all PCa-related deaths 71% occur in men aged ≥ 75 years [354], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [355-357]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [358].

5.4.2 Life expectancy

Life expectancy tables for European men are available at: https://ec.europa.eu/eurostat/web/products-eurostat-news/-/EDN-20191118-1. Survival may be very variable and therefore must be individualised. Gait speed is a good single predictive measure (from a standing start, at usual pace, generally over 6 meters). For men at age 75, 10-year survival ranged from 19% < 0.4 m/s to 87%, for ≥ 1.4 m/s [359].

Figure 5.4.1: Predicted Median Life Expectancy by Age and Gait Speed for males* [359]**.**

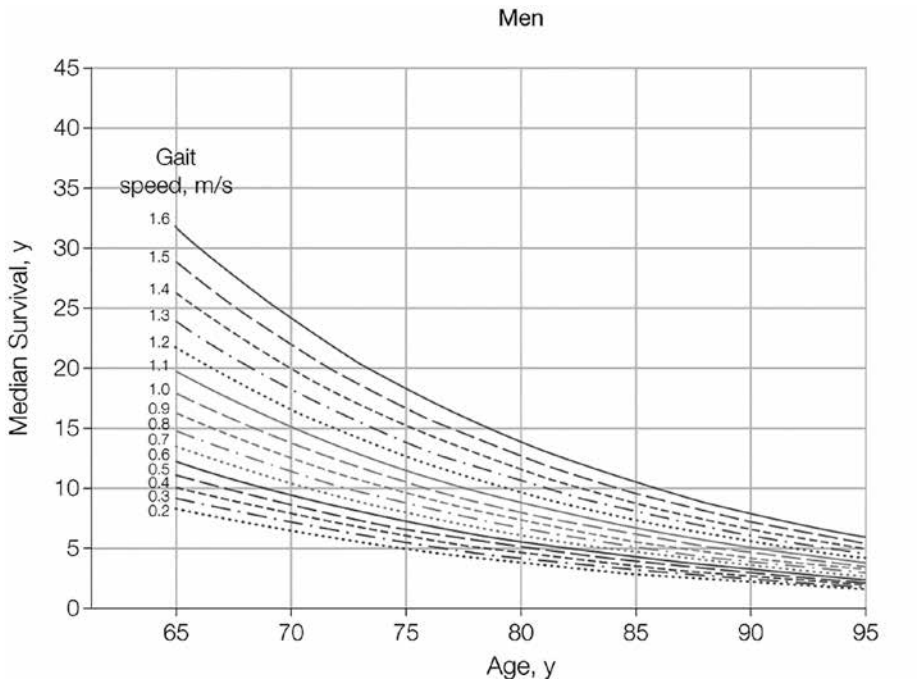


**Figure reproduced with permission of the publisher, from Studenski S, et al. JAMA 2011 305(1)50.*

5.4.3 Health status screening

The International SIOG PCa Working Group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (Table 5.4.1) [360]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (Figure 5.4.1) [360]. Patients with a G8 score ≤ 14 should undergo a full geriatric evaluation as this score is associated with 3-year mortality, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [361].

5.4.3.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [362, 363]. Ten years after not receiving active treatment for PCa, most men with a high comorbidity score had died from competing causes, irrespective of age or tumour aggressiveness [362]. Measures for comorbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [364, 365] (Table 5.4.2) and Charlson Comorbidity Index (CCI) [366].

5.4.3.2 Nutritional status

Malnutrition can be estimated from body weight during the previous 3 months (good nutritional status < 5% weight loss; risk of malnutrition: 5-10% weight loss; severe malnutrition: > 10% weight loss) [367].

5.4.3.3 Cognitive function

Cognitive impairment can be measured using mini-COG (https://mini-cog.com/), which assesses the patient's ability to make an informed decision which is an increasingly important factor in health status assessment [368-370].

5.4.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [371]. Measures for dependence in daily activities include: Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [372-374].

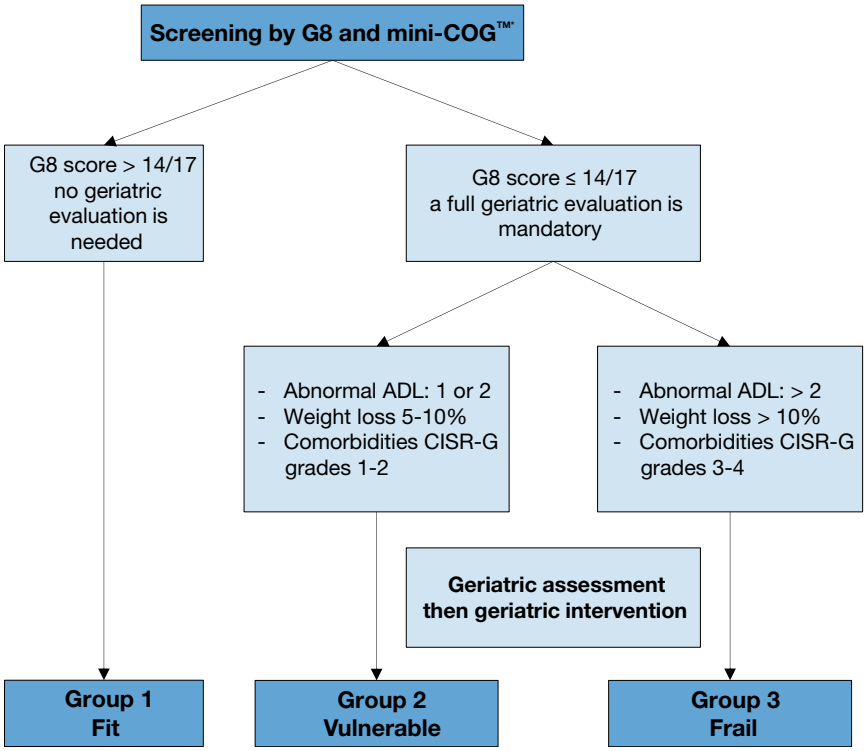
5.4.4 Conclusion

Individual life expectancy, health status, and comorbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of 10 years is most commonly used as a threshold for benefit of local treatment. Older men may be undertreated. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

Table 5.4.1: G8 screening tool (adapted from [375]**)**

	Items	**Possible responses (score)**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0: ≥ 85
		1: 80-85
		2: < 80
	Total score	**0-17**

Figure 5.4.1: Decision tree for health status screening (men > 70 years)** [360]



Mini-COG™ = Mini-COG™ cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.
**For Mini-COG™, a cut-off point of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*
***Reproduced with permission of Elsevier, from Boyle H.J., et al. Eur J Cancer 2019:116; 116 [360].*

Table 5.4.2: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (esophagus, stomach, duodenum. Biliar and parcreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculo-Skeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioural (includes dementia, depression, anxiety, agitation, psychosis)
	All body systems are scores on a 0 - 4 scale. - 0: No problem affecting that system. - 1: Current mild problem or past significant problem. - 2: Moderate disability or morbidity and/or requires first line therapy. - 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. - 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
Total score 0-52	

5.4.5 Guidelines for evaluating health status and life expectancy

Recommendations	Strength rating
Use individual life expectancy, health status, and comorbidity in PCa management.	Strong
Use the Geriatric-8 and mini-COG tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

6. TREATMENT

This chapter reviews the available treatment modalities, followed by separate sections addressing treatment for the various disease stages.

6.1 Treatment modalities

6.1.1 Deferred treatment (active surveillance/watchful waiting)

In localised disease a life expectancy of at least 10 years is considered mandatory for any benefit from local treatment. Indeed data is available on patients who did not undergo local treatment with up to 25 years of follow-up, and endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82-87% at 10 years [376-381], and 80-95% for T1/T2 and ISUP grade ≤ 2 PCas [382]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [378, 380, 381], and two reported 20-year CSS rates of 57% and 32%, respectively [378, 380]. In addition, many patients classified as ISUP grade 1 would now be classified as ISUP grade 2-3 based on the 2005 Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly-differentiated tumours had 10-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [382]. Observation was most effective in men aged 65-75 years with low-risk PCa [383].

Remember that comorbidity is more important than age in predicting life expectancy in men with PCa. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes and for those men with a short life expectancy. In an analysis at 10 years follow up in 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score ≥ 2 died from competing causes at 10 years whatever their initial age. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at 10 years, especially for well- or moderately-differentiated lesions [362]. This highlights the importance of assessing co-morbidity before considering a biopsy.

In screening-detected localised PCa the lead-time bias is likely to be greater. Mortality from untreated screen-detected PCa in patients with ISUP grade 1-2 might be as low as 7% at 15 years follow-up [384]. Consequently, approximately 45% of men with PSA-detected PCa are suitable for close follow-up through a robust surveillance programme. There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and WW (Table 6.1.1).

6.1.1.1 Definitions

Active surveillance aims to avoid unnecessary treatment in men with clinically localised PCa who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [385]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up, and curative treatment is prompted by predefined thresholds indicative of potentially life-threatening disease which is still potentially curable, while considering individual life expectancy.

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment right from the outset, and patients are ‘watched’ for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms, in order to maintain QoL.

Table 6.1.1: Definitions of active surveillance and watchful waiting [384]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

6.1.1.2 Active surveillance

No formal RCT is available comparing this modality to standard treatment. The Prostate Testing for Cancer and Treatment (ProtecT) trial is discussed later as it is not a formal AS strategy but rather Active Monitoring (AM), which is a significantly less stringent surveillance strategy in terms of clinical follow-up, imaging and repeat biopsies [386].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review [387]. More recently, the largest prospective series of men with low-risk PCa managed by AS was published [388]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS for patients on AS are extremely good. However, more than one-third of patients are 'reclassified' during follow-up, most of whom undergo curative treatment due to disease upgrading, increase in disease extent, disease stage, progression or patient preference. There is considerable variation and heterogeneity between studies regarding patient selection and eligibility, follow-up policies (including frequency and type of imaging such as mpMRI scan, type and frequency of repeat prostate biopsies, such as MRI-targeted biopsies or transperineal template biopsies, use of PSA kinetics and density, and frequency of clinical follow-up), when active treatment should be instigated (i.e. reclassification criteria), and which outcome measures should be prioritised [385]. These will be discussed further in section 6.2.1.

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [389]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [390]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [391]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [392]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [393]	278	41	-	89	100
Khatami, *et al.* 2007 [394]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [395]	993	77	-	85	98.1
Tosoian, *et al.* 2015 [388]	1,298	60	-	93	99.9
Total	**4,204-4,671**	**46.5**	**-**	**93**	**100**

** Patients receiving active therapy following initial active surveillance.*
CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

6.1.1.3 Watchful Waiting

6.1.1.3.1 Outcome of watchful waiting compared with active treatment

The SPCG-4 study randomised patients to either WW or RP (Table 6.1.3) [350] before the PSA era and found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 13.4 years (range 3 weeks-23.2 years). The PIVOT trial made a similar comparison in 731 randomised men (50% with non-palpable disease) [396] but in contrast to SPCG-4, it found no benefit of RP within a median follow-up period of 12.7 years (interquartile range, 7.3 to 15.5 years). Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a RR reduction in mortality of 33% and 31%, respectively. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%). Overall, no adverse effects on HRQoL and psychological well-being was apparent in the first years

[397]. However, one of the criticisms of the PIVOT trial is the relatively high-observed overall mortality rate in the WW group (almost 50% at a median of 10 years), compared with more contemporary series.

Table 6.1.3: Outcome of SPCG-4 at 15-year follow-up [350]

	RP (n = 348) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	p-value
Disease-specific mortality	14.6	20.7	0.62	0.010
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	n.r.

CI = confidence interval; n.r. = not reported; RP = radical prostatectomy.

6.1.1.4 The ProtecT study

The ProtecT trial randomised 1,643 patients, three-ways, between active treatment (RP or EBRT) and AM [386]. In this AM schedule, patients with a PSA rise of more than 50% in 12 months underwent a repeat biopsy, but none had systematic repeat biopsies. Fifty-six percent of patients had low-risk disease, with 90% having a PSA < 10 ng/mL, 77% ISUP grade 1 (20% ISUP grade 2-3), and 76% T1c, while the other patients were mainly intermediate risk. After 10 years of follow up, the CSS was the same between those actively treated and those on AM (99% and 98.8%, respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group).

The key finding is that AM is as effective as active treatment at 10 years, at a cost of increased progression and double the metastatic risk. Metastases remained quite rare (6%), but more frequent than seen with AS protocols probably driven by differences in intensity of monitoring and patient selection. It is important to note that the AM arm in ProtecT represents an intermediate approach between contemporary AS protocols and WW in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of mpMRI scan either at recruitment nor during the monitoring period, nor was there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease.

Nevertheless, in spite of these caveats, the ProtecT study has reinforced the role of deferred active treatment (i.e. either AS or some form of initial AM) as a feasible alternative to active curative interventions for patients with low-grade and low-stage disease. Beyond 10 years, no data is available as yet, although AS is likely to give more reassurance, especially in younger men, based on initial patient selection and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must be evaluated before considering any active treatment in low-risk situations, and for those with up to 10 years individual life expectancy.

6.1.2 Radical prostatectomy

6.1.2.1 Introduction

The goal of RP by any approach is the eradication of cancer, while whenever possible, preserving pelvic organ function [398]. The procedure involves removing the entire prostate with its capsule intact and seminal vesicles, followed by undertaking vesico-urethral anastomosis. Since its description in 1904, the technique has evolved markedly. Surgical approaches have expanded from perineal and retropubic open approaches to laparoscopic and robotic-assisted techniques; anastomoses have evolved from Vest approximation sutures to continuous-suture watertight anastomoses under direct vision and mapping of the anatomy of the dorsal venous complex (DVC) and cavernous nerves has led to excellent visualisation and potential for preservation of erectile function [399]. The main results from multicentre RCTs involving RP are summarised in Table 6.1.4.

Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Year of treatment	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [400]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [396]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2016 [386]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate risk	99 (at 10 yr.)

CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

6.1.2.2 Pre-operative preparation

6.1.2.2.1 Pre-operative patient education

As before any surgery, appropriate education and patient consent is mandatory prior to RP. Peri-operative education has been shown to improve long-term patient satisfaction following RP [401]. Augmentation of standard verbal and written educational materials, such as use of interactive multimedia tools [402, 403] and pre-operative patient-specific 3D printed prostate models [404] has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care.

Pre-operative pelvic floor exercises

Although many patients who have undergone RP will experience a return to urinary continence [405], temporary urinary incontinence is common early after surgery, reducing quality of life. Pre-operative pelvic floor exercises (PFE), with or without biofeedback, have been used with the aim of reducing this early post-operative incontinence. A systematic review and meta-analysis of the effect of pre-RP PFE on post-operative urinary incontinence showed a significant improvement in incontinence rates at 3 months post-op with an OR of 0.64 ($p = 0.005$), but not at 1 month or 6 months [406]). Pre-operative PFE may therefore provide some benefit, however the analysis was hampered by the variety of PFE regimens and a lack of consensus on the definition of incontinence.

Prophylactic antibiotics

Prophylactic antibiotics should be used; however no high-level evidence is available to recommend specific prophylactic antibiotics prior to RP (See EAU Urological Infections Guidelines). In addition, as the susceptibility of bacterial pathogens and antibiotic availability varies worldwide, any use of prophylactic antibiotics should adhere to local guidelines.

6.1.2.3 Surgical techniques

Prostatectomy can be performed by open-, laparoscopic- or robot-assisted (RARP) approaches. The initial open technique of RP described by Young in 1904 was via the perineum [399], but suffered from a lack of access to pelvic LNs. If lymphadenectomy is required during perineal RP, it must be done via a separate open retropubic (RRP)- or laparoscopic approach. The open retropubic approach was popularised by Walsh in 1982 following his anatomical description of the DVC, enabling its early control, and of the cavernous nerves, permitting a bilateral nerve-sparing procedure [407]. This led to the demise in popularity of perineal RP, and eventually to the first laparoscopic RP reported in 1997 using retropubic principles, but performed transperitoneally [408]. The initial 9 cases averaged 9.4 hours, indicating significant technical and ergonomic difficulties of the technique. Most recently, RARP was introduced using the da Vinci Surgical System® by Binder in 2002 [409]. This technology combined the minimally-invasive advantages of laparoscopic RP with improved surgeon ergonomics and greater technical ease of suture reconstruction of the vesico-urethral anastomosis, and has now become the preferred minimally-invasive approach, where the equipment is available.

In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss but not early (12 weeks) functional or oncological outcomes, compared to open RP [410]. An updated analysis with follow-up at 24 months did not reveal any significant differences in functional outcomes between the approaches [411]. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [380-383]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, can improve cancer control with RP [412-414]. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [379, 396, 397, 415]. A first systematic review and meta-analysis of non-RCTs demonstrated that RARP had lower perioperative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [416]. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions based on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes. Another systematic review and meta-analysis included two small RCTs comparing RARP vs. LRP [417]. The results suggested higher rates of return of erectile function (RR: 1.51; 95% CI: 1.19-1.92) and return to continence function (RR: 1.14; 95% CI: 1.04-1.24) in the RARP group. However, a recent Cochrane review comparing either RARP or LRP vs. open RP included two RCTs and found no significant differences between the comparisons for oncological-, urinary function- and sexual function outcomes, although RARP and LRP both resulted in statistically significant improvements in duration of hospital stay and blood transfusion rates over open RP [418]. Therefore, no surgical approach can be recommended over another.

Outcome after prostatectomy has been shown to be dependent on both surgeon [419] as well as hospital

volume [420]. Although various volume criteria have been set worldwide, the level of evidence is insufficient to pinpoint a specific lower volume limit.

6.1.2.3.1 Robotic anterior versus Retzius-sparing dissection

Robot-assisted RP has typically been performed via the anterior approach, first dropping the bladder to expose the space of Retzius. However, recently the posterior approach (Retzius-sparing - RS-RARP) has gained favour following two RCTs showing improved early post-operative continence.

Galfano *et al.* first described RS-RARP in 2010 [421]. This approach commences dissection posteriorly at the pouch of Douglas, first dissecting the seminal vesicles and progressing caudally behind the prostate. All of the anterior support structures are avoided, giving rise to the hypothetical mechanism for improved early post-operative continence. Retzius-sparing-RARP thus offers the same potential advantage as the open perineal approach, but without disturbance of the perineal musculature.

Both RCTs were single-surgeon studies comparing post-operative continence in RS-RARP vs. traditional anterior dissection RARP in men with low- to intermediate-risk PCa. Defining continence as 0-1 pad per day in 120 patients, Dalela *et al.* found a continence rate of 71% at 1 week post-catheter removal in the RS-RARP group vs. 48% in the control group ($p = 0.01$) [422]. The positive margin rate was higher in the RS-RARP group (25% vs. 13%), but this was not statistically significant ($p = 0.1$). Asimakopoulos *et al.* studied 102 patients, assessing continence more stringently as 0 pads at catheter removal [423]. Fifty-one percent of patients following RS-RARP were continent at catheter removal vs. 21% in the standard group ($p = 0.001$). Positive margin rates were again higher in the RS-RARP group (28% vs. 10%), however this was attributed to the higher incidence of pT3 disease in the RS-RARP group (44% vs. 23%).

Until these results are replicated in larger numbers in a multi-centre setting, it remains too early to recommend RS-RARP over the traditional anterior dissection, Furthermore, no high level evidence is available on high-risk disease, with some concerns that RS-RARP may confer an increased positive margin rate based on the pT3 results. In addition, RS-RARP may be more technically challenging in various scenarios such as anterior tumours, post-TURP, a grossly enlarged gland or a bulky median lobe [424].

6.1.2.3.2 Pelvic lymph node dissection

A recent systematic review demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [425]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [425]. The individual risk of finding positive LNs can be estimated using pre-operative tools. Another systematic review and meta-analysis found similar diagnostic accuracy in predicting LN invasion for the Briganti, Partin and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms [426]. However, only a few of these tools are based on eLND templates and have been externally validated. A risk of nodal metastases over 5% (Briganti nomogram [427, 428] or Roach formula [429] which has been shown to be almost as good as the nomogram) is an indication to perform nodal sampling by an extended nodal dissection [430-432]. Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. With this template, 94% of patients are correctly staged [433].

6.1.2.3.3 Sentinel node biopsy analysis

The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, when this node is negative it is possible to avoid an ePLND. There is heterogeneity and variation in techniques in relation to SNB (e.g. the optimal tracer), but a multidisciplinary collaborative endeavour attempted to standardise definitions, thresholds and strategies in relation to techniques of SNB using consensus methods [434].

Intraprostatic injections of indocyanine green (ICG) has been used to visualise prostate-related LNs during lymphadenectomy. In a randomised comparison, Harke *et al.* found more cancer containing LNs in men that underwent a LN dissection guided by ICG, but no difference in BCR at 22.9 month follow up [435]. A systematic review showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at eLND [436]. However, there is still insufficient quality evidence supporting oncological effectiveness of SNB for nodal staging. Sentinel node biopsy is therefore still considered as an experimental nodal staging procedure.

6.1.2.3.4 Prostatic anterior fat pad dissection and histologic analysis

Several multi-centre and large single-centre series have shown the presence of lymphoid tissue within the fat pad anterior to the endopelvic fascia - the prostatic anterior fat pad (PAFP) [437-443]. This lymphoid tissue is present in 5.5-10.6% of cases and contains metastatic PCa in up to 1.3% of intermediate- and high-risk cases.

When positive, the PAFP is often the only site of LN metastasis. The PAFP is therefore a rare but recognised route of spread of disease. Unlike PLND, there is no morbidity associated with removal of the PAFP. The PAFP is always removed at RP for exposure of the endopelvic fascia and should be sent for histologic analysis as per all removed tissue.

6.1.2.3.5 Management of the dorsal venous complex

Since the description of the anatomical open RP by Walsh and Donker in the 1980s, various methods of controlling bleeding from the DVC have been proposed to optimise visualisation [407]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [444]. However, concerns have been raised regarding the effect of prior DVC ligation on apical margin positivity and continence recovery due to the proximity of the DVC to both the prostatic apex and the urethral sphincter muscle fibres. In the robotic-assisted laparoscopic technique, due to the increased pressure of pneumoperitoneum, whether prior DVC ligation was used or not, blood loss was not found to be significantly different in one study [445]. In another study, mean blood loss was statistically significantly less with prior DVC ligation (184 vs. 176 mL, $p = 0.033$), however it is debatable whether this was clinically significant [446]. The positive apical margin rate was not different, however the latter study showed earlier return to full continence at 5 months post-operatively in the no prior DVC ligation group (61% vs. 40%, $p < 0.01$).

Ligation of the DVC can be performed with standard suture or using a vascular stapler. One study found significantly reduced blood loss (494 mL vs. 288 mL) and improved apical margin status (13% vs. 2%) when using the stapler [447].

Given the relatively small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler, will depend on their familiarity with the technique and the equipment available.

6.1.2.3.6 Nerve-sparing surgery

During prostatectomy, preservation of the neurovascular bundles with parasympathetic nerve branches of the pelvic plexus may spare erectile function [448, 449].

Although age and pre-operative function may remain the most important predictors for postoperative erectile function, nerve-sparing has also been associated with improved continence outcomes and may therefore still be relevant for men with poor erectile function [450, 451]. The association with continence may be mainly due to the dissection technique used during nerve-sparing surgery, and not due to the preservation of the nerve bundles themselves [450].

Extra-, inter-, and intra-fascial dissection planes can be planned, with those closer to the prostate and performed bilaterally associated with superior (early) functional outcomes [452-455]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [456-458]. Nerve-sparing does not compromise cancer control if patients are carefully selected depending on tumour location, size and grade [459-461].

6.1.2.3.7 Lymph-node-positive patients during radical prostatectomy

Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [462]. As a consequence there is no role for performing frozen section of suspicious LNs.

6.1.2.3.8 Removal of seminal vesicles

The more aggressive forms of PCa may spread directly into the seminal vesicles (SVs). For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [463]. However, in some patients the tips of the SVs can be challenging to dissect free. Furthermore, the cavernous nerves run past the SV tips such that indiscriminate dissection of the SV tips could potentially lead to ED [464]. However, an RCT comparing nerve-sparing RP with and without SV-sparing found no difference in margin status, PSA recurrence, continence or erectile function outcomes. Another study of 71 consecutive RPs showed no cancer in any of the distal 1 cm of SVs, even in 12 patients with SV invasion [465]. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

6.1.2.3.9 Techniques of vesico-urethral anastomosis

Following prostate removal, the bladder neck is anastomosed to the membranous urethra. The objective is to create a precisely aligned, watertight, tension-free, and stricture-free anastomosis that preserves the integrity of the intrinsic sphincter mechanism. Several methods have been described, based on the direct or indirect approach, the type of suture (i.e. barbed vs. non-barbed/monofilament), and variation in suturing technique

(e.g. continuous vs. interrupted, or single-needle vs. double-needle running suture). The direct vesico-urethral anastomosis, which involves the construction of a primary end-to-end, inter-mucosal anastomosis of the bladder neck to the membranous urethra by using 6 interrupted sutures placed circumferentially, has become the standard method of reconstruction for open RP [466].

The development of laparoscopic- and robotic-assisted techniques to perform RP have facilitated the introduction of new suturing techniques for the anastomosis. A systematic review and meta-analysis [467] compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP). The review included 3 RCTs and found significantly reduced anastomosis time, operative time and posterior reconstruction time in favour of the unidirectional barbed suture technique, but there were no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data. In regard to suturing technique, a systematic review and meta-analysis [468] compared continuous vs. interrupted suturing for vesico-urethral anastomosis during RP. The study included only one RCT [469] which had only 60 patients. Although the review found slight advantages of continuous suturing over interrupted suturing in terms of catheterisation time, anastomosis time and rate of extravasation, the overall quality of evidence was low, and no clear recommendations were possible. A recent RCT [470] compared the technique of suturing using a single absorbable running suture vs. a double-needle, single-knot running suture (i.e. Van Velthoven technique) [471] in laparoscopic RP. The study found slightly reduced anastomosis time with the single running suture technique, but anastomotic leak, stricture and continence rates were similar.

Overall, although there are a variety of approaches, methods and techniques for performing the vesico-urethral anastomosis, no clear recommendations are possible due to the lack of high certainty evidence. In practice, the chosen method should be based on surgeon experience and individual preference [466-477].

6.1.2.3.10 Bladder neck management

Bladder neck mucosal eversion

Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP in the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. Whilst bringing bladder and urethral mucosa together, by the everted bladder mucosa covering the bladder muscle layer, this step may actually retard healing of the muscle layers. An alternative is to simply ensure bladder mucosa is included in the full thickness anastomotic sutures. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [478]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [479].

Bladder neck preservation

Whilst the majority of urinary continence is maintained by the external urethral sphincter at the membranous urethra (see below), a minor component is contributed by the internal lissosphincter at the bladder neck [480]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. An RCT assessing incontinence recovery at 12 months and 4 years showed improved objective and subjective urinary continence in both the short- and long-term without any adverse effect on oncological outcome [481]. These findings were confirmed by a systematic review [482]. However, concern remains regarding margin status for cancers located at the prostate base.

A systematic review addressing site-specific margin status found a mean base-specific positive margin rate of 4.9% with bladder neck preservation vs. only 1.9% without [480]. This study was inconclusive, but it would be sensible to exercise caution when considering bladder neck preservation if significant cancer is known to be at the prostate base. Bladder neck preservation should be performed routinely when the cancer is distant from the base. Bladder neck preservation, however, cannot be performed in the presence of a large median lobe, or a previous TURP.

6.1.2.3.11 Urethral length preservation

The membranous urethra sits immediately distal to the prostatic apex and is chiefly responsible, along with its surrounding pelvic floor support structures, for urinary continence. It consists of the external rhabdosphincter which surrounds an inner layer of smooth muscle. Using pre-operative MRI, the length of membranous urethra has been shown to vary widely. A systematic review and meta-analysis has found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [483]. It is likely therefore that preservation of as much urethral length as possible during RP will maximise the chance of early return to continence. It may also be useful to measure this urethral length pre-operatively in order to advise patients on their relative likelihood of early post-operative continence.

6.1.2.3.12 Cystography prior to catheter removal

Cystography may be used prior to catheter removal to check for a substantial anastomotic leak. If such a leak is found, catheter removal may then be deferred to allow further healing and sealing of the anastomosis. However, small comparative studies suggest that a cystogram to assess anastomotic leakage is not indicated as standard of care before catheter removal 8-10 days after surgery [484]. If a cystogram is used, men with LUTS, large prostates, previous TURP, or bladder neck reconstruction may benefit, as these factors have been associated with leakage [485, 486]. Contrast-enhanced transrectal US is an alternative [487].

6.1.2.3.13 Urinary catheter

A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesico-urethral anastomosis heals. Compared to a traditional catheter duration of around 1 week, some centres remove the transurethral catheter early (post-operative day 2-3), usually after thorough anastomosis with posterior reconstruction, or in patients selected peri-operatively on the basis of anastomosis quality [488-491]. No higher complication rates were found. Although shorter catheterisation has been associated with more favourable short-term functional outcomes, no differences in long-term function were found [492]. One RCT has shown no difference in rate of UTI following indwelling catheter (IDC) removal whether prophylactic ciprofloxacin was given prior to IDC removal or not, suggesting antibiotics should not be given at catheter removal [493].

As an alternative to transurethral catheterisation, suprapubic catheter insertion during RP has been suggested. Some reports suggest less bother regarding post-operative hygiene and pain [494-498], while others did not find any differences [499, 500]. No impact on long-term functional outcomes were seen.

6.1.2.3.14 Use of a pelvic drain

A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood, or lymphatic fluid when a PLND has been performed. Two RCTs in the robotic-assisted laparoscopic setting have been performed [501, 502]. Patients with urine leak at intra-operative anastomosis watertight testing were excluded. Both trials showed non-inferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intra-operatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

6.1.2.4 Acute and chronic complications of surgery

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Recent systematic reviews have documented complication rates after RALP [416, 503-506], and can be compared with contemporaneous reports after radical retropubic prostatectomy (RRP) [507]. Recently, a prospective, controlled, non-RCT of patients undergoing RP in 14 centres using RALP or RRP was published. At 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [508]. A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [410]. Urinary function scores did not differ significantly between RRP vs. RALP at 6 and 12 weeks post-surgery (74-50 vs. 71-10, p = 0.09; 83-80 vs. 82-50, p = 0.48), with comparable outcomes for sexual function scores (30-70 vs. 32-70, p = 0.45; 35-00 vs. 38-90, p = 0.18). In the RRP group 14 (9%) patients had post-operative complications vs. 6 (4%) in the RALP group. The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 6.1.5. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations (see Section 8.3.2).

6.1.2.4.1 Effect of anterior and posterior reconstruction on continence

Preservation of integrity of the external urethral sphincter is critical for continence post-RP. Less clear is the effect of reconstruction of surrounding support structures to return to continence. Several small RCTs have been conducted, however pooling analyses is hampered by variation in the definitions of incontinence, and surgical approach, such as open vs. robotic and intraperitoneal vs. extraperitoneal. In addition, techniques used to perform both anterior suspension or reconstruction and posterior reconstruction are varied. For example, anterior suspension is performed either through periosteum of the pubis or the combination of ligated DVC and puboprostatic ligaments (PPL). Posterior reconstruction from rhabdosphincter is described to either Denonvilliers fascia posterior to bladder or to posterior bladder wall itself.

Two trials assessing posterior reconstruction in RALRP found no significant improvement in return to continence [509, 510]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days, p = 0.024) [511]. When combining both anterior and posterior reconstruction, where for anterior reconstruction, the PPL were sutured to the anterior bladder neck, another RCT found no improvement compared to a standard anastomosis with no reconstruction [512].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone, through the pubic periosteum, in the setting of extraperitoneal RALRP, showed no advantage [513]. However, when combined with posterior reconstruction in RRP, one RCT showed significant improvement in return to continence at one month (7.1% vs. 26.5%, p = 0.047) and 3 months (15.4% vs. 45.2%, p = 0.016), but not at 6 months (57.9% vs. 65.4%, p = 0.609) [514]. Another anterior plus posterior reconstruction RCT using the Advanced Reconstruction of VesicoUrethral Support (ARVUS) technique and the strict definition of continence of no pads, showed statistically significant improvement in continence at 2 weeks (43.8% vs. 11.8%), 4 weeks (62.5% vs. 14.7%), 8 weeks (68.8% vs. 20.6%), 6 months (75% vs. 44.1%) and 12 months (86.7% vs. 61.3%), when compared to standard posterior Rocco reconstruction [515]. Anterior suspension alone through the DVC and PPL combined, without posterior construction in the setting of RRP has shown improvement in continence at one month (20% vs. 53%, p = 0.029), 3 months (47% vs. 73%, p = 0.034) and 6 months (83% vs. 100%, p = 0.02), but not at 12 months (97% vs. 100%, p = 0.313) [516]. Together, these results suggest a possible earlier return to continence, but no long-term difference.

As there is conflicting evidence on the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.1.2.4.2 Deep venous thrombosis prophylaxis

For EAU Guidelines recommendations on post-RP deep venous thrombosis prophylaxis, please see the Thromboprophylaxis Guidelines Section 3.1.6 [517]. However these recommendations should be adapted based on national recommendations when available.

Table 6.1.5: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [416]**)**

Predicted probability of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

6.1.2.4.3 Early complications of extended lymph node dissection

Pelvic eLND increases morbidity in the treatment of PCa [425]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event. Other authors have reported more acceptable complication rates [518]. Similar rates of lymphoceles have been observed in RALP series; however, in one subgroup analysis lymphoceles were more common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [519, 520]. Briganti *et al.* [521] also showed more complications after extended compared to limited LND. Twenty percent of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

6.1.2.5 Comparing effectiveness of radical prostatectomy versus other interventions for localised disease

6.1.2.5.1 Radical prostatectomy versus deferred treatment

Currently, three large prospective RCTs have compared RP over deferred treatment (see Section 6.1.2). In summary, there was conflicting evidence regarding the benefit of RP over deferred treatment. The only study to find a benefit of RP over WW (SPCG-4) was conducted in the pre-PSA era [350]. When comparing RP against WW [396] or against AM [386], no statistically significant benefit in OS at 10 years' of follow-up was observed. These findings indicate the good prognosis for the majority of patients with low-risk localised PCa,

and highlight the need to carefully risk stratify patients to ensure that patients are appropriately managed and treated.

6.1.2.5.2 Radical prostatectomy versus radiotherapy

ProtecT compared RP vs. AM vs. EBRT (combined with 6 months of ADT) [386]. At a median follow-up of 10 years, there were no differences between surgery vs. EBRT in all oncological outcomes.

6.1.2.5.3 Neoadjuvant androgen deprivation therapy

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of them using a 3-month period. The main findings were summarised in a Cochrane review [522]. Neoadjuvant ADT is associated with a decreased rate of pT3 (downstaging), decreased positive margins, and a lower incidence of positive LNs. These benefits are greater with increased treatment duration (up to 8 months). However, since neither the PSA relapse-free survival nor CSS were shown to improve, neoadjuvant ADT should not be considered as standard clinical practice. One recent RCT compared neoadjuvant luteinising hormone-releasing hormone (LHRH) alone vs. LHRH plus abiraterone plus prednisone prior to RP in 65 localised high-risk PCa patients [523]. Patients in the combination arm were found to have both significantly lower tumour volume and significantly lower BCR at > 4 years follow-up ($p = 0.0014$). Further supportive evidence is required before recommending combination neoadjuvant therapy including abiraterone prior to RP.

6.1.3 Radiotherapy

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT.

6.1.3.1 External beam radiation therapy

6.1.3.1.1 Technical aspects: intensity-modulated external-beam radiotherapy and volumetric arc external-beam radiotherapy (VMAT)

Intensity-modulated external-beam radiotherapy and VMAT employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes. Both techniques allow for a more complex distribution of the dose to be delivered within the treatment field and provide concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning', and the appropriate physics expertise. Treatment plans must conform to pre-specified dose constraints to critical organs at risk of normal tissue damage, and a formal quality assurance process should be routine.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [524]. Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

6.1.3.1.2 Dose escalation

Several RCTs have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year biochemical relapse [525-531]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (HT) has varied (see Table 6.1.6). The best evidence of an OS benefit for patients with intermediate- or high-risk PCa, but not with low-risk PCa, comes from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database covering a total of 42,481 patients [532]. In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT plus HT, with no different recommendations according to the patient's risk group. If IMRT and IGRT are used for

dose escalation, rates of severe late side-effects (≥ grade 3) for the rectum are 2-3% and for the GU tract 2-5% [528, 531, 533-546].

Table 6.1.6: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [526]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs.78 Gy	9 yr.	DSM vs. other cause of death	High risk/PSA > 10 16% DSM at 70 Gy 4% DSM at 78 Gy (p = 0.05) Higher risk 15% DSM at 70 Gy 2% DSM at 78 Gy (p = 0.03)
PROG 95-09 2010 [527]	393	T1b-T2b PSA 15 ng/mL 75%	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy (p < 0.0001)
MRC RT01 2014 [547]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	10 yr.	BFS; OS	43% BFS at 64 Gy 55% BFS at 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial 2014 [531]	664	T1b-T4 143 pts. with (neo) adjuvant HT	68 vs. 78 Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr.	43% FFF at 68 Gy 49% FFF at 78 Gy (p = 0.045)
GETUG 06 2011 [530]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	61 mo.	BCF (ASTRO)	39% BF at 70 Gy 28% BF at 80 Gy
RTOG 0126 2018 [525]	1,532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/mL or ISUP grade 2/3 + PSA < 15 ng/mL	70.2 vs. 79.2 Gy	100 mo.	OS DM BCF (ASTRO)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy (p = 0.05) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy (p < 0.001; Phoenix, p < 0.001)

(B)CF = biochemical failure; BFS = biochemical progression-free survival; DM = distant metastases; DSM = disease specific mortality; FFF = freedom from biochemical or clinical failure; HT = hormone therapy; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; yr. = year.

6.1.3.1.3 Hypofractionation (HFX)

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [548]. A meta-analysis of 25 studies including > 14,000 patients concluded that since PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8-2 Gy [549]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at with lower cost.

Moderate HFX is defined as RT with 2.5-4 Gy/fx. Several studies report on moderate HFX applied in various techniques and, in part, also including HT [550-560]. A systematic review concludes that studies on moderate HFX (2.5-4 Gy/fx) delivered with conventional three-dimensional conformal radiotherapy (3D-CRT)/ IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking

[559]. Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT in carefully selected patients and adhere to published phase III protocols (see Table 6.1.7 below).

Table 6.1.7: Major phase III randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, ISUP grade, or NCCN	ADT	RT Regimen	BED, Gy	Median FU, mo	Outcome
Lee, *et al.* 2016 [554]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	5 yr. DFS 86.3% (n.s.) 5 yr. DFS 85.3%
Dearnaley, *et al.* CHHiP 2012 [550] and 2016 [555]	1077/19 fx 1074/20 fx 1065/37 fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	5 yr. BCDF 85.9% (19 fx) 90.6% (20 fx) 88.3% (37 fx)
Aluwini, *et al.* 2015 [553], 2016 [556, 557]	403 392	30% ISUP grade 1 45% ISUP grade 2-3, 25% ISUP grade 4-5	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	60	5 yr. RFS 80.5% (n.s.) 5 yr. RFS 77.1%
Catton, *et al.* 2017 [558]	608	intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20 fx	77.1	72	5 yr. BCDF both arms 85% HR: 0.96 (n.s)
	598	9% ISUP grade 1 63% ISUP grade 2 28% ISUP grade 3		78 Gy/39 fx	78		

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an $\alpha/ß$ of 1.5 Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; HR = hazard ratio; mo. = month; n = number of patients; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; n.s. = not significant; yr. = year.

Ultra-HFX has been defined as radiotherapy with > 3.4 Gy per fraction [560]. It requires IGRT and stereotactic body radiotherapy (SBRT). Table 6.1.8 provides an overview of selected studies. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity and long-term side-effects may not all be known yet [559, 561, 562]. In the HYPO-RT-PC randomised trial by Widmark *et al.* (n = 1,200), no difference in failure-free survival was seen for conventional or ultra-HFX but acute Grade ≥ 2 GU toxicity was 23% vs. 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [563]. A systematic review by Jackson *et al.* included 38 studies with 6,116 patients who received RT with < 10 fractions and ≥ 5 Gy per fraction. Five- and 7-year bRFS rates were 95.3% and 93.7%, respectively and estimated late grade ≥ 3 genitourinary- and gastrointestinal toxicity rates were 2.0% and 1.1%, respectively [564]. The authors conclude that there is sufficient evidence to support SBRT as a standard treatment option for localised PCa, even though the median follow-up in this review was only 39 months and it included at least one trial (HYPO-RT-PC) which used "conventional" IMRT/VMAT for ultra-HFX. In their review on SBRT, Cushman and co-workers evaluated 14 trials, including 2,038 patients and concluded that despite a lack of long-term follow-up and the heterogeneity of the available evidence, prostate SBRT affords appropriate biochemical control with few high-grade toxicities [565]. In the Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B) trial, acute grade ≥ 2 GU or GI toxicities did not differ significantly between conventional

fractionation and ultra-HFX [566]. Therefore, it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.1.8: Selected trials on ultra-hypofractionation for intact localised PCa

Reference	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark *et al.* 2019 HYPO-RT-PC [563]	1,200	60	89% intermediate 11% high	78 Gy / 39 fx, 8 w 42.7 Gy / 7 fx, 2.5 w No SBRT	FFS at 5 yr. 84% in both arms
Brand *et al.* 2019 PACE-B [566]	847	variable	8% low 92% intermediate	78 Gy / 39 fx, 8 w 36.25 Gy / 5 fx, 1-2 w SBRT	Grade ≥ 2 acute GI 12% vs. 10%, p = 0.38 Grade ≥ 2 acute GU 27% vs. 23%, p = 0.16

FFS = failure-free survival; FU = follow-up; fx = number fractions; GI = gastrointestinal toxicity, GU: genitourinary toxicity, mo. = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; w = weeks, yr. = years.

6.1.3.1.4 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with LHRH ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [567-571] (Table 6.1.9). The main message is that for intermediate risk a short duration of around 6 months is optimal, while a longer one, around 3 years, is needed for high-risk patients.

Table 6.1.9: Selected studies of use and duration of ADT in combination with RT for PCa

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [568]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade 2-5
RTOG 94-13 2007 [572]	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10 2008 [569]	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 yr.
D'Amico AV, *et al.* 2008 [570]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0·55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity
RTOG 92-02 2008 [573]	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65-70 Gy RT	p = 0.73, p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with ISUP grade 4-5

EORTC 22961 2009 [574]	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	Better result with 3 yr. treatment than with 6 mo. (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [567]	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	Significant benefit at 10 yr. for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, p = 0.0004).
TROG 96-01 2011 [571]	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56, 95% CI: 0.32-0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65-1.08, p = 0.18)
RTOG 99-10 2015 [575]	intermediate risk (94% T1-T2, 6% T3-4)	1,579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk.	70.2 Gy 2D/3D	67 vs. 68%, p = 0.62, confirms 8 + 8 wk. LHRH as a standard

ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiotherapy in standard fractionation; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; wk = week; yr. = year.

The question of the added value of EBRT combined with ADT has been clarified with 3 RCTs. All showed a clear benefit of adding EBRT to long-term ADT (see Table 6.1.10).

Table 6.1.10: Selected studies of ADT in combination with, or without, RT for PCa

Trial	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [576]	T1b-2 WHO Grade 1-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. plus continuous flutamide	70 Gy 3D-CRT vs. no RT	34% (95% CI: 29-39%) vs. 17% (95% CI: 13-22% CSM at 12 (15) yr. favouring combined treatment (p < 0.0001 for 15-yr. results) NCIC CTG PR.3/ MRC
PRO7/NCIC 2011 [577] and 2015 [578]	T3-4 (88%), PSA > 20 ng/ mL (64%), ISUP grade 4-5 (36%) N0 M0	1,205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10-yr. OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Sargos P, *et al.* 2019 [579]	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

ADT = androgen deprivation therapy; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

6.1.3.1.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy

Zelefsky *et al.* reported a retrospective analysis comprising 571 patients with low-risk PCa, 1,074 with intermediate-risk PCa, and 906 with high-risk PCa. 3D-conformal RT or IMRT were administered [580]. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT. The 10-year biochemical disease-free rate was significantly improved by dose escalation: above 75.6 Gy in low risk, and above 81 Gy for the intermediate- and high-risk groups. It was also improved by adding 6 months of ADT in intermediate- and high-risk patients. In the

multivariate analysis, neither the dose > 81 Gy, nor adding ADT influenced OS. Three RCTs have shown that the benefits of ADT are independent of dose escalation, and that the use of ADT would not compensate for a lower radiotherapy dose:

1. The GICOR study which shows a better biochemical DFS for high-risk patients for 3D-CRT radiation dose > 72 GY when combined with long-term ADT [538].
2. DART01/05 GICOR which shows that 2 years of adjuvant ADT combined with high-dose RT improved biochemical control and OS in high-risk patients [581].
3. EORTC trial 22991 which shows that 6 months ADT improves biochemical and clinical DFS whatever the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa [582].

6.1.3.2 Proton beam therapy

In theory, proton beams are an attractive alternative to photon-beam RT for PCa, as they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [527]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database and from Harvard describing toxicity and patient-reported outcomes do not point to an inherent superiority for protons [583, 584]. In terms of longer-term gastrointestinal (GI) toxicity, proton therapy might even be inferior to IMRT [584].

A RCT comparing equivalent doses of proton-beam therapy with IMRT is underway. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy.

6.1.3.3 Brachytherapy

6.1.3.3.1 Low-dose rate (LDR) brachytherapy

Low-dose rate brachytherapy uses radioactive seeds permanently implanted into the prostate. There is a consensus on the following eligibility criteria for LDR monotherapy [585]: Stage cT1b-T2a N0, M0; ISUP grade 1 with ≤ 50% of biopsy cores involved with cancer or ISUP grade 2 with ≤ 33% of biopsy cores involved with cancer; an initial PSA level of ≤ 10 ng/mL; a prostate volume of < 50 cm^3; an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow tests [586].

The only available RCT comparing RP and brachytherapy as monotherapy was closed due to poor accrual [587]. Outcome data are available from a number of large population cohorts with mature follow-up [588-595]. The biochemical disease-free survival for ISUP grade 1 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [588-595]. A significant correlation has been shown between the implanted dose and biochemical control [596]. A D90 (dose covering 90% of the prostate volume) of > 140 Gy leads to a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years (92 vs. 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [588].

Low-dose rate brachytherapy can be combined with EBRT in intermediate-/high-risk patients (see Section 6.2.3.2.3).

6.1.3.3.2 High-dose rate brachytherapy

High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of published guidelines is strongly recommended [597]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [598]. A single RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy (17 Gy in two fractions over 24 hours) has been reported [599]. In 218 patients with organ-confined PCa the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical disease-free rate ($p = 0.04$) at 5 and 10 year (75% and 46% compared to 61% and 39%). However, a very high, uncommon, rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to a dose lower than the current standard used [599]. A systematic review of non-RCTs has suggested outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective RCT [600].

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres [601, 602]. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no or very minimal grade 3+ GI toxicity rates [601, 602].

Table 6.1.11: Difference between LDR and HDR brachytherapy

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	• Permanent seeds implanted • Uses Iodine-125 (I-125) (most common), ^{103}Palladium (Pd-103) or Cesium-131 isotopes • Radiation dose delivered over weeks and months • Acute side-effects resolve over months • Radiation protection issues for patient and carers
High dose rate (HDR)	• Temporary implantation • Iridium-192 (IR-192) isotope introduced through implanted needles or catheters • Radiation dose delivered in minutes • Acute side-effects resolve over weeks • No radiation protection issues for patient or carers

6.1.3.4 Acute side-effects of external beam radiotherapy and brachytherapy

Gastrointestinal and urinary side-effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% of grade 2, and 2% grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than 1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [537]. In addition, general side-effects such as fatigue are common. It should be noted that the incidence of acute side-effects is greater than that of late effects (see Section 8.2.2.1), implying that most acute effects resolve. In a RCT of conventional dose EBRT vs. EBRT and LDR brachytherapy the incidence of acute proctitis was reduced in the brachytherapy arm, but other acute toxicities were equivalent [603]. Acute toxicity of HDR brachytherapy has not been documented in a RCT, but retrospective reports confirm lower rates of GI toxicity compared with EBRT alone and grade 3 GU toxicity in 10%, or fewer, patients, but a higher incidence of urinary retention [604]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic radiotherapy, declines in urinary and bowel domains were noted at 3 months, which returned to baseline, or better, by 6 months [605].

6.1.4 Hormonal therapy

6.1.4.1 Introduction

6.1.4.1.1 Different types of hormonal therapy

Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned anti-androgens [606].

6.1.4.1.1.1 Testosterone-lowering therapy (castration)

6.1.4.1.1.1.1 Castration level

The castration level is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [607]. Therefore, a more appropriate level should be defined as < 20 ng/dL (1 nmol/L). This definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [608-610]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50 ng/dL (1.7 mmol/L).

6.1.4.1.1.1.2 Bilateral orchiectomy

Bilateral orchiectomy, or subcapsular pulpectomy, is still considered the primary treatment modality for ADT. It is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia and it is the quickest way to achieve a castration level, which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [611].

6.1.4.1.1.2 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [612]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side-effects, especially thromboembolic complications, even at lower doses these drugs are not considered as standard first-line treatment [613-615].

6.1.4.1.1.3 Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly, basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [616]. Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare but does not completely remove the risk.

Anti-androgen therapy is usually continued for 4 weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare-up' is unknown [617, 618].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2 to 4 weeks [619]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [620]. No survival difference with orchiectomy has been reported, despite the lack of high quality trials [621].

The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.1.4.1.1.4 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available.

Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [619]. An extended follow-up has been published, suggesting a better PSA PFS compared to monthly leuprorelin [622]. A systematic review did not show major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond 12 months as well as the lack of survival data [623]. Its definitive superiority over the LHRH analogues remains to be proven.

6.1.4.1.1.5 Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

6.1.4.1.1.5.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

6.1.4.1.1.5.1.1 Cyproterone acetate

Cyproterone acetate was the first licensed anti-androgen, but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT, CPA showed a poorer OS when compared with LHRH analogues [624]. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in disease-specific and OS at a median follow-up of 8.6 years [625]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.1.4.1.1.5.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [626]. Non-androgen-related pharmacological side-effects differ between agents. Bicalutamide shows a more favourable

safety and tolerability profile than flutamide and nilutamide [627]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.1.4.1.1.5.2.1 Nilutamide

Nilutamide monotherapy has not been compared to castration and is not licensed for monotherapy. Direct drug-related side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and of note, severe interstitial pneumonitis (potentially life-threatening). As a consequence it is rarely used.

6.1.4.1.1.5.2.2 Flutamide

Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metabolite is 5 to 6 hours, requiring a three times daily dose. The recommended total daily dose is 750 mg. The non-androgen-related pharmacological side-effect of flutamide is diarrhoea.

6.1.4.1.1.5.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [626, 628].

6.1.4.1.1.6 New compounds

Once on ADT, the development of castration-resistance (CRPC) is only a matter of time. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms (see Section 6.5 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed, suggesting an adaptive mechanism [629]. This has led to the development of several new compounds targeting the androgen axis. Abiraterone acetate and enzalutamide are both approved for mCRPC. Abiraterone acetate has also been approved for hormone-sensitive PCa, combined with ADT. Apalutamide, darolutamide and enzalutamide have been approved for M0 CRPC at high risk of further metastases [630, 631].

6.1.4.1.1.6.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition). By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism.

6.1.4.1.1.6.2 Enzalutamide

Enzalutamide is a novel non-steroidal anti-androgen with a higher affinity for the AR receptor than bicalutamide. While previous non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer and therefore suppresses any possible agonist-like activity.

6.1.4.1.1.6.3 Apalutamide

Apalutamide is a novel non-steroidal anti-androgen with similar properties as enzalutamide and an identical mechanism of action.

6.1.4.1.1.6.4 Darolutamide

Darolutamide is a novel non-steroidal anti-androgen with, compared to the other new anti-androgens, structurally unique properties and distinct pharmacokinetics. In particular it does not cross the blood-brain barrier, has a high affinity for AR and a low affinity for GABA receptors, and therefore a lower potential for drug-drug interactions. It has been approved by the FDA and the EMA.

6.1.5 Investigational therapies

6.1.5.1 Background

Besides RP, EBRT and brachytherapy, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa [632-635]. In this section, both whole gland and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy, as sufficient data are available to form the basis of some initial judgements. Other options, such as radiofrequency ablation and electroporation, among others, are considered to be in the early phases of evaluation [636]. In addition, a relatively newer development is focal ablative therapy [636, 637], whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner. All

these modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes.

6.1.5.2 Cryotherapy

Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [632-635]. Freezing of the prostate is ensured by the placement of 17 gauge cryo-needles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryotherapy devices are mainly used. Since its inception, cryotherapy has been used for whole-gland treatment in PCa either as a primary or salvage treatment option.

The main adverse effects of cryosurgery are ED (18%), urinary incontinence (2-20%), urethral sloughing (0-38%), rectal pain and bleeding (3%) and recto-urethral fistula formation (0-6%) [638]. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being non-comparative single-arm case series with short follow-up periods [638].

6.1.5.3 High-intensity focused ultrasound

High-intensity focused ultrasound consists of focused US waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation [639]. The goal of HIFU is to heat malignant tissues above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. High-intensity focused US has previously been widely used for whole-gland therapy. The major adverse effects of HIFU include acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula (0-5%) and urinary incontinence 10%) [638]. Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 mL, and in targeting cancers in the anterior zone of the prostate. Similar to cryosurgery, the lack of any long-term prospective comparative data on oncological outcomes prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [638].

6.1.5.4 Focal therapy

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [640-642]. Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, photodynamic therapy, electroporation, and focal RT by brachytherapy or CyberKnife® Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to ablate tumours selectively whilst limiting toxicity by sparing the neurovascular bundles, sphincter and urethra [643-645].

A previous systematic review and network meta-analysis [638] on ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT. Nine case series reporting on focal therapy were identified (5 studies reporting on focal cryosurgical ablation of the prostate [CSAP], three studies on focal HIFU, and one study reported on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at 3 years. For focal HIFU vs. RP or EBRT, there were neither comparable data on oncological-, continence- nor potency outcomes at one year, or more. More recently, Valerio *et al.* [637] performed a systematic review to summarise the evidence regarding the effectiveness of focal therapy in localised PCa. Data from 3,230 patients across 37 studies were included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions, approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short to medium-term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT.

In order to update the evidence base, a systematic review incorporating a narrative synthesis was performed by the panel, including comparative studies assessing focal ablative therapy vs. radical treatment, AS or alternative focal ablative therapy, published in English between January 1st 2010 and May 31st 2019. Primary outcomes included oncological outcomes, adverse events and functional outcomes. A total of 707 abstracts

were screened; 12 articles were eligible for full text screening, and ultimately only 4 articles (3 studies) were eligible for inclusion [646-649]. Azzouzi *et al.* [646] and Gill *et al.* [647] reported on a RCT comparing focal therapy using padeliporfin-based vascular-targeted photodynamic therapy (PDT) vs. AS in men with very low-risk PCa. The study found, at a median follow-up of 24 months, less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24-0.46), and needed less radical therapy (6% vs. 29%, $p < 0.0001$). In addition, more men in the PDT arm had a negative prostate biopsy at two years than men in the AS arm (adjusted RR: 3.67, 95% CI: 2.53-5.33). Updated results were published in 2018 [647], showing that these benefits were maintained after four years. Nevertheless, limitations of the study include inappropriately comparing an intervention designed to destroy cancer tissue in men with low-risk PCa against an intervention primarily aimed at avoiding unnecessary treatment in men with low-risk PCa, and an unusually high observed rate of disease progression in the AS arm (58% in two years). Furthermore, more patients in the AS arm chose to undergo radical therapy without a clinical indication, and this may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy nor any mpMRI scanning, which is not representative of contemporary practice. Two further studies identified in the review were non-randomised comparative studies. Albisinni *et al.* was a small retrospective matched-pair study comparing focal HIFU vs. RALRP; Tourinho-Barbosa *et al.* was a retrospective cohort study comparing focal HIFU vs. focal cryotherapy for patients with low- or intermediate-risk localised PCa. The certainty of the evidence relating to both studies was low due to the retrospective and unmatched nature of the data.

Given the lack of robust comparative data on medium to long-term oncological outcomes for focal therapy against curative interventions (i.e. RP or EBRT), significant uncertainties remain in regard to focal therapy as a proven alternative to either AS or radical therapy. Consequently, robust prospective trials reporting standardised outcomes [650] are needed before recommendations in support of focal therapy for routine clinical practice can be made [636, 650, 651]. For now, focal therapy should only be performed within the context of a clinical trial setting or well-designed prospective cohort study.

6.1.6 General guidelines for active treatment

Recommendations	**Strength rating**
Inform patients that no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and prostate cancer-specific survival for clinically localised disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multiparametric magnetic resonance imaging).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

6.1.7 Discussing treatment options

Management decisions should be made after all treatments have been discussed in a multidisciplinary team (including urologists, radiation oncologists, medical oncologists pathologists and radiologists), and after the balance of benefits and side-effects of appropriate therapy modalities has been considered together with the patient. The following paragraphs will only address active modalities where the aim is to try to be "curative" in patients where that is appropriate.

6.2 Treatment by disease stages

6.2.1 Treatment of low-risk disease

6.2.1.1 Active surveillance

The main risk for men with low-risk disease is over-treatment (see Sections 6.1.1.2 and 6.1.1.4) and therefore AS should be considered for all such patients.

6.2.1.1.1 Active surveillance - inclusion criteria

Selection criteria for AS are limited by a lack of prospective RCTs. As a consequence, the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [7]. The criteria most often published include: ISUP grade 1, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc [387, 652]. The latter threshold remains controversial [652, 653]. These criteria were supported by the DETECTIVE consensus. There was no agreement around the maximum number of cores that can be involved with cancer or the maximum percentage core involvement although there was recognition that T2c disease and extensive disease on mpMRI should exclude men from AS.

DETECTIVE did agree that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, clinical stage [≤ cT2a] and a low number of positive cores) should also be considered for deferred treatment [7]. In this setting, re-biopsy within 6 to 12 months to exclude sampling error is mandatory [652, 654] even if this could be modified in the future [655]. A systematic review and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, which were; PSA density, > 2 positive cores, and African-American race [656].

The DETECTIVE consensus group were clear that those with ISUP 3 disease should not be considered. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [657] and perineal invasion [658] and this view was supported.

6.2.1.1.2 Biological markers

Biological markers, including urine PCA3, transmembrane protease, serine *2-TMPRSS2-ERG* fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [659-661]. However, further data will be needed before such markers can be used in standard clinical practice [167].

6.2.1.1.3 Imaging for treatment selection

In men eligible for AS based upon systematic biopsy findings alone, mpMRI can detect suspicious lesions inducing reclassification at confirmatory biopsy [662, 663]. However, systematic biopsy retains substantial added value at confirmatory biopsy.

A recent meta-analysis evaluated the proportion of men eligible for AS based on systematic TRUS-guided biopsy in whom the cancer was upgraded by MRI-TBx (17%) and systematic biopsy (20%) at confirmatory biopsy [664]. Ten per cent of patients were upgraded by both biopsy methods, meaning MRI-TBx upgraded an additional 7% (95% CI: 5-10%) of men, whilst systematic biopsy upgraded an additional 10% (95% CI: 8-14%) of men. Even if the analysed series used different definitions for csPCa (and thus for cancer upgrading), MRI-TBx and systematic biopsy appear to be complementary to each other, both missing a significant proportion of cancer upgrading or reclassification. Therefore, combining the two biopsy techniques seems the best way to select patients for AS at confirmatory biopsy.

The Active Surveillance Magnetic Resonance Imaging Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated) combined with systematic biopsy, up to 12 cores in total, avoiding oversampling in the MRI arm [665]. The initial report showed little benefit from targeted biopsy. However, after 2 years of follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP ≥ 2 cancer (9.9% vs 23%, p = 0.048) [666].

Upgrading at 1-year confirmatory biopsy by saturation biopsy (24 cores) in combination with MRI-

targeted biopsy (2 cores) was investigated in two subgroups of men eligible for AS [662]. Upgrading in men who were eligible for active surveillance, based on initial 12-core systematic biopsy findings, occurred in 59% (93/157), in contrast to 19% (22/116) upgrading in men eligible based on initial 12-core systematic and MRI-targeted biopsy ($p < 0.001$).

At the DECTECTIVE consensus meeting it was agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy [7].

6.2.1.1.4 Monitoring during active surveillance

The follow-up strategy is based on serial DRE (at least once yearly), PSA (at least once, every 6 months) and repeated biopsy [7]. Several authors have reported data on sequential mpMRI evaluation, summarised in a review [667], the overall upgrading from ISUP 1 to ISUP ≥ 2 PCa was 30% (81/269), following combined targeted and standard biopsies. Upgrading occurred in 39% of patients with MRI showing progression and in 21% of patients with MRI showing stable findings or regression. However, in a recent study not included in this review, an association between mpMRI progression and pathological upgrade was not observed [668]. Data is more limited on unchanged negative mpMRI. In a small study on 75 men included within PRIAS, with an mpMRI at baseline, 46 (61%) had a negative mpMRI. Twenty-six percent (12/46) were reclassified at 12 months by systematic biopsies; however, this reclassification was based on volume ISUP grade 1 in five, and on upgrading to ISUP grade 2 cancers in 7 men [669]. Two other studies on serial negative MRI showed upgrading to ISUP grade 2 in only 2% (1/56) [663] and 5% (2/41) [668].

Data on the combination of serial mpMRI and PSA as a trigger for re-biopsy are even more limited. Using mpMRI and PSA changes as the sole triggers for re-biopsy would have detected only 14/20 (70%) of progressions and resulted in 15 additional biopsy procedures which failed to show pathological progression [670]. Protocol based re-biopsy, without mpMRI or PSA changes, however, detected pathological progressions in 6 out of 87 (6.9%) men. In another study of serial mpMRI in AS, PSA velocity was significantly associated with subsequent requirement for radical therapy in patients with no visible lesions (negative MRI). PSA doubling time was significant in patients with visible lesions (positive MRI). The AUC of PSA velocity for prediction of progression in MRI-negative patients was 0.85 (95% CI: 0.75-0.94); for PSA doubling time in MRI-positive patients, the AUC was 0.65 (95% CI: 0.52-0.78). In patients with no visible lesions on first MRI, a cut-off of 0.5 ng/mL/year in PSA velocity had a sensitivity of 89% (8/9 progressions identified) and a specificity of 75% for progression to radical therapy.

6.2.1.1.5 Active Surveillance - when to change strategy

Men may remain on AS whilst they continue to consent, have a life expectancy of > 10 years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [671] and was recognised as a valid reason for active treatment [7]. More common is the development of other co-morbidities which may result in a decision to transfer to a WW strategy.

A PSA change alone (especially a PSA-DT < 3 years) is a less powerful indicator to change management based on its weak link with grade progression [672, 673]. As a consequence, this should instead trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-mpMRI and biopsy. It was also agreed that changes on follow-up mpMRI needed a confirmatory biopsy before considering active treatment. However, there was no agreement on the histopathology criteria (neither the extent of core involvement nor the number of cores involved) required to trigger a change in management [7].

6.2.1.2 *Guidelines for the treatment of low-risk disease*

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
If required perform mpMRI before a confirmatory biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
Perform digital rectal examination (DRE) every 12 months.	Strong
Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	
Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	
Do not perform a PLND (estimated risk for pN+ ≤ 5%).	Strong
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate, with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
Use intensity-modulated radiation therapy with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy.	Strong
Other therapeutic options	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

6.2.2 *Treatment of Intermediate-risk disease*

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6%, respectively [674].

6.2.2.1 *Active Surveillance*

In the ProtecT trial, up to 22% of the randomised patients in the AM arm had ISUP grade > 1 and 10% a PSA > 10 ng/mL [386]. A Canadian consensus group proposes that low volume ISUP grade 2 (< 10% Gleason pattern 4) may also be considered for AS. These recommendations have been endorsed by the American Society of Clinical Oncology ASCO [675] and the recent DETECTIVE consensus meeting [7] for those with a PSA < 10 ng/mL and low core positivity. However, data is less consistent. It is clear that the presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases although from a low baseline, compared to ISUP grade 1, while a PSA up to 20 ng/mL might be an acceptable threshold [654, 676, 677]. In addition, it is likely that mpMRI and targeted biopsies will detect small focuses of Gleason 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy especially in patients with the longest life expectancy.

6.2.2.2 *Surgery*

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71; 95% CI: 0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32-0.74) were significantly reduced in intermediate-risk PCa at 18 years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality

(HR: 0.69 [95% CI: 0.49-0.98]), but not death from PCa (0.50; 95% CI: 0.21-1.21) at 10 years. The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [678]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [427]. In all other cases eLND can be omitted, which means accepting a low risk of missing positive nodes.

6.2.2.3 Radiation therapy

6.2.2.3.1 Recommended external beam radiation therapy for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) [679-681]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT or VMAT at an escalated dose (76-80 Gy) or a combination of IMRT or VMAT and brachytherapy (see Section 6.2.3.2.3).

6.2.2.3.2 Brachytherapy monotherapy

Low-dose rate brachytherapy can be offered to highly selected patients (ISUP grade 2 with ≤ 33% of biopsy cores involved with cancer), provided they fulfil all the other criteria. Fractionated HDR brachytherapy as monotherapy can be offered to selected patients with intermediate-risk PCa although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [601, 682]. There are no direct data to inform on the use of ADT in this setting.

6.2.2.4 Other options for the primary treatment of intermediate-risk PCa (experimental therapies)

A prospective study on focal therapy using HIFU on patients with localised intermediate-risk disease was recently published [651], but the data was derived from an uncontrolled, single-arm case series. There is a paucity of high certainty data for either whole-gland or focal ablative therapy in the setting of intermediate-risk disease. Consequently, neither whole-gland treatment nor focal treatment can be considered as standard therapy for intermediate-risk patients, and if offered it should only be in the setting of clinical trials [636].

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from EORTC 30891 [678], which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0-4 N0-2 M0 disease. The trial showed a small but statistically significant difference in OS in favour of immediate ADT monotherapy but there was no significant difference in CSS, predominantly because the risk of cancer-specific mortality was low in patients with PSA < 8 ng/mL. Consequently, the use of ADT monotherapy for this group of patients is not considered as standard, even if they are not eligible for radical treatment.

6.2.2.5 Guidelines for the treatment of intermediate-risk disease

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to highly selected patients (< 10% pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with intermediate-risk disease and a life expectancy of > 10 years.	Strong
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
Pelvic lymph node dissection (ePLND)	
Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to selected patients (see Section 6.2.3.2.3); patients without a previous transurethral resection of the prostate, with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term neoadjuvant plus concomitant androgen deprivation therapy (ADT) (4 to 6 months).	Strong
In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak

6.2.3 Treatment of high-risk localised disease

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [683]. When managed with non-curative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [674]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

6.2.3.1 Radical prostatectomy

Provided that the tumour is not fixed to the pelvic wall, or there is no invasion of the urethral sphincter, RP is a reasonable option in selected patients with a low tumour volume. Extended PLND should be performed in all high-risk PCa cases undergoing RP as the estimated risk for positive LNs is > 5% [427]. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment.

6.2.3.1.1 ISUP grade 4-5

The incidence of organ-confined disease is 26-31% in men with an ISUP grade ≥ 4 on systematic biopsy. A high rate of downgrading exists between the biopsy ISUP grade and the ISUP grade of the resected specimen [684]. Several retrospective case series have demonstrated CSS rates over 60% at 15 years after RP in the context of a multi-modal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy ISUP grade 5 [350, 410, 685, 686].

6.2.3.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multi-modal approach demonstrated a CSS at 15 years of over 70% [350, 410, 417, 687-689].

6.2.3.1.3 Radical prostatectomy in cN0 patients who are found to have pathologically confirmed lymph node invasion (pN1)

cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42%, respectively, at 15 years [690-696]. However, this is a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Section 6.2.5.2).

6.2.3.2 External beam radiation therapy

6.2.3.2.1 Recommended external beam radiation therapy treatment policy for high-risk localised PCa

For high-risk localised PCa, use a combined modality approach, consisting of dose-escalated IMRT or VMAT, plus long-term ADT. The duration of ADT has to take into account PS, comorbidities and the number of poor prognostic factors. It is important to recognise that in several studies, EBRT plus short-term ADT did not improve OS in high-risk localised PCa [569, 570, 572], and long-term ADT (at least 2 to 3 years) is currently recommended for these patients.

6.2.3.2.2 Lymph node irradiation in cN0

There is no high level evidence for prophylactic whole-pelvic irradiation, since RCTs have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic LNs in high-risk cases [697-699]. In the RTOG 94-13 study [572], there were no PFS differences between patients treated with whole-pelvic or prostate-only RT, but interactions between whole-pelvic RT and the duration of ADT were reported following the subgroup analysis. Furthermore, in most trials dealing with high-risk PCa, a whole pelvis field was considered standard of care. The benefits of pelvic nodal irradiation using IMRT or VMAT merit further investigation in RCTs as conducted by the RTOG or the UK NCRI group. Performing an ePLND in order to decide whether or not pelvic RT is required (in addition to combined prostate EBRT plus long-term ADT) remains purely experimental in the absence of high level evidence.

6.2.3.2.3 Low-dose rate brachytherapy boost

In men with intermediate- or high-risk PCa, LDR brachytherapy boost with supplemental EBRT and hormonal treatment [700] may be considered. Dose-escalated EBRT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in a randomised trial with 12 months of ADT in both arms [701]. The LDR boost resulted in 5- and 7-year PSA PFS increase (89% and 86%, respectively, compared to 84% and 75%). This improvement came with an increase in late grade 3+ urinary toxicity (18% compared to 8%) [702]. Toxicity was mainly due to urethral strictures and incontinence and great care should be taken during treatment planning.

6.2.3.3 Options other than surgery and radiotherapy for the primary treatment of localised PCa

Currently there is a lack of evidence supporting any other treatment option or focal therapy in localised high-risk PCa.

6.2.3.4 Guidelines for radical treatment of high-risk localised disease

Recommendations	Strength rating
Radical Prostatectomy (RP)	
Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatment	
In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
In patients with high-risk localised disease, use EBRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery and radiotherapy	
Do not offer either whole gland or focal therapy to high-risk patients.	Strong
Do not use ADT monotherapy in asymptomatic patients.	Strong

6.2.4 Treatment of locally advanced PCa

No standard treatment can be defined in the absence of high level evidence. But a local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. The optimal local treatment is still a matter of debate [703]. Randomised controlled trials are only available for EBRT.

6.2.4.1 Surgery

Surgery for locally advanced disease as part of a multi-modal therapy has been reported [684, 704, 705].

However, the comparative oncological effectiveness of RP as part of a multi-modal treatment strategy vs. upfront EBRT with ADT for locally advanced PCa remains unknown, although a prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally advanced (T3) disease is currently recruiting [706]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at 10 years [682, 684, 704, 705, 707-710]. For cT3b-T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [711-713]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0). In case of suspected positive LNs during RP (initially considered cN0), the procedure should not be abandoned since RP may have a survival benefit in these patients. Intra-operative frozen section analysis is not justified in this case [462]. Only limited evidence exists supporting RP for cN+ patients. Moschini *et al.* compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [714]. An ePLND is considered standard if a RP is planned.

6.2.4.2 Radiotherapy for locally advanced PCa

In locally advanced disease, RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS than ADT or RT alone (see Section 6.1.3.1.4 and Tables 6.1.9 and 6.1.10). In clinical or pathological node-positive disease, RT monotherapy is associated with poor outcomes [574], and these patients should receive RT plus long-term ADT. A subgroup analysis from RTOG 85-31 with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic RT with immediate HT had better 5-year (54%) and 9-year (10%) PFS rates vs. 33% and 4%, respectively, for radiation alone ($p < 0.0001$). Multivariate analysis showed that this combination had a statistically significant impact on OS [568]. These findings were also confirmed by the control arm of the STAMPEDE trial (HR: 0.48 [95% CI: 0.29-0.79]) in a non-randomised comparison [715].

6.2.4.3 Treatment of cN1 PCa

The treatment of cN+ PCa was evaluated in a systematic review including 5 studies. Papers addressing LND-proven pelvic nodal metastases after RP for cN0M0 disease and publications including cM+ patients were excluded from the review [716-721].

The findings suggest an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT, as compared to ADT alone, but none of the included studies were RCTs and neither of the two local treatment approaches proved superior in this setting.

6.2.4.4 Options other than surgery and radiotherapy for primary treatment

6.2.4.4.1 Investigational therapies

Currently cryotherapy, HIFU or focal therapies have no place in the management of locally advanced PCa.

6.2.4.4.2 Androgen deprivation therapy monotherapy

The deferred use of ADT as single treatment modality has been answered by the EORTC 30891 trial [678]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS favoured immediate treatment (HR: 1.21 [95% CI: 1.05-1.39]). Surprisingly, no different disease-free or symptom-free survival was observed, raising the question of survival benefit. In locally advanced T3-T4 M0 disease unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < 12 months [678, 722], or those that are symptomatic. The median time to start deferred treatment was 7 years. In the deferred treatment arm, 25.6% died without needing treatment.

6.2.4.4.3 Adjuvant androgen ablation in pN1 disease

6.2.4.4.3.1 Adjuvant androgen ablation alone

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [723, 724]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and the findings may not apply to men with less extensive nodal metastases.

6.2.4.4.3.2 Adjuvant radiotherapy combined with ADT in pN1 disease

In a retrospective multicentre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated “adjuvantly” (within 6 months after surgery irrespective of PSA) with continuous ADT. The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade 2-5 and pT3-4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while

the other subgroups were not [725].

These results were confirmed by a US National Cancer Database analysis based on 5,498 patients [726]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT + EBRT (including pelvic LNs) vs. observation and vs. ADT alone, in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [727].

In a series of 2,596 pN1 patients receiving ADT (n = 1,663) or ADT plus RT (n = 906), combined treatment was associated with improved OS, with a HR of 1.5 for ADT alone [728]. In a SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend to improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [716]. Radiotherapy should be given to the pelvic lymphatics and the prostatic fossa [725, 729-731]. No data is available regarding adjuvant EBRT without ADT.

6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendations	Strength rating
Radical Prostatectomy (RP)	
Offer RP to highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Radiotherapeutic treatments	
In patients with locally advanced cN0 disease, offer radiotherapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer long-term ADT for at least two years.	Weak
Therapeutic options outside surgery and radiotherapy	
Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
Offer patients with cN1 disease a local treatment (either RP or external beam radiation therapy) plus long-term ADT.	Weak

6.2.5 Adjuvant treatment after radical prostatectomy

6.2.5.1 Introduction

Adjuvant treatment is by definition additional to the primary or initial therapy with the aim of decreasing the risk of relapse. Clearly a post-operative detectable PSA is an indication of persistent prostate cells (see Section 6.2.6). All information listed below, refers to patients with a post-operative undetectable PSA.

6.2.5.2 Risk factors for relapse

ISUP score ≥ 2 or patients classified as pT3 pN0 after RP due to positive margins (highest impact), capsule rupture and/or invasion of the seminal vesicles are at high risk of relapse which can be as high as 50% after 5 years [732]. Irrespective of the pT stage, the number of removed nodes [733-740], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [741]. A LN density (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) over 20% was found to be associated with poor prognosis [742]. Finally the number of involved nodes seems to be a major factor for predicting relapse [735, 736, 743], the threshold being considered to be less than 3 positive nodes from an ePLND [425, 735, 743]. However, prospective data are needed before defining a definitive threshold value.

6.2.5.3 Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0)

Four prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g. pT2/pT3 with positive surgical margins and GS 8-10) post-RP (Table 6.2.5.1). In the ARO 96-02 trial, 80% of the pT3/R1/GS 8-10 patients randomised to observation developed BCR within 10 years. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial, representing a major limitation in interpretation, as patients with a detectable PSA would now be considered for salvage therapy rather than adjuvant radiotherapy (ART) [744]. Therefore, for patients at increased risk of local relapse, who present with a PSA level of < 0.1 ng/mL,

two options can be offered in the framework of informed consent.
These are:

- Immediate ART to the surgical bed after recovery of urinary function, during the first 6 months post-surgery [744-746];

or

- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [747, 748] (see Section 6.3.5.1 on Salvage EBRT).

Table 6.2.5.1: Overview of all four randomised trials for adjuvant surgical bed radiation therapy after RP* (without ADT)

Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [744]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% (p < 0.05)	10 yr.: 74% vs. 66% Median time: 15.2 vs. 13.3 yr., p = 0.023
EORTC 22911 2012 [745]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% (p < 0.001)	81% vs. 77% n.s.
ARO 96-02 2014 [746]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr.: 56% vs. 35% (p = 0.0001)	10 yr.: 82% vs. 86% n.s.
FinnProstate Group 2019 [749]	250	pT2,R1/ pT3a	66.6 Gy vs. observation (+SRT)	> 0.4 (in 2 successive measurements)	112 vs. 103 (patients alive)	10 yr.: 82% vs. 61% p < 0.001	10 yr.: 92% vs. 87% n.s.

**See Section 6.3.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.*
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

Preliminary data from RAVES and RADICALS, as well as a meta-analysis combining all findings have been reported, suggesting that SRT and ART offer similar outcomes for event-free survival [750-752]. Full publications are needed before any further conclusions can be drawn. Until then, ART remains a recommended treatment option in highly selected patients with combined high-risk features, such as pT3/R1/GS 8-10.

6.2.5.4 Adjuvant androgen ablation

6.2.5.4.1 Adjuvant androgen ablation in men with N0 disease

Adjuvant androgen ablation with bicalutamide 150 mg daily did not improve PFS in localised disease while it did for locally advanced disease after RT. However this never translated to an OS benefit [753]. A systematic review showed a possible benefit for PFS, but not OS for adjuvant androgen ablation [522].

6.2.5.5 Adjuvant chemotherapy

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A recent phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [754]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [755].

6.2.5.6 Guidelines for adjuvant treatment options after radical prostatectomy

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients.	Strong
Offer adjuvant external-beam radiation therapy to the surgical field to highly selected patients.	Strong
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional radiotherapy; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

6.2.5.7 Guidelines for non-curative or palliative treatments in prostate cancer

Recommendations	LE	Strength rating
Watchful waiting (WW) for localised prostate cancer		
Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	1b	Strong
Watchful waiting for locally advanced prostate cancer		
Offer a deferred treatment policy using androgen deprivation (ADT) monotherapy to M0 asymptomatic patients with a prostate-specific antigen (PSA) doubling time > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment.	1b	Weak

6.2.6 Persistent PSA after radical prostatectomy

6.2.6.1 Introduction

Between 5 and 20% of men continue to have detectable or persistent PSA after RP (when defined in the majority of studies as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery) [756, 757]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

6.2.6.2 Natural history of persistently elevated PSA after RP

Several studies (See table 6.2.6.1) have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins (PSM), pathologic stage ≥ T3a, positive nodal status and/or pathologic ISUP grade ≥ 3) and poor prognosis. Initially defined as ≥ 0.1 ng/mL, improvements in the sensitivity of PSA assays now allow for the detection of PSA at much lower levels.

Moreira *et al.* demonstrated that failure to achieve a PSA of less than 0.03 ng/mL within 6 months of surgery was associated with an increased risk of BCR and overall mortality [758, 759]. However, since the majority of the published literature is based on the ≥ 0.1 ng/mL PSA cut-off, there is significantly more long-term data for this definition.

Predictors of PSA persistence were higher BMI, higher pre-operative PSA and ISUP grade ≥ 3 [759]. In patients with PSA persistence, one and 5-year BCR-free survival were 68% and 36%, compared to 95% and 72%, respectively, in men without PSA persistence [758]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively. In line with these data, Ploussard *et al.* reported that approximately 74% of patients with persistent PSA develop BCR [756]. Spratt *et al.* confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [760]. Of 150 patients with a persistent PSA, 95% received RT before detectable metastasis. In a multivariable analysis, the presence of a persistently detectable PSA post-RP was associated with a 4-fold increase in the risk of developing metastasis. This was confirmed by recent data from Preisser *et al.* who showed that persistent PSA is prognostic of an increased risk of metastasis and death [761]. At 15 years after RP, metastasis-free survival rates, OS and CSS rates were 53.0 vs. 93.2% ($p < 0.001$), 64.7 vs. 81.2% ($p < 0.001$) and 75.5 vs. 96.2% ($p < 0.001$) for persistent vs. undetectable PSA, respectively. The median follow-up was 61.8 months for patients with undetectable PSA vs. 46.4 months for patients with persistent PSA. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$) and cancer-specific death (HR: 3.15, $p < 0.001$).

However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al.* showed that 5-year BCR-free survival for men who had a persistent PSA level > 0.1 but ≤ 0.2 ng/mL at 6-8 weeks after RP and were monitored was 50% [762].

Rogers *et al.* assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [763]. No patient received adjuvant therapy before documented metastasis. In their study, 38% of patients had no evidence of metastases for ≥ 7 years while 32% of the patients were reported to develop metastases within 3 years. Noteworthy is that a significant proportion of patients had low-risk disease. In multivariable analysis, the PSA slope after RP (as calculated using PSA levels 3 to 12 months after surgery) and pathological ISUP grade were significantly associated with the development of distant metastases.

Table 6.2.6.1: Studies on the natural history of patients with persistent PSA after RP

Authors	Study population	n	Definition PSA persistence	Treatment	Outcome	Other details/comments
Ploussard *et al.*, J Urol 2013 [756]	496 men pN0 with persistent PSA 14 centres 1998 - 2011		PSA ≥ 0.1 ng/mL at 6 wk.		74.4% with BCR 5% with metastasis	
Moreira *et al.*, BJUI 2010 [759]	901 men Shared Equal Access Regional Cancer Hospital (SEARCH) database. 2001-2008	230 (8 pN1)	PSA persistence definition of a PSA nadir ≥ 0.03 ng/mL,	No RT info	Increased risk for BCR after surgery	Relative to men with undetectable PSA levels, those with a PSA nadir of 0.03 (HR: 3.88, p < 0.001), 0.04 (HR: 4.87, p < 0.001), 0.05-0.09 (HR: 12.69, p < 0.001), 0.1-0.19 (HR: 13.17, p < 0.001), and 0.2 ng/mL (HR: 13.23, p < 0.001) were at increased risk of BCR while men with a nadir of 0.01 (HR: 1.36, p = 0.400) and 0.02 (HR: 1.64, p = 0.180) were not.
Moreira *et al.*, J Urol 2009 [758]	1,156 men Shared Equal Access Regional Cancer Hospital (SEARCH) database. After 1997	291 (10 pN1)	PSA > 0.03 ng/mL within 6 mo.	No RT info	Increased BCR and overall mortality	Median FU 48 mo. In patients with persistent PSA 1 and 5-yr. BFS was 68% and 36%, significantly lower than 95% and 72%, respectively, in men without persistent PSA. 10-year OS in patients with vs. without persistent PSA was 63% vs. 80%. In men with persistent PSA independent predictors of BCR were higher PSA nadir (HR: 2.19, p < 0.001), positive surgical margins (HR: 1.75, p = 0.022) and high pathological ISUP grade (4-5 vs. 1, HR: 2.40, p = 0.026). Independent predictors of OM were a higher PSA nadir (HR: 1.46, p 0.013) and seminal vesicle invasion (HR: 3.15, p = 0.047)

Rogers *et al.*, Cancer 2004 [763]	224 men Single centre (Johns Hopkins) 1989 - 2002	160 men (58 pN1)	PSA ≥ 0.1 ng/mL at 3 mo.	No treatment before onset of metastasis	Metastasis-free survival at 3, 5 and 10 yr. was 68%, 49%, and 22%, respectively.	Mean FU 5.3 yr. 75 men (47%) developed distant metastases after RP (median time to metastases 5.0 yr.; range, 0.5-13 yr.). The slope of PSA changes approximately 3-12 mo. after RP at a cut-off value ≥ 0.05 ng/mL was found to be predictive of distant metastasis-free survival (HR: 2.9, p < 0.01).

BCR = biochemical recurrence; FU = follow-up; HR = hazard ratio; mo = months; n = number of patients; OM = overall mortality; PSA = prostate-specific antigen; RT = radiotherapy.

6.2.6.3 Imaging in patients with persistently elevated PSA after RP

Standard imaging with bone scan and MRI has a low pick-up rate for men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with a positivity rate of 33%, 46%, 57%, 82%, and 97%, in men with post-RP PSA ranges of 0-0.19, 0.2-0.49, 0.5-0.99, 1-1.99, and ≥ 2ng/mL, respectively [325, 764-768] which can guide salvage radiation therapy (SRT) planning [769]. Using this, Schmidt-Hegemann *et al.* studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP [770]. Interestingly, men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease.

6.2.6.4 Impact of post-operative RT and/or ADT in patients with persistent PSA

The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs, however, it would appear that men with a persistent PSA do less well than men with BCR undergoing RT.

Wiegel *et al.* [757] showed that following salvage RT to the prostate bed, patients with a detectable PSA after RP had significantly worse oncological outcomes when compared with those who achieved an undetectable PSA. Ten-year metastasis-free survival was 67% vs. 83% and OS was 68% vs. 84%, respectively. Recent data from Preisser *et al.* [761] also compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with salvage RT vs. no RT, OS rates at 10 years after RP were 86.6 vs. 72.6% in the entire cohort (p < 0.01), 86.3 vs. 60.0% in patients with positive surgical margin (p = 0.02), 77.8 vs. 49.0% in pT3b disease (p < 0.001), 79.3 vs. 55.8% in ISUP grade 1 disease (p < 0.01) and 87.4 vs. 50.5% in pN1 disease (p < 0.01), for salvage RT and no RT, respectively. Moreover, CSS rates at 10 years after RP were 93.7 vs. 81.6% in the entire cohort (p < 0.01), 90.8 vs. 69.7% in patients with positive surgical margin (p = 0.04), 82.7 vs. 55.3% in pT3b disease (p < 0.01), 85.4 vs. 69.7% in ISUP grade 1 disease (p < 0.01) and 96.2 vs. 55.8% in pN1 disease (p < 0.01), for salvage RT and no RT, respectively. In multivariable models, after 1:1 propensity score matching, salvage RT was associated with lower risk for death (HR: 0.42, p = 0.02) and lower cancer-specific death (HR: 0.29, p = 0.03). These survival outcomes for patients with persistent PSA who underwent SRT suggest they benefit although outcomes are worse than for men experiencing BCR.

It is clear from a number of studies [757, 771-775] that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade ≥ 4 in the RP histology and pT3b disease. Fossati *et al.* suggested that only men with a persistent PSA after RP and ISUP grade ≤ 3 benefited significantly [776], although this is not supported by Preisser *et al.* [761]. The current data does not allow making any clear treatment decisions.

Addition of ADT may improve PFS [771]. Choo *et al.* studied the addition of 2-year ADT to immediate RT to the prostate bed for patients with pathologic T3 disease (pT3) and/or positive surgical margins after RP [771]. Twenty-nine of 78 included patients had persistently detectable post-operative PSA. The relapse-free rate was 85% at 5 years and 68% at 7 years, which was superior to the 5-year progression-free estimates of 74% and 61% in the post-operative RT arms of the EORTC and the SWOG studies, respectively, which included patients with undetectable PSA after RP [744, 745]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12% of the study cohorts in the EORTC and the SWOG studies, respectively.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only with 66 Gy per protocol (arm C). The 10-year clinical relapse-free survival was 63% [757]. The

GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2-2.0 ng/mL) reported good tolerability of the combined treatment. The oncological end-points are yet to be published [777].

6.2.6.5 Conclusion

The available data, suggests that patients with PSA persistence after RP may benefit from early aggressive multi-modality treatment, however, the lack of prospective RCTs makes firm recommendations difficult.

6.2.6.6 Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.3 Management of PSA-only recurrence after treatment with curative intent

The follow-up policy is described in Chapter 7 and will not be discussed here.

6.3.1 Background

Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.3.2 Definitions of clinically relevant PSA relapse

The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR end-points when comparing treatments.

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [778-780]. However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients. After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [781].

After HIFU or cryotherapy no end-points have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [782].

6.3.3 Natural history of biochemical recurrence

Once a PSA relapse has been diagnosed, it is important to determine, whether the recurrence has developed at local or distant sites. A recent systematic review and meta-analysis investigated the impact of BCR on hard end-points and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [782]. However, the effect size of BCR as a risk factor for mortality is highly variable. After primary RP, its impact ranges from HR 1.03 (95% CI: 1.004-1.06) to HR 2.32 (95% CI: 1.45-3.71) [783, 784]. After primary RT, OS rates are approximately 20% lower at 8 to 10 years follow-up, even in men with minimal comorbidity [785, 786]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, PCa-specific - and overall mortality may be predicted by the initial clinical and pathologic factors (e.g. T-category, PSA, ISUP grade) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by this systematic review [782].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors:

- distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP grade, high pT category, short PSA-DT, high pre-sRT PSA;

- prostate-cancer-specific mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure as defined by investigators, short PSA-DT;
- overall mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure, high PSA-DT.

For patients with biochemical recurrence after RT, the corresponding outcomes are:
- distant metastatic recurrence: high biopsy ISUP grade, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure;
- overall mortality: high age, high biopsy ISUP grade, short interval to biochemical failure, high initial (pre-treatment) PSA.

Based on the meta-analysis, proposal is to stratify patients into EAU Low-Risk BCR (PSA-DT > 1 year AND pathological ISUP grade < 4 for RP; interval to biochemical failure > 18 months AND biopsy ISUP grade < 4 for RT) or EAU High-Risk BCR (PSA-DT < 1 year OR pathological ISUP grade 4-5 for RP, interval to biochemical failure < 18 months OR biopsy ISUP grade 4-5 for RT), since not all patients with BCR will have similar outcomes. The stratification into "EAU Low-Risk" or "EAU High-Risk" BCR has recently been validated in a European cohort [787].

6.3.4 The role of imaging in PSA-only recurrence

Imaging is only of value if it leads to a treatment change and therefore to a better outcome. In practice, limited data are available regarding the outcome based on imaging at relapse.

6.3.4.1 Assessment of metastases

6.3.4.1.1 Bone scan and abdominopelvic CT

Because BCR after RP or RT precedes clinical metastases by 7 to 8 years on average [737, 788], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [789]. In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [790, 791].

Only 11-14% of patients with BCR after RP have a positive CT [790]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT were 27.4 ng/mL and 1.8 ng/mL/month, respectively [792].

6.3.4.1.2 Choline PET/CT

In two different meta-analyses, the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86-89% and 89-93%, respectively [793, 794].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [795] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [796]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [330]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.2). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [337, 797, 798]. In patients with BCR after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. Despite its limitations, choline PET/CT may change medical management in 18-48% of patients with BCR after primary treatment [799-801].

Choline PET/CT should only be recommended in patients fit enough for curative loco-regional salvage treatment. The sensitivity of choline PET is well known to be strongly influenced by PSA level and kinetics and drops to sub-optimal values in patients with a low PSA [798]; after RP a possible PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL [798].

6.3.4.1.3 Fluoride PET and PET/CT

^{18}F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [802]. However, ^{18}F-NaF PET is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [803].

6.3.4.1.4 Fluciclovine PET/CT

^{18}F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [804]. In a recent multicentre trial evaluating 596 patients with BCR in a mixed population (33.3% after RP, 59.5% after RT ± RP, 7.1% other), fluciclovine PET/CT showed an overall detection rate of 67.7%, with a sensitivity of 62.7% (95% CI: 56-69%); lesions could be visualised either at local level (38.7%) or in LNs and

bones (9%) [805]. As for Choline PET/CT, fluciclovine PET/CT sensitivity is dependent on the PSA level, with a sensitivity likely inferior to 50% at PSA < 1 ng/mL.

It is noteworthy that ^{18}F-fluciclovine has been approved in the US and Europe, and therefore it is currently the only PCa-specific radiotracer widely commercially available.

6.3.4.1.5 Prostate-specific membrane antigen PET/CT

Prostate-specific membrane antigen PET/CT has shown good potential in patients with BCR, although most studies are limited by their retrospective design. Reported predictors of ^{68}Ga-PSMA PET in the recurrence setting were recently updated in a high-volume series [325]. Scan positivity of ^{68}Ga-PSMA PET scans increased with higher PSA levels, reaching 33% (95% CI: 16-51), 45% (95% CI: 39-52), 59% (95% CI: 50-68), 75% (95% CI: 66-84), and 95% (95% CI: 92-97), for PSA categories 0-0.19, 0.2-0.49, 0.5-0.99, 1-1.99, and ≥ 2 ng/mL, respectively. Gleason sum was not a strong predictor of a positive ^{68}Ga-PSMA PET scan. Positivity rates in the prostate bed were significantly different in patients after RP (22%) and RT (52%). High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [806, 807]. PSMA PET/CT identified the site of recurrence in 59 of 88 patients (67%) in a recent prospective trial [808]. A higher PSA velocity seems associated with higher PSMA PET/CT-positivity rates [325, 765].

In a prospective multicentre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [343]. A recent prospective study in a subgroup of 119 BCR patients with low PSA (< 0.5 ng/mL) reported a change in the intended treatment in 30.2% of patients [764]; however, no data exist on the impact on final outcome. Another prospective study in 272 patients with early biochemical recurrent PCa after RP showed that ^{68}Ga-PSMA-ligand PET/CT may tailor further therapy decisions (e.g., local vs. systemic treatment) at low PSA values (0.2 to 1 ng/mL) [766].

A single-centre study retrospectively assessed 164 men from a prospectively-acquired database who underwent imaging with PSMA PET/CT for a rising PSA after RP with PSA levels < 0.5 ng/mL. In men with a negative PSMA PET/CT who received salvage RT, 85% (23 out of 27) demonstrated a treatment response, compared to a further PSA increase in 65% of those not treated (22 out of 34). In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (29 out of 36) responded to salvage RT [809]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to the prostate) and poor response (positive nodes or distant disease) to salvage RT.

It is worth noting that the term “PSMA PET” refers to several different radiopharmaceuticals; the majority of published studies used ^{68}Ga-PSMA-11 [325, 764-766, 809, 810] but other authors are reporting data with ^{18}F-labelled PSMA [767, 768]. At present there are no conclusive data about comparison of such tracers [811].

6.3.4.1.6 Whole-body and axial MRI

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [812]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

6.3.4.2 Assessment of local recurrences

6.3.4.2.1 Local recurrence after radical prostatectomy

Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [789], salvage RT is usually decided on the basis of BCR without histological proof of local recurrence. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Therefore, most patients undergo salvage RT without local imaging.

Multiparametric MRI can detect local recurrences in the prostatic bed, but its sensitivity in patients with a PSA level < 0.5 ng/mL remains controversial [813, 814]. Choline PET/CT is less sensitive than mpMRI when the PSA level is < 1 ng/mL [815]. PSMA PET/CT is positive in 15-58% of patients with BCR and PSA levels < 0.5 ng/mL, but published series are difficult to interpret since they usually mix patients with a history of RP and RT [768, 806, 816]. Recent data support the potential role of PSMA PET/CT especially for the identification of distant metastases; even at PSA levels < 0.5 ng/mL [764]. A recent systematic review and meta-analysis on ^{68}Ga-PSMA PET in advanced PCa revealed a scan positivity-rate in up to 46% in patients with BCR after prostatectomy and PSA levels < 0.5 ng/mL [325].

Precise detection and location of local recurrences after RP will be needed but not until it has been proven that stereotaxic boost to the recurrence site during salvage RT improves the patient outcome which, so far, remains investigational.

6.3.4.2.2 Local recurrence after radiation therapy

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [789].

Transrectal US is not reliable in identifying local recurrence after RT. In contrast, mpMRI has yielded excellent results and can be used for biopsy targeting and guiding local salvage treatment [789, 817-819] even if it slightly underestimates the volume of the local recurrence [820]. Detection of recurrent cancer is also feasible with choline PET/CT [821], but choline PET/CT has not been compared to mpMRI yet. Prostate-specific membrane antigen PET/CT can play a role in the detection of local recurrences after RT [325], but data are still limited by a lack of robust results from well-designed trials.

6.3.4.3 Summary of evidence on imaging in case of biochemical recurrence

In patients with BCR, imaging has the potential to play a role in detecting both distant metastases and local recurrence. Early detection of metastases in a BCR setting is clinically highly relevant, either after RT or after RP in order to optimise salvage treatment. Many recent studies suggest that PSMA PET/CT is substantially more sensitive than abdominopelvic CT, bone scan and choline PET/CT in the detection of distant metastases in patients with BCR. Although most studies are retrospective and/or monocentric, they all come to the same conclusion as confirmed by a recent systematic review [822]. After RP, compared to choline PET/CT, PSMA PET/CT showed high positivity rates, even for PSA levels < 1 ng/mL. Following RT, mpMRI is the best technique to evaluate local recurrence, to guide targeted biopsies and to plan salvage treatment strategies [823].

6.3.4.4 Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	**LE**	**Strength rating**
Perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	2b	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.		Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	3	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	2b	Strong

6.3.5 Treatment of PSA-only recurrences

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.3.5.1 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.* reported a 75% reduced risk of systemic progression with SRT, when comparing 856 SRT patients with 1,801 non-SRT patients [824]. The RAVES and RADICAL trials assessing SRT in post-RP patients with PSA levels exceeding 0.1-0.2 ng/mL showed 5-year freedom from BCR and BCR-free survival rates of 88% [750, 751].

The PSA level at BCR was shown to be prognostic [824]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [825-828], corresponding to a ~80% chance of being progression-free 5 years later [748]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or salvage RT alone (n = 160) within 2 years of BCR showed that salvage RT was associated with a 3-fold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage RT has been shown to be effective mainly in patients with a short PSA-DT [829]. According to an EAU review which also proposed a scoring system [782], men with a PSA-DT > 1 year and a pathological GS (pGS) < 8 have a significantly lower risk of clinical progression and can be classified as 'EAU low risk"; men with a PSA-DT ≤ 1 year or a pGS 8-10 are at increased risk of clinical progression and should be classified as 'EAU high risk'. These definitions have been externally validated and may be helpful for individualised treatment decisions [787]. Despite the indication for salvage RT, a "wait and see" strategy remains an option in patients with a PSA-DT of more than 12 months and other favourable factors such a time to BCR > 3 years, ≤ pT3a,

ISUP grade ≤ 2/3 [782, 830]. For an overview see Table 6.3.1.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease specific- and OS are more meaningful end-points to support clinical decision making. A systematic review and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and PCa-specific mortality. In particular SRT should be initiated in patients with rapid PSA kinetics after RP and with a PSA cut-off of 0.4 ng/mL [782]. A recent, international multi-institutional, analysis of pooled data from RCTs has suggested that metastasis-free survival is the most valid surrogate end-point with respect to impact on OS [831, 832]. Table 6.3.2 summarises results of recent studies on clinical end-points after SRT.

Table 6.3.1: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy (SRT) PSA level*

Reference	Year	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, *et al.* [833]	2017	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Soto, *et al.* [834]	2012	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, *et al.* [825]	2016	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Tendulkar, *et al.* [835]	2016	2,460	60	0.5	66 Gy 16% ADT	56% (5)	SRT; PSA < 0.2 ng/mL 71% 0.21-0.5 ng/mL 63% 0.51-1.0 ng/mL 54% 1.01-2.0 ng/mL 43% > 2 ng/mL 37% p < 0.001

** Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.*
ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; yr = year.

Table 6.3.2: Recent studies reporting clinical end-points after SRT (the majority of included patients did not receive ADT)

Reference	Year	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, *et al.* [833]	2017	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005

Jackson, *et al.*[836]	2014	448	64	68.4 Gy no ADT	5 yr. DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr. DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001
Stish, *et al.* [825]	2016	1,106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr. DM SRT: PSA ≤ 0.5 ng/mL 7% and 12% SRT: PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr. DSM SRT: PSA ≤ 0.5 ng/mL < 1% and 6% SRT: PSA > 0.5 ng/mL 5% and 10% p = 0.02 5 and 8.9 yr. OS SRT: PSA ≤ 0.5 ng/mL 94% and 86% SRT: PSA > 0.5 ng/mL 91% and 78% p = 0.14
Tendulkar, *et al.* [835]	2016	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10 yr. DM SRT: PSA 0.01-0.2 ng/mL 9% SRT: PSA 0.21-0.50 ng/mL 15% SRT: PSA 0.51-1.0 ng/mL 19% SRT: PSA 1.01-2.0 ng/mL 20% SRT: PSA > 2 ng/mL 37%, p < 0.001

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; FU = follow up; mo. = month; n = number of patients; OS = overall survival; PSA = prostate specific antigen; SRT = salvage radiotherapy.

6.3.5.2 Salvage radiotherapy combined with androgen deprivation therapy

Data from RTOG 9601 [837] suggest both CSS and OS benefit when adding 2 years of bicalutamide (150 mg daily) to SRT. According to GETUG-AFU 16, also 6 months treatment with a LHRH-analogue can significantly improve 10-year BCR, biochemical PFS and, modestly, metastasis-free survival (MFS). However, SRT combined with either goserelin or placebo, showed similar DSS and OS rates [838]. Table 6.3.3 provides an overview of these two RCTs.

These RCTs support adding ADT to SRT. However when interpreting these data, it has to be kept in mind that RTOG 9601 used outdated radiation dosages (< 66 Gy) and technique. The question with respect to the patient risk profile, whether to offer combination treatment, or not, and the optimal combination (LHRH or bicalutamide) remains, as yet, unsolved. The EAU risk classification may offer guidance in this respect [782, 787].

One of these RCTs reports improved OS and the other one improved MFS but due to methodological discrepancies, also related to follow-up and risk patterns, it is, as yet, not evident which patients should receive ADT, which type of ADT and for how long. Men at high risk of further progression (e.g. with a PSA ≥ 0.7 ng/mL and GS ≥ 8) may benefit from SRT combined with two years of ADT; for those at lower risk (e.g. PSA < 0.7 ng/mL and GS 8) SRT combined with 6 months of ADT may be sufficient. Men with a low-risk profile (PSA < 0.5 ng/mL and GS < 8) may receive SRT alone.

A recent review addressing the benefit from combining HT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6-1, > 1 ng/mL), margin status, and ISUP grade, as a framework to individualise treatment [839]. In a retrospective multicentre-study including 525 patients, only in patients with more aggressive disease characteristics (pT3b/4 and ISUP grade > 4 or pT3b/4 and PSA at early SRT > 0.4 ng/mL) the administration of concomitant ADT was associated with a reduction in distant metastasis [840]. Similarly, in a retrospective analysis of 1,125 patients, stage ≥ pT3b, GS ≥ 8 and a PSA level at SRT > 5 ng/mL were identified as risk factors for clinical recurrence. A significant effect of long-term ADT was observed in patients with ≥ 2 adverse features. For patients with a single risk factor, short-term HT was

sufficient whilst patients without risk factors showed no significant benefit from concomitant ADT [841].

Table 6.3.3: RCTs comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone

Reference	Year	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 Carrie, *et al.* [838]	2019	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89%, ISUP grade ≥ 4 11% cN0	112	66 Gy + GnRH analogue 6 mo. 66 Gy	10 yr. PFS 64% p < 0.0001 10 yr. PFS 49% 10 yr. MFS 75% p = 0.034 10 yr. MFS 69%
RTOG 9601 Shipley, *et al.* [837]	2017	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo. 64.8 Gy + placebo	12 yr. DM 14% p = 0.005 12 yr. DM 23% 12 yr. OS 76% p = 0.04 12 yr. OS 71% 12 yr. DSM 5.8% p < 0.001 12 yr. DSM 13.4%

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FU = follow-up; GnRH = gonadotropin-releasing hormone; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year.

6.3.5.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for "clinical target volumes" of PCa [842-845] and for organs at risk of normal tissue complications [846]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not MFS has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [847].

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP) [826, 848]. In a SR, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level [849]. The combination of pT stage, margin status and ISUP grade and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [850-852]. In a study on 894 node-negative PCa patients, doses ranging from 64 to ≥ 74 Gy were assigned to twelve risk groups, defined by their pre-SRT PSA classes < 0.1, 0.1-0.2, 0.2-0.4, and > 0.4 ng/mL and ISUP grade, ≤ 1 vs. 2/3 vs. ≥ 4 [853]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [835].

Salvage RT is also associated with toxicity. In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract. Severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [833].

In a RCT on dose escalation for SRT involving 350 patients, acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastrointestinal tract toxicity of grades 2 and 3 occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects have yet to be reported [854, 855].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side-effects, especially genitourinary symptoms, clearly increases, even with newer planning and treatment techniques [856, 857]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02), but had no differential effect on the relatively high level of GU toxicity (5-year, 3D-CRT

15.8% vs. IMRT 16.8%) [856]. After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for genitourinary and 8% for gastrointestinal symptoms, respectively [857]. Doses of at least 66 Gy, and up to 72 Gy can be recommended [833, 854].

6.3.5.2.2 Comparison of adjuvant radiotherapy and salvage radiotherapy

The largest retrospective risk-matched study evaluating ART vs. early SRT comprised 510 pT3N0 R0/R1 patients (ADT was excluded). With a median follow-up of 94 months, MFS did not differ significantly when comparing 243 patients who had ART and 267 patients who had SRT at a PSA < 0.5 ng/mL (92% vs. 91%, p = 0.9) or OS (89% vs. 92%, p = 0.9). Conclusion was that early salvage RT does not impair PCa control but clearly helps reducing over-treatment, which is a major issue in both ART and in SRT [851]. Similarly, Buscarillo *et al.* reported no difference in MFS or OS among two groups of 149 propensity-matched PCa patients with adverse pathologic features [858]. However, these retrospective studies are underpowered for high-risk cases such as pT3b/R1/ ISUP grade 4-5. In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5 ng/mL, ART given at an undetectable PSA (< 0.1 ng/mL) improved all three end-points, biochemically no evidence of disease, MFS, and OS [859].

Both approaches (ART and SRT) together with the efficacy of adjuvant ADT are currently being compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG 17). Preliminary data from RAVES and RADICALS, as well as a meta-analysis combining all three RCTs have been presented, suggesting that SRT and ART offer similar outcomes for event-free survival [750-752]. Full publications are needed before any further conclusions can be drawn. Until then, ART remains a recommended treatment option in highly selected patients with combined high-risk features, such as pT3/R1/ GS 8-10.

6.3.5.2.3 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as salvage RP (SRP), cryotherapy, interstitial brachytherapy and HIFU [860-869]. As the available evidence for these treatment options is of low quality, strong recommendations regarding the choice of any of these techniques cannot be made as. The following is an overview of the most important findings for each of these techniques with a proposal for their indications.

6.3.5.3 Salvage radical prostatectomy

Salvage RP after RT has the best likelihood of achieving local control relative to other salvage treatments. However, this must be weighed against the possible adverse events, which are increased compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation.

6.3.5.3.1 Oncological outcomes

In a systematic review of the literature, Chade, *et al.* showed that SRP provided 5- and 10-year BCR-free survival estimates ranging from 47-82% and from 28-53%, respectively. The 10-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy ISUP grade were the strongest predictors of the presence of organ-confined disease, progression, and CSS [870].

In most contemporary series, organ-confined disease, negative surgical margins, and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [869].

Table 6.3.4: Oncological results of selected salvage radical prostatectomy case series, including at least 30 patients

Reference	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability (yr.)
Sanderson, *et al.* 2006 [871]	51	-	25	36	28	47	-	5
Leonardo, *et al.* 2009 [872]	32	35	53	34	0	75	-	3
Heidenreich, *et al.* 2010 [868]	55	23 (2-56)	73	11	20	87	-	2
Chade, *et al.* 2011 [873]	404	55	55	25	16	37	83	10
Mandel, *et al.* 2016 [874]	55	36	50	27	22	49	89	5

BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin.

6.3.5.3.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [875]. In more recent series, these complications appear to be less common [867, 870]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [870].

Table 6.3.5: Peri-operative morbidity in selected salvage radical prostatectomy case series, including at least 30 patients

Reference	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Stephenson, *et al.* 2004 [867]	100	15 vs. 2*	30	33 vs. 13*	-
Ward, *et al.* 2005 [876]	138	5	22	-	-
Sanderson, *et al.* 2006 [871]	51	2	41	6	-
Gotto, *et al.* 2010 [875]	98	9	41	25	-
Heidenreich, *et al.* 2010 [868]	55	2	11	3.6	360 (150-1450)

** SRP performed before vs. after 1993.*
n = number of patients.

6.3.5.3.3 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRP PSA < 10 ng/mL and biopsy ISUP grade ≤ 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2 [870]. A meta-regression analysis suggested that SRP may be associated with worse continence outcomes than non-surgical approaches [877].

6.3.5.4 Salvage cryoablation of the prostate

6.3.5.4.1 Oncological outcomes

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year biochemical DFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [878]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year BCR-free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [879].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The 5-year OS was significantly higher in the SRP group (95% vs. 85%) [880].

Table 6.3.6: Oncological results of selected salvage cryoablation of the prostate case series, including at least 50 patients

Reference	n	Median FU (mo)	BCR-free probability (%)	Time probability (yr.)	Definition of failure
Pisters, *et al.* 1997 [880]	150	17	44	-	Nadir + 0.2
Bahn, *et al.* 2003 [881]	59	82	59	7	PSA > 0.5
Ismail, *et al.* 2007 [878]	100	33	73 (low risk)	5	ASTRO
Pisters, *et al.* 2008 [879]	279	22	58	5	ASTRO and Phoenix
Williams, *et al.* 2011 [882]	187	7.46 yr.	39	10	Nadir +2
Spiess, *et al.* 2010 [883]	450	40.8	34	-	PSA > 0.5

ASTRO = American Society for Therapeutic Radiology and Oncology; BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; PSA = prostate-specific antigen; yr. = year.

6.3.5.4.2 Morbidity

According to Cespedes, *et al.*, the risks of urinary incontinence and ED at at least 12 months after SCAP were as high as 28% and 90%, respectively [884]. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In an on-line registry by Pisters, *et al.*, urinary incontinence rates were 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients requiring a TURP for removal of sloughed tissue [879]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.3.5) [885].

Table 6.3.7: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage cryoablation of the prostate case series, including at least 50 patients

Reference	n	Incontinence (%)	Obstruction/ Retention (%)	Rectourethral fistula (%)	ED (%)
Pisters, *et al.* 1997 [886]	150	73	67	1	72
Bahn, *et al.* 2003 [881]	59	8	-	3.4	-
Ismail, *et al.* 2007 [878]	100	13	4	1	-
Pisters, *et al.* 2008 [879]	279	4.4	3.2	1.2	-
Ahmad, *et al.* 2013 [887]	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.3.5.4.3 Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an initial organ-confined PCa cT1c to cT2, initial ISUP grade ≤ 2/3, a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL.

6.3.5.5 Salvage brachytherapy for radiotherapy failure

Although there is no role for salvage EBRT following local recurrence after previous definitive RT, in carefully selected patients with a good PS, primary localised PCa and histologically proven local recurrence (based on Phoenix criteria [885]), HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [888-890]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR brachytherapy over a period of 9 years [888]. With a median follow-up of 60 months the 5-year biochemical control was 51% and only 2% grade 3 genitourinary toxicities were reported (Phoenix criteria). Comparable with these data, 42 patients were treated in a phase II trial at MSKCC in New York [891]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after 5 years was 69% (median follow-up 36 months). Grade 2 late side-effects were seen in 15% and one patient developed grade 3 incontinence. However, older data with higher rates of side-effects have been reported [892].

Using LDR brachytherapy with ^{103}palladium, long-term outcome was reported in 37 patients with a median follow-up of 86 months [889]. The biochemical control rate after 10 years was 54%. However, the crude rate of ≥ grade 2 toxicity was 46% and ≥ grade 3 toxicity was 11%. These side-effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side-effects seem to be lower with HDR brachytherapy [893]. In conclusion, freedom from BCR

after salvage HDR- and LDR brachytherapy is promising and the rate of severe side-effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.3.5.6 Salvage high-intensity focused ultrasound

6.3.5.6.1 Oncological outcomes

Salvage HIFU has more recently emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data were generated by one high-volume centre. Median follow-up was very short, and outcome measures were non-standardised.

Table 6.3.8: Oncological results of selected salvage high-intensity focused ultrasound case series, including at least 20 patients

Reference	n	Median FU (mo)	BCR-free probability (%) ASTRO and Phoenix criteria	Negative biopsy rate
Colombel, *et al.* 2006 [894]	224	15-18	-	80
Uchida, *et al.* 2011 [895]	22	24	59 (Phoenix) (24 mo)	92 (only 12 biopsied)
Berge, *et al.* 2011 [896]	46	9	60.9 (9 mo)	-
Crouzet, *et al.* 2017 [897]	418	42	49% (5 y.); 82% CSS (7 yr.)	-

BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; yr. = year.

6.3.5.6.2 Morbidity

Most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.3.5.6.3 Summary of salvage high-intensity focused ultrasound

There is a lack of quality data which prohibits any recommendation regarding the indications for salvage HIFU.

6.3.6 Salvage lymph node dissection

Novel imaging modalities improve the early detection of nodal metastases [898]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [898-900]. The majority of treated patients showed BCR but clinical recurrence-free and CSS 10-year survival over 70% has been reported [899, 901]. Neither the template nor the real value of nodal salvage dissection is available. It must, however, be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [902]. Addition of RT to the lymphatic template after salvage LND may improve the BCR rate [903]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [904].

6.3.7 Hormonal therapy

The Guidelines Panel conducted a systematic review including studies published from 2000 onwards [905]. Conflicting results were found on the clinical effectiveness of HT after previous curative therapy of the primary tumour. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [906]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [907]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic work-up and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. Predictive factors for poor outcomes were; CRPC, distant metastases, CSS, OS, short PSA-DT, high ISUP grade, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, *et al.* study [830], high-risk patients, mainly defined by a high ISUP grade and a short PSA-DT (most often less than 6 months), seem to benefit most from (early) HT, especially in men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [829]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [908]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors.

Based on the lack of definitive efficacy and the undoubtedly associated significant side-effects, patients with recurrence after primary curative therapy should not receive standard HT. Only a minority of them will progress to metastases or PCa-related death. The objective of HT should be to improve OS, postpone distant metastases, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with comorbidities, the side-effects of HT may even decrease life expectancy; in particular, cardiovascular risk factors need to be considered [909, 910]. Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA-DT at relapse (< 6-12 months) or a high initial ISUP grade (> 2/3), and a long life expectancy.

6.3.8 Observation

In unselected relapsing patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [737]. For patients with EAU low-risk BCR features (see Section 6.3.3), unfit patients with a life expectancy of less than 10 years or patients unwilling to undergo salvage treatment, active follow-up may represent a viable option.

6.3.9 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence after radical prostatectomy	
Offer prostate-specific antigen (PSA) monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
Offer salvage radiotherapy (SRT) to patients with a PSA rise from the undetectable range. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak
Recommendations for biochemical recurrence after radiotherapy	
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
Salvage RP should only be performed in experienced centres.	Weak
Only offer salvage high intensity focused ultrasound, salvage cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling-time > 12 months.	Strong

6.4 Treatment: Metastatic prostate cancer

6.4.1 Introduction

All prospective data available rely on the definition of M1 disease based on CT scan and bone scan. The influence on treatment and outcome of newer, more sensitive imaging has not been assessed yet.

6.4.2 Prognostic factors

Median survival of patients with newly diagnosed metastases is approximately 42 months [911], however, the M1 population is heterogeneous. Several prognostic factors for survival have been suggested including the number and location of bone metastases, presence of visceral metastases, ISUP grade, PS status and initial PSA alkaline phosphatase, but only few have been validated [912-915].

"Volume" of disease as a potential predictor was introduced by CHAARTED (Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) [915-917] and has been shown to be predictive in a powered subgroup analysis for benefit of addition of prostate radiotherapy ADT [918].

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups (see Table 6.4.1) [919]. A PSA ≤ 0.2 ng/mL at 7 months has been confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [920].

Table 6.4.1 Definition of high- and low-volume and risk in CHAARTED [915-917] **and LATITIDE** [921]

	High	Low
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or spine **OR** Visceral metastasis	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

Table 6.4.2: Prognostic factors based on the SWOG 9346 study [919]

PSA after 7 months of ADT	Median survival
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 month
> 4 ng/mL	13 months

6.4.3 First-line hormonal treatment

Primary ADT has been the standard of care for over 50 years [606]. There is no high level evidence in favour of a specific type of ADT, neither for orchiectomy or for an LHRH analogue or antagonist, with the exception of patients with impending spinal cord compression for whom either a bilateral orchidectomy or LHRH antagonists are the preferred options.

6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events [922]. The evidence quality of the studies included in this review was rated as moderate.

6.4.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [923-925] and two meta-analyses [926, 927], looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included 8 RCTs of which only 3 were conducted in patients with exclusively M1 disease. The 5 remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [928]. Out of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that, at best, only 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1; CI: 0.99-1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out.

Other trials did not show any survival difference with an overall HR for OS of 1.02 (0.94-1.11) [923]. These reviews and the meta-analyses came to the conclusion that a difference in OS or CSS between IAD and continuous ADT is unlikely. A recent review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [929]. None of the trials that addressed IAD vs. continuous ADT in M1 patients showed a survival benefit, but there was a constant trend towards improved OS and PFS with continuous ADT. However, most of these trials were non-inferiority trials. In some cohorts the negative impact on sexual function was less pronounced with IAD. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side-effects, such as hot flushes [930, 931].

6.4.3.3 Immediate versus deferred androgen deprivation therapy

In symptomatic patients immediate treatment is mandatory, however, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. A first Cochrane review extracted four RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [920, 922]. These studies were conducted in the pre-PSA era and included patients with advanced metastatic or non-metastatic PCa who received immediate vs. deferred ADT [932]. No improvement in PCa CSS was observed, although immediate ADT

significantly reduced disease progression. The Cochrane analysis was updated in 2019 and concluded that early ADT probably extends time to death of any cause and time to death from PCa [933]. Since the analysis included only a very limited number of M1 patients who were not evaluated separately, the benefit of immediate ADT in this setting remains unclear.

6.4.4 Combination therapies

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.4.4.1 Complete androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [934]. However, results with other anti-androgens or castration modalities have differed and systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [935, 936] beyond 5 years of survival [937] but this minimal advantage in a small subset of patients must be balanced against the increased side-effects associated with long-term use of NSAAs.

6.4.4.2 Androgen deprivation combined with other agents

6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [679, 915, 938]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 6.4.3.

Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy

	STAMPEDE James [679]		**GETUG Gravis** [938]		**CHAARTED Sweeney** [915]	
	ADT	ADT + Docetaxel + P	ADT	ADT + Docetaxel	ADT	ADT + Docetaxel
n	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥ 70%		Metastatic disease ECOG PS 0, 1 or 2	
Primary objective	OS		OS		OS	
Median follow up (mo)	43		50		29	
HR (95% CI)	0.78 (0.66-0.93)		1.01 (0.75-1.36)		0.61 (0.47-0.80)	
M1 only						
n	1,086		-		-	
HR (95% CI)	0.76 (0.62-0.92)		-		-	

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; ISUP = ISUP = International Society for Urological Pathology; mo = month; n = number of patients; OS = overall survival; P = prednisone; PSA-DT = prostate-specific antigen-doubling time.

In the GETUG 15 trial, all patients had newly diagnosed M1 PCa, either *de novo* or after a primary treatment [938]. They were stratified based on previous treatment, and Glass risk factors [912]. In the CHAARTED trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being

defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [915].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1, or N1, or having two of the following 3 criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade 4-5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < 6 months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [679].

In all 3 trials toxicity was mainly haematological with around 12-15% grade 3-4 neutropenia, and 6-12% grade 3-4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [939, 940].

Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [940]. Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as pre-medication. Continuous oral corticosteroid therapy is not mandatory.

In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT is most evident in men with *de novo* metastatic high-volume disease [916, 917], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [941]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower.

A recent systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to standard of care improved survival [940]. The HR of 0.77 (95% CI: 0.68-0.87; p < 0.0001) translates to an absolute improvement in 4-year survival of 9% (95% CI: 5-14). Docetaxel in addition to standard of care also improves failure-free survival, with a HR of 0.64 (0.58-0.70; p < 0.0001) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12-19).

6.4.4.2.2 Combination with the new hormonal treatments (abiraterone, apalutamide, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with hormone-sensitive PCa (mHSPC) was studied [35, 921, 942]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit, but in LATITUDE in high-risk metastatic patients only with a HR of 0.62 (0.51-0.76) [921]. The HR in STAMPEDE was very similar with 0.63 (0.52-0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [35]. The inclusion criteria in the two trials differed, but both trials were positive for OS. While only high-risk patients were included in the LATITUDE trial, a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume stratification [943].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were positive and in favour of the combination. The key findings are summarised in Table 6.4.4. No difference in treatment-related deaths was observed with the combination of ADT plus abiraterone acetate and prednisone compared to ADT monotherapy [HR: 1.37 (0.82-2.29]. However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%). Based on these data, upfront abiraterone acetate plus prednisone combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug (see Table 6.4.4) [942].

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with hormone-sensitive PCa (mHSPC) was tested [944-946]. In ARCHES the primary endpoint was radiographic progression-free survival (rPFS). Radiographic PFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3-0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT improved OS with a HR of 0.67 (0.52-0.86). Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [946]. In the TITAN trial, apalutamide was used as AR antagonist with rPFS and OS as co-primary endpoints. Radiographic PFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39-0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51-0.89). In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [944].

In summary, the addition of AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. Again the majority of patients treated had *de novo*

metastatic disease and the evidence is most compelling in this situation. It may still be considered for men progressing after local therapy but this men make up a smaller fraction of the included patients. Lastly, whether the addition of an AR antagonist plus docetaxel adds further benefit is currently not clear as longer follow-up is needed. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

Table 6.4.4: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [James] [35]		**LATITUDE [Fizazi]** [921]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
n	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP grade ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	40		30.4	
3-yr. OS	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52 - 0.76)		0.62 (0.51-0.76)	
M1 only				
n	1,002		1,199	
3-yr. OS	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49-0.75)		0.62 (0.51-0.76)	
HR	Failure-free survival (biological, radiological, clinical or death): 0.29 (0.25-0.34)		Radiographic PFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; yr. = year.

Table 6.4.5 Results from the ENZAMET and TITAN studies

	ENZAMET [945]		**TITAN** [944]	
	ADT+ older antagonist +/-docetaxel (SOC)	ADT + enzalutamide +/-docetaxel	ADT + placebo	ADT + apalutamide
n	562	563	527	525
Newly diagnosed M+	61.7%	59.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	34		30.4	
3-yr. OS	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.67 (0.52-0.86)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = month; n = number of patients; NA = not available; OS = overall survival; SOC = standard of care; PFS = progression-free survival; yr = year.

6.4.5 Treatment selection and patient selection

There are no head-to-head data comparing 6 cycles of docetaxel and the long-term use of abiraterone acetate plus prednisone in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to standard of care. Data from the two experimental arms has been extracted although this was not pre-specified in the protocol and therefore the data were not powered for this comparison. The survival advantage for both drugs appeared similar [947]. A recent meta-analysis also found no significant OS benefit for either drug [948]. In the STOPCAP systematic review and meta-analysis, abiraterone acetate plus prednisone was found to have the highest probability of being the most effective treatment [949]. Both modalities have different and agent-specific side-effects and require strict monitoring of side-effects during treatment. Therefore, the choice will most likely be driven by patient preference, the specific side-effects, availability and cost.

6.4.6 Deferred treatment for metastatic PCa (stage M1)

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. However, since the median survival is only 42 months, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even dying from PCa, without receiving any benefit from hormone treatment has been highlighted [674, 683]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.4.7 Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. 432 patients were randomised to ADT alone or ADT plus EBRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7-1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63-0.97]) [950]. The STAMPEDE trial evaluated 2,061 men with mCSPC who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed radiotherapy to the primary tumour did not improve OS in unselected patients [918]. However, following the results from CHAARTED, and prior to analysing the data, the original screening investigations were retrieved and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT. Therefore RT of the prostate in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel, and no patients had additional abiraterone acetate plus prednisone so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment, results of ongoing trials are awaited.

In a recent systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81-1.04, p = 0.195; heterogeneity chi-square = 0.08, degree of freedom = 1, p = 0.78) [951]. However, there was a clear difference in the effect of metastatic burden on survival, with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

6.4.8 Metastasis-directed therapy

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There is one randomised phase II trial testing metastasis-directed therapy (MDT) vs. surveillance in men with oligo-recurrent PCa. Oligo-recurrence was defined as ≤ 3 lesions on pet-choline only. The sample size was small with 62 patients and only about half of them had nodal disease. Androgen deprivation therapy-free survival was the primary end-point which was longer with MDT than with surveillance [952]. Currently there is no data to suggest an improvement in OS. A systematic review highlighted that at this time this approach must, as yet, be considered as experimental [902].

6.4.9 Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment also to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

6.5 Treatment: Castration-resistant PCa (CRPC)

6.5.1 Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

or

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [953]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

6.5.2 Management of mCRPC - general aspects

Selection of treatment for mCRPC is multifactorial and in general dependent on:

- previous treatment for mHSPC and for non-mHSPC;
- previous treatment for mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor targeted agents (ARTA);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations;
- known histological variants and DNA repair deficiency (consider platinum or targeted therapy like poly-ADP ribose polymerase (PARP) inhibitors [still unapproved, but first phase III data available]);
- local approval status of drugs and reimbursement situation;
- available clinical trials.

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel and radium-223. In general, sequencing of ARTA like abiraterone/prednisolone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARTA was short (≤ 12 months) and high-risk features of rapid progression are present [954, 955]. In case the ARTA sequence is the only option, first prospective cross-over data suggest that abiraterone followed by enzalutamide is the preferred choice [956].

The earlier use of chemotherapy with cabazitaxel in the treatment sequence is recommended and supported by high level evidence [954].

Clinical parameters of aggressive disease like a short response to mHSPC therapy, high tumour burden, rapid pace of progression, visceral metastases, poor genomics (p53, RB, myc) should rather prompt the use of chemotherapy or clinical trials than e.g. ARTA [957]. Clinical trials should be the preferred treatment option whenever available.

Genetic sequencing of the primary tumour, liquid biopsy (ctDNA), or the use of fresh tissue biopsies of metastatic spread should be considered early on and in particular as soon as the patient becomes castration resistant. Open questions for genetic testing include the quality of tissue, which panels to use, availability of a molecular tumour board and interpretation of results. Level 1 evidence for the use of PARP (poly-ADP ribose polymerase)-inhibitors has been reported [958]. Microsatellite instability (MSI)-high is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA [959, 960] and could be a valuable additional treatment option.

6.5.3 Non-metastatic CRPC

Frequent PSA testing for men on treatment with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases detectable on bone scan within two years [961].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free and OS [961, 962]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [963] suggested a bone scan and a CT scan when the PSA reached 2 ng/mL; and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are expected to be diagnosed with early mCRPC.

Three large randomised controlled phase III trials, PROSPER [630], SPARTAN [964] and ARAMIS [631], evaluated MFS as the primary end-point in patients with non-metastatic CRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide vs. placebo (ARAMIS), respectively. The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 months were included. Patient characteristics in both trials revealed that about two-thirds of participants had a PSA-DT of < 6 months. All trials showed a significant MFS benefit (PROSPER: median MFS was 36.6 months in the enzalutamide group vs. 14.7 months in the placebo group [HR for metastasis or death, 0.29; 95% CI: 0.24-0.35, p < 0.001]; SPARTAN: median MFS was 40.5 months in the apalutamide group vs. 16.2 months in the placebo group [HR for metastasis or death, 0.28, 95% CI: 0.23-0.35, p < 0.001]); ARAMIS: median MFS was 40.4 months in the darolutamide group vs. 18.4 months in the placebo group (HR: 0.41, 95% CI: 0.34-0.50; 2-sided p < 0.0001). None of the trials showed a survival benefit, after a median follow-up of approximately 20 months. In view of the long-term treatment with these AR targeted agents in asymptomatic patients, potential adverse events need to be taken into consideration and the patient informed accordingly.

6.5.4 Metastatic CRPC

The remainder of this section focuses on the management of men with proven metastatic CRPC (mCRPC).

6.5.4.1 Conventional androgen deprivation in CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [965, 966]. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

Table 6.5.1: Randomised phase III controlled trials - first-line treatment of mCRPC

Author	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 Petrylak, DP, *et al.* 2004 [967]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) PFS: 6.3 vs. 3.2 mo. (p < 0.001)
TAX 327 2008 [968, 969]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group. (p = 0.004, HR: 0.79 95% CI: 0.67-0.93)
ABIRATERONE				
COU-AA-302 Ryan CJ, *et al.* 2013 [970-972]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	OS: 34.7 vs. 30.3 mo. (HR: 0.81, p = 0.0033). FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo. (p < 0.0001)
ENZALUTAMIDE				
PREVAIL Beer TM, *et al.* 2014 [973]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	OS: 32.4 vs. 30.2 mo. (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) rPFS: 20.0 mo. vs. 5.4 mo. HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)
SIPULEUCEL-T				
SIPULEUCEL-T Kantoff PW, *et al.* 2010 [974]	sipuleucel-T [975]	placebo [975]	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	OS: 25.8 vs. 21.7 mo. (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo. (no difference)
Small EJ, *et al.* 2006 [976]	sipuleucel-T [976]	placebo [976]	- ECOG 0-1. - No visceral metastases. - No prior immunotheraphy - No corticosteroids.	OS: 25.9 vs. 21.4 mo. (p = 0.1). FU: 36 mo. PFS: 11.7 vs. 10.0 wk.

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mo = month; PFS = progression-free survival; (r)PFS = (radiographic) progression-free survival; OS = overall survival.

6.5.5 First-line treatment of metastatic CRPC

6.5.5.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [970]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and radiographic PFS (rPFS) were the co-primary end-points. After a median follow-up of 22.2 months, there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS end-point was significantly positive (34.7 vs. 30.3 months, HR: 0.81,

95% CI: 0.70-0.93, p = 0.0033) [972]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1-2. Sub-set analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [977].

6.5.5.2 Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [973]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1,717 men and showed a significant improvement in both co-primary end-points, rPFS (HR: 0.186; CI: 0.15-0.23, p < 0.0001), and OS (HR: 0.706; CI: 0.6-0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant adverse events were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [978] as well as in those with or without visceral metastases [979]. However, for men with liver metastases, there seems to be no discernible benefit [979, 980].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double blind phase II study (TERRAIN) [981] showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, p < 0.0001) in favour of enzalutamide. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [982].

6.5.5.3 Docetaxel

A significant improvement in median survival of 2-2.9 months has been shown with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone therapy [969, 983]. The standard first-line chemotherapy is docetaxel 75 mg/m^2, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted if there are contraindications or no major symptoms. The following independent prognostic factors; visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [984].

Age by itself is not a contraindication to docetaxel [985] but attention must be paid to careful monitoring and comorbidities as discussed in Section 5.4 [986]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well tolerated with less grade 3-4 adverse events and a prolonged time to treatment failure [987].

6.5.5.4 Sipuleucel-T

In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [962]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related adverse events grade 1-2 in the sipuleucel-T group, but the same grade 3-4 adverse events in both arms. Sipuleucel-T is not available in Europe (and has had its licence withdrawn).

Table 6.5.2: Randomised controlled phase III - second-line / third-line trials in mCRPC

Author	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
Fizazi, *et al.* 2012 [988]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	**OS: 15.8 vs. 11.2 mo.** HR: 0.74, 95% CI: 0.64-0.86; p < 0.0001). FU: 20.2 mo. **rPFS: no change**
de Bono, *et al.* 2011 [989]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**

Radium-223				
Parker, *et al.* 2013 [990]	radium-223	placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46-0.81). All secondary end-points show a benefit over best standard of care.
CABAZITAXEL				
Bahl, *et al.* 2013 [991]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33-3.33). FU: 25.5 months OS ≥ 2 yr 27% vs. 16% PFS: not reported.
deBono, *et al.* 2010 [992]				**OS: 15.1 vs. 12.7 mo.** (p < 0.0001, HR: 0.70; 95% CI: 0.59-0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74; 95% CI: 0.64-0.86)
De Wit, *et al.* 2019 [954]	Cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	Abiraterone+ prednisone OR Enzalutamide (ARTA)	Previous docetaxel. Progression ≤ 12 mo. on prior alternative ARTA (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46-0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54 95% CI: 0.40-0.73). FU: 9.2 mo.
ENZALUTAMIDE				
Scher, *et al.* 2012 [993]	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	OS: 18.4 vs. 13.6 mo. (p < 0.001 HR: 0.63; 95% CI: 0.53-0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35-0.47 p < 0.0001).
PARP inhibitor				
Hussain, *et al.* 2019 [958]	Olaparib	Abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARTA, alterations in Cohort A: *BRCA1, BRCA2* or *ATM*	**rPFS: 7.39 vs. 3.55 mo.** (p < 0.0001; HR: 0.34; 95% CI: 0.25-0.47). ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18-379.18).

**Only studies reporting survival outcomes as primary end-points have been included.*
ARTA = androgen receptor targeting agents; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; yr = year.

6.5.6 Second-line treatment for mCRPC and sequencing

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.2. High level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

6.5.6.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [992]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day). Overall survival was the primary end-point, which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA

response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3-4 adverse events developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also non-haematological (57.4 vs. 39.8%, p < 0.0002) toxicity [994]. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m^2 cabazitaxel was not inferior to 25 mg/m^2, but less toxic. Therefore, the lower dose should be preferred [995, 996]. Cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [997].

6.5.6.2 Abiraterone acetate after prior docetaxel

Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [989] and confirmed by the final analysis [988]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate plus prednisone or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, p < 0.0001). The benefit was observed in all subgroups and all the secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3-4 adverse events did not differ significantly between arms, but mineralocorticoid-related side-effects were more frequent in the abiraterone group, mainly grade 1-2 (fluid retention, oedema and hypokalaemia).

6.5.6.3 Enzalutamide after docetaxel

The planned interim analysis of the AFFIRM study was published in 2012 [993]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, p < 0.001). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [982]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side-effects was observed in the two groups, with a lower incidence of grade 3-4 adverse events in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.5.6.4 Radium-223

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo, plus standard of care. The primary end-point was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, p < 0.001) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [990]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, it did not differ significantly from that in the placebo arm [990]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [998]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [999]. In particular, the use of radium-223 in combination with abiraterone acetate plus prednisolone showed significant safety risks related to fractures and more deaths. This was particularly striking in patients without the concurrent use of anti-resorptive agents [1000].

6.5.7 Treatment after docetaxel and one line of hormonal treatment for mCRPC

For men progressing quickly on AR targeted therapy (< 12 months) it is now clear that cabazitaxel is the treatment with the best supporting data. The CARD, an open label randomised phase III trial evaluated cabazitaxel after docetaxel and one line of ARTA (either abiraterone plus prednisolone or enzalutamide) [954]. It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARTA and reduced the risk of death by 36% vs. ARTA. The rPFS with cabazitaxel remained superior regardless of the ARTA sequence and if docetaxel was given before, or after, the first ARTA.

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1001]. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1002, 1003] and there is evidence of cross-resistance between enzalutamide and abiraterone [1004, 1005]. Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one novel hormonal agent and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate [1006].

In a randomised phase II trial which assigned 142 patients to receive olaparib and abiraterone (n = 71) or placebo and abiraterone (n = 71) patients demonstrated clinical benefit regardless of HRD status. Combination treatment is toxic with serious side effects reported in 34% of the olaparib/abiraterone group vs. 18% in the placebo/abiraterone group [1007]. Nevertheless, although not yet available, PARP inhibitors offer an exciting new opportunity to tailor therapy based on the mutation profile contained within a tumour [960].

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARTA in mCRPC with alterations in ≥ 1 of any qualifying gene with a role in HRR and progression on an ARTA. Most patients were heavily pre-treated with 1-2 chemotherapies and up to 2 ARTAs [958]. Radiographic PFS by blinded independent central review in the overall cohort favoured olaparib (HR: 0.49, 95% CI: 0.38-0.63). The interim results for OS demonstrated improved non-significant survival among men with *BRCA1/2* or *ATM* mutations (Cohort A) (HR: 0.64, 95% CI: 0.43-0.97), as well as for Cohort A and in men with any HRR alteration (Cohort B) (HR: 0.67, 95% CI: 0.49-0.93). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 80.6% in Cohort A and 84.6% in Cohort B, crossed over to receive olaparib. When looking specifically at the Cohort B patients, there was no advantage to olaparib in the rPFS by blinded independent central review (HR: 0.88, 95% CI: 0.58-1.36) or in OS (HR: 0.73, 95% CI: 0.45-1.23), however there was a benefit to olaparib for rPFS by investigator assessment (HR: 0.60, 95% CI: > 0.39-0.93).

The most common adverse events were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib, 16.4% discontinued treatment secondary to an adverse event, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine for mCRPC.

For patients with mismatch repair deficiency, the PD-1 inhibitor pembrolizumab was approved by the FDA irrespective of the tumour origin, which also includes PCa.

6.5.8 Prostate-specific membrane antigen (PSMA) therapy

6.5.8.1 Background

During the 90s several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 [1008] were developed for the treatment of bone pain secondary to metastasis from PCa. They were effective at palliation; relieving pain and improving QoL, especially in the setting of diffuse bone metastasis. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.5.5.4.)

6.5.8.2 PSMA-based therapy

The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope, which accumulates where the tumour is demonstrated (theranostics) [1009]. Therefore, after identification of the target, usually with diagnostic ^{68}Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with beta (lutetium-177 or ytrium-90) or α (actinium-225) emitting isotopes could be used to treat metastatic PCa. At present, all of these agents should be regarded as investigational.

6.5.8.3 Lutetium (Lu)-PSMA

The PSMA therapeutic radiopharmaceutical supported with the most robust data is Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1010]. Nonetheless, most of the literature is based on single-centre experience and RCTs are lacking [1011]. Recently, data from uncontrolled prospective phase II trials have been published [1012, 1013], reporting high response rates, with low toxic effects. More robust data are expected from ongoing trials.

6.5.9 *Monitoring of treatment*

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, FBC, renal function, LFTs, ALP), bone scan and CT of chest, abdomen and pelvis [1014]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naïve disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARTA have been described [1015]. Prostate-specific antigen alone is not reliable enough [1016] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1017]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [983]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [1014]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost, and patients with no objective benefit should have treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of "no longer clinically benefiting" to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1018]. These recommendations also seem valid for clinical practice outside trials.

6.5.10 *When to change treatment*

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Although, the number of effective treatments is increasing, head-to-head comparisons are still lacking, as are data assessing the sequencing of available agents. Therefore it is not clear how to choose the appropriate "second-line" treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing [954].

The ECOG performance status (PS) has been used to stratify patients. Generally men with a PS of 0-1 are likely to tolerate treatments and those with a PS of ≥ 2 are less likely to benefit. However, it is important that treatment decisions are individualised, in particular when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in a summery paper published following the St. Gallen Advanced Prostate Cancer Consensus Conference 2017 [1014, 1019].

6.5.11 *Symptomatic management in metastatic CRPC*

Castration-resistant PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [1019, 1020]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.5.11.1 *Common complications due to bone metastases*

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective, even as a single fraction [1021, 1022]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1023]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [1024]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1025, 1026]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [1027]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

6.5.12 *Preventing skeletal-related events*

6.5.12.1 *Bisphosphonates*

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, was available. Six hundred and forty three patients who had CRPC [1028] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg

every three weeks for 15 consecutive months, or placebo. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, p = 0.021) and in particular fewer pathological fractures (13.1 vs. 22.1%, p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.5.12.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa-B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028) [1021]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA or the EMA have approved denosumab for this indication [1029].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82, p = 0.008). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit and in a recent *post-hoc* re-evaluation of end-points, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1030].

The potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5-8.2% in M0 CRPC and mCRPC, respectively) [1030-1032]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection [1033]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in the pivotal trial [1034] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1029]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab as well as zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [1035].

Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively [1032]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU equivalent) are recommended in all patients, unless in case of hypercalcaemia [1032, 1036, 1037].

6.5.13 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease

Summary of evidence	**LE**
First-line treatment for mCRPC will be influenced by which treatments were used when metastatic cancer was first discovered.	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.	3

Recommendations	**Strength rating**
Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong

6.5.14 Guidelines for cytotoxic treatment of castrate-resistant disease

Recommendations	**Strength rating**
Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every 3 weeks.	Strong

Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
Base further treatment decisions of mCRPC on pre-treatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease and patient preference.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong

6.5.15 Guidelines for supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.5.16 Guidelines for non-metastatic castrate-resistant disease

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases.	Strong

6.6 Summary of guidelines for the treatment of prostate cancer

Table 6.6.1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

6.6.1 General guidelines recommendations for active treatment

Recommendations	Strength rating
Inform patients that no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and prostate cancer-specific survival for clinically localised disease.	Strong
Offer a watchful waiting (WW) policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong

Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multiparametric magnetic resonance imaging).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

6.6.2 Guidelines recommendations for the various disease stages

Recommendations		**Strength rating**
Low-risk disease		
Active surveillance (AS)	Offer AS to patients with life expectancy > 10 years and low-risk disease.	Strong
	If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
	If required, perform mpMRI before a confirmatory biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if confirmatory biopsy performed.	Strong
	Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
	Perform digital rectal examination (DRE) every 12 months.	Strong
	Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
	During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
	Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND (estimated risk for pN+ ≤ 5%).	Strong
Radiotherapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP), with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks, or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other options	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

Intermediate-risk disease		
Active surveillance	Offer AS to highly selected patients (< 10% Gleason pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical Prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapeutic treatment	Offer LDR brachytherapy to selected patients; patients without a previous TURP, with a good IPSS and a prostate volume < 50 mL.	Strong
	For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term neoadjuvant plus concomitant ADT (4 to 6 months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak
High-risk localised disease		
Radical prostatectomy	Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	In patients with high-risk localised disease, use ERBT with 76-78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery and radiotherapy	Do not offer either whole gland or focal therapy to high-risk patients.	Strong
	Do not use ADT monotherapy in asymptomatic patients.	Strong
Locally-advanced disease		
Radical prostatectomy	Offer RP to highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
Radiotherapeutic treatments	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.	Strong
	Offer long-term ADT for at least two years.	Weak
Therapeutic options outside surgery and radiotherapy	Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or EBRT) plus long-term ADT.	Weak

Adjuvant treatment after radical prostatectomy		
	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Offer adjuvant EBRT to the surgical field to highly-selected patients.	Strong
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional RT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak
Non-curative or palliative treatments in a first-line setting		
Localised disease		
Watchful waiting	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
Locally-advanced disease		
Watchful waiting	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour who are unwilling or unable to receive any form of local treatment.	Weak
Persistent PSA after radical prostatectomy		
	Offer a prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	Weak
	Treat men with no evidence of metastatic disease with salvage RT and additional hormonal therapy.	Weak

6.6.3 Guidelines for metastatic disease, second-line and palliative treatments

Recommendations		**Strength rating**
Metastatic disease in a first-line setting		
M1 patients	Offer immediate systemic treatment with ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
	Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
	Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
	Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
	Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
	Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
	Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high-volume M1 disease (CHAARTED criteria) outside of clinical trials (except for symptom control).	Strong

Biochemical recurrence after treatment with curative intent		
Biochemical recurrence after radical prostatectomy (RP)	Offer PSA monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
	Offer SRT to patients with a PSA rise from the undetectable range. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak
Biochemical recurrence after RT	Treat highly selected patients with localised PCa and a histologically proven local recurrence with SRP.	Weak
	Salvage RP should only be performed in experienced centres.	Weak
	Only offer salvage high intensity focused ultrasound, salvage cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > 12 months.	Strong
Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
Cytotoxic treatments of castration-resistant disease		
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
	Base further treatment decisions of mCRPC on pre-treatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease and patient preference.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as EBRT, and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
Non-metastatic castrate-resistant disease		
	Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases.	Strong

7. FOLLOW-UP

The rationale for following up patients is to assess immediate- and long-term oncological results, ensure treatment compliance and allow initiation of further therapy, when appropriate. In addition follow-up allows monitoring of side-effects or complications of therapy, functional outcomes and an opportunity to provide psychological support to PCa survivors, all of which is covered in Chapter 8.

7.1 Follow-up: After local treatment

7.1.1 Definition

Local treatment is defined as RP or RT, either by EBRT or LDR- or HDR-brachytherapy, or any combination of these. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do not have a well-defined, validated, PSA cut-off to define BCR, but follow the general principles as presented in this section. In general, a rising PSA is considered a sign of disease recurrence.

7.1.2 Why follow-up?

The first post-treatment clinic visit focuses on detecting treatment-related complications and assist patients in coping with their new situation apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention for mental health status is required [1038, 1039]. Tumour or patient characteristics may prompt changing the follow-up schedule.

7.1.3 How to follow-up?

The procedures indicated at follow-up visits vary according to the clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised, which is beyond the scope of these Guidelines. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Normal PSA values differ after RP and RT, but PSA recurrence almost always precedes clinical recurrence [780, 1040]. No recent consensus exists regarding the best definition of PSA relapse after local treatment. Main aim is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.3) [782].

7.1.3.2 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [1041]. Persistently measurable PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual disease in the prostatic fossa (see chapter on persistent PSA). Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with an ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of biochemical relapse within 2 years [1042]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 67% remained free of biochemical disease at 5 years [1043]. If survival is improved by early additional treatment after RP (before the PSA level reaches > 0.2 ng/mL), lower PSA nadir levels, as well as a lower PSA-DT calculated based on the first detectable PSA level up to 0.2 ng/mL, may help identify suitable candidates [1044]. Post-prostatectomy ultrasensitive PSA levels > 0.01 ng/mL in combination with clinical characteristics such as ISUP grade and surgical margin status may predict PSA progression and can be useful to establish follow-up intervals [1045].

7.1.3.3 Prostate-specific antigen monitoring after radiotherapy

Following RT, PSA drops more slowly as compared to RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT, although the optimal cut-off value remains controversial [1046]. The interval before reaching the nadir can be up to 3 years, or more. At the 2006 RTOG-ASTRO Consensus Conference, the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [781]. This definition also applies to patients who received HT [781]. After RT, PSA-DT correlates with the site of recurrence; patients with local recurrence have a PSA-DT of 13 months compared to 3 months for those with distant failure [1047].

7.1.3.4 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [1048]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT but the role of DRE was questioned since it failed to detect any local recurrence in the absence of a rising PSA in a series of 899 patients [1049]. In a series of 1,118 prostatectomy patients no local histologically proven recurrence was found by DRE alone and PSA measurement may be the only test needed after RP [1050, 1051].

7.1.3.5 Transrectal ultrasound, bone scintigraphy, CT, MRI and PET/CT

Imaging techniques have no place in routine follow-up of localised PCa as long as the PSA is not rising. Imaging is only justified in patients for whom the findings will affect treatment decisions, either in case of BCR or in patients with symptoms. (See Section 6.3.4 for a more detailed discussion).

7.1.3.5.1 TRUS/MRI-guided biopsy

Biopsy of the prostate bed and urethrovesical anastomosis of the remaining prostate after radiotherapy are only indicated if detection of a local recurrence affects treatment decisions (See Section 6.2.6.3 on imaging).

7.1.4 How long to follow-up?

Most patients who fail treatment for PCa do so within 7 years after local therapy [396]. Patients should be followed up more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement, disease-specific history and DRE (if considered) are recommended at 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually. Whether follow-up should be stopped in case PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question.

7.1.5 Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	**LE**
After radical prostatectomy rising serum PSA level is considered a BCR.	3
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is considered as clinically meaningful BCR.	3
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	**Strength rating**
Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	Strong
At recurrence, only perform imaging to detect local recurrence if the outcome will affect treatment planning.	Strong
Only offer bone scans and other imaging modalities to men with biochemical recurrence or symptoms suggestive of progression without signs of biochemical relapse.	Strong

7.2 Follow-up: During first line hormonal treatment (androgen sensitive period)

7.2.1 Introduction

Follow-up must be individualised as a rising PSA might be associated with rapid symptomatic progression or evolve without progression on imaging or symptoms over time. Follow-up for mCRPC is addressed in treatment Section 6.5.8, as management of mCRPC and follow-up are closely linked.

7.2.2 Purpose of follow-up

The main objectives of follow-up in these patients are to ensure treatment compliance, to monitor treatment response and side-effects, and to guide treatment at the time of CRPC.

Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs.

7.2.3 Methods of follow-up

7.2.3.1 Clinical follow-up

Clinical follow-up is mandatory on a regular basis, and it cannot be replaced, neither by laboratory tests or by

imaging modalities. Of utmost importance in metastatic situations is to advise patients about early signs of spinal cord compression, check for occult cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk.

7.2.3.1.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive PCa. Treatment response may be assessed using the change in serum PSA level as a surrogate end-point for survival in patients with newly diagnosed metastatic PCa receiving ADT [919], or ADT combined with docetaxel [920]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. Clinical progression has been reported without a rising PSA in up to 25% of patients [1052]. However, due to a lack of follow-up data a recommendation cannot be provided.

Other serum markers may be considered for prognostication [1053-1055] but the effects of their use on patient outcome are, as yet, unknown.

7.2.3.1.2 Creatinine, haemoglobin and liver function monitoring

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to bilateral ureteral obstruction or bladder retention. Liver function tests may suggest treatment toxicity (especially NSAA), but rarely disease progression. A decline in Hb after 3 months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue [1056]. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis, therefore, it may be helpful to determine bone-specific isoenzymes as none are directly influenced by HT [1057].

7.2.3.1.3 Imaging

Asymptomatic patients with a stable PSA level should not undergo imaging [1058]. New symptomatic bone lesions require a bone scan, as well as a PSA progression suggesting CRPC status if a treatment modification is considered. The PCWG has clarified the definition of bone scan progression as the appearance of at least two new lesions, which was later confirmed [983].

Suspicion of disease progression indicates the need for additional imaging modalities, most often initially a CT-scan but further imaging will be guided by symptoms or possible subsequent treatments. In CRPC imaging must be individualised with the aim of maintaining the patient's QoL.

7.2.3.1.4 Testosterone monitoring

Testosterone monitoring should be considered part of clinical practice in men on LHRH therapy. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13-38% of patients fail to achieve this goal and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1041], known as the 'acute on-chronic effect' or 'breakthrough response'.

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment has been suggested to ensure castration is achieved and maintained. If not, switching to another agonist or antagonist or to an orchiectomy, should be considered. In patients with a rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with mass spectrometry or an immunoassay [1059, 1060].

7.2.3.1.5 Monitoring of metabolic complications

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems, and bone resorption (see Section 8.2.4.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely), in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT, a cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years. Men on enzalutamide or abiraterone acetate are at increased risk of cardiovascular problems and hypertension and regular checks are required [1061]. Monitoring serum levels of vitamin D and calcium is important. It is suggested that routine bone monitoring should be performed every two years during castration [1062], or yearly if there are other risk factors [1063, 1064]. However, there is no evidence that this favourably impacts on bone complications due to ADT. The FRAX score can help identify men at risk of osteoporotic complications but validation of the score in the ADT settings is required [1065, 1066].

Men on ADT should have their transaminase levels checked at least twice a year in view of potential liver toxicity.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [1056, 1057]. Androgen deprivation therapy may affect mental health and men with ADT are three times more likely to report depression [1067]. Attention for mental health should therefore be part of the follow-up scheme. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

7.2.4 When to follow-up

After the initiation of ADT, it is recommended that patients are followed at 3 to 6 month intervals. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

7.2.4.1 Stage M0 - M1 patients

In case there is a favourable treatment response, i.e. PSA response (< 4 ng/mL), symptomatic improvement, good psychological coping and good treatment compliance, follow-up visits may be scheduled every 3 to 6 months.

7.2.5 Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [1068, 1069].

Quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1070]. Nonetheless, bone scan is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan which, after longer observation, actually represent a favourable response. Flare is observed within 8 to 12 weeks of treatment initiation and can lead to a false-positive diagnosis of disease progression. As a result, the PCWG suggested that all patients with at least two new lesions on the first follow-up bone scan require a confirmatory bone scan at least 6 weeks later while the treatment is continued [983]. This means that a management change for primary therapy resistance cannot occur until after at least 14 weeks of treatment. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. The ability of PET/CT to assess response has been evaluated in a few studies but, until further data are available, PET/CT has no role in this setting. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1071].

In practice, imaging to assess progression leading to treatment change must be limited to a clear progression: RECIST criteria for non-bone lesions; for bone lesions, only bone scan progression (occurrence of two new hot spots, later confirmed) should be considered. The practical impact of mpMRI in assessing bone progression remains unclear.

7.2.6 Disease progression during androgen deprivation therapy

The PCWG3 recommendations, which were developed for clinical trial design, may serve as a guide to plan follow-up in men with progression during ADT [983].

Progression of disease whilst undergoing ADT is defined by the development of cancer-related symptoms or a PSA rise. The most recently proposed PCWG3 definitions do not suggest that a treatment change is needed in case of documented progression, however, in order to monitor PSA doubling time as a useful predictor of outcome, it is recommended to follow up men on ADT with a rising PSA at least every 3 months [983].

In case of radiographical progression, a more frequent follow-up scheme can be recommended depending on location, size and complaints of metastases [983].

7.2.6.1 CRPC patients

Follow-up care of CRPC patients will be guided by the type of treatment provided. Generally, PSA assessment is included in the follow-up of men treated for non-metastatic CRPC even though clinical progression may occur without PSA progression and regular imaging is advised (bone scan and CT imaging every 6 months, at PSA progression or development of symptoms). In non-metastatic CRPC a PSADT < 3 months was associated with an approximately 9-fold increased risk of metastases (HR: 8.63, 95% CI: 5.07-14.7) [1072, 1073].

Prostate-specific membrane antigen/PET imaging has not been prospectively evaluated in CRPC patients and can therefore not be recommended in a CRCP setting.

7.2.7 Guidelines for follow-up during hormonal treatment

Recommendations	Strength rating
Evaluate patients at 3 to 6 months after the initiation of treatment.	Strong
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In patients with stage M1 disease, schedule follow-up every 3 to 6 months. As a minimum requirement, include an initial FRAX-score assessment, disease-specific history, digital-rectal examination (DRE), serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year. Pay attention to symptoms associated with metabolic syndrome as a side effect of androgen deprivation therapy. Phospholipid profiles and glucose levels should be checked and treated if abnormal.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow-up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Weak

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (8.2) will summarise long-term consequences (≥ 12 months) of therapies for PCa. Based on two systematic reviews, the second (8.3) will make evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of QoL [1074]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others. Attention to the psychosocial concerns of men with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1075]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side-effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed.

8.2 Adverse effects of PCa therapies

8.2.1 Surgery

The absence of standardisation in reporting surgical complications for RP and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1076-1079]. The most common post-operative issue is ED but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1080]. The second most commonly occurring complication is long-term incontinence [1076-1079] but voiding difficulties may also occur associated with bladder neck contracture (e.g. 1.1% after RALP) [1081].

For those men undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar [1082] and can occur more rarely with 8 mm and 5 mm trocars [1082]. A key consideration for men is whether long-term consequences of surgery are reduced by using

newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [416, 503-506], and can be compared with contemporaneous reports after RRP [507]. From these reports, the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP. A prospective, controlled, non-randomised trial of patients undergoing RP in 14 centres using RALP or RRP demonstrates that at 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The unadjusted OR was 0.81 (95% CI: 0.66-0.98) [508, 1083]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1083, 1084]. A single centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [411].

8.2.2 Radiotherapy

8.2.2.1 Side-effects of external beam radiotherapy

Analysis of the toxicity outcomes of the Prostate Testing for Cancer and Treatment (ProtecT) trial [1085] shows that men treated with EBRT and 6 months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (described in detail in section 8.3.1.1 below). Participants in the ProtecT study were treated with 3D CRT and more recent studies using IMRT demonstrate less bowel toxicity than noted previously with 3D CRT [1086].

A systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to radiotherapy in the course of treatment for PCa demonstrates an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of 5 and 10 years. Absolute excess risks over 10 years are small (1-4%) but should be discussed with younger men in particular [1087].

8.2.2.2 Side-effects from brachytherapy

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0-19%) [1088]. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of IPSS score, backed up by urodynamic studies.

8.2.3 Local primary whole-gland treatments other than surgery or radiotherapy

8.2.3.1 Cryosurgery

In Ramsay *et al.*'s systematic review and meta-analysis there was evidence that the rate of urinary incontinence at one year was lower for cryotherapy than for RP, but the size of the difference decreased with longer follow-up [638]. There was no significant difference between cryotherapy vs. EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0-40%) to RP at one year. There was insufficient data to compare cryotherapy vs. EBRT in terms of ED.

8.2.3.2 High-intensity focused ultrasound

In terms of toxicity, there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01-0.48) [638].

8.2.4 Hormonal therapy

A summary of impacts on psychological factors due to the use of ADT such as sexual function, mood, depression, cognitive function and impact on men's partners can be found in two clinical reviews [1089, 1090]. A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. ADT patients reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1091]. Conversely, a prospective observational study with follow-up to 3 years failed to demonstrate an association with cognitive decline in men on ADT when compared to men with PCa not treated with ADT and healthy controls [1092]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1093]. Another retrospective, non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than orchiectomised patients. The stage at diagnosis had no effect on health outcomes [1094].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12

months [1095]. A *post-hoc* analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [1096], preserved libido and erectile function [1097]. Intermittent androgen deprivation has been discussed elsewhere (see Section 6.4.3.2).

8.2.4.1 Sexual function

Cessation of sexual activity is very common in men undergoing ADT, affecting up to 93% of men [1098]. ADT reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1099].

8.2.4.2 Hot flushes

Hot flushes are a common side-effect of ADT (prevalence estimated between 44-80% of men on ADT) [1098]. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL. Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications [1100].

Serotonin re-uptake inhibitors (e.g. venlafaxine or sertraline) also appear to be effective in men, but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1101]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (IQR -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group. With a placebo effect influencing up to 30% of patients [1102], the efficacy of clonidine, veralipride, gabapentine [1103] and acupuncture [1104] need to be compared in prospective RCTs.

8.2.4.3 Non-metastatic bone fractures

Due to increased bone turnover and decreased bone mineral density (BMD) in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% RR with long-term ADT) [1105]. Hip fractures in men are associated with a significant risk of death [1106]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool (http://www.shef.ac.uk/FRAX) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT [1107]. These changes increase the fracture risk [1108].

8.2.4.3.1 Hormonal treatment modalities

Bicalutamide monotherapy may have less impact on BMD [1109, 1110], but is limited by its suboptimal efficacy (see Section 6.1.4.1.1.5.2.3). The intermittent LHRH-agonist modality might be associated with less bone impact [1111].

8.2.4.4 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [1107]. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1112], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The definition requires at least three of the following criteria [1113]:

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol < 1 mmol/L;
- glycaemia > 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [1114].

Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1115]. Androgen deprivation therapy-induced hypogonadism results in negative effects on skeletal

muscle health. A prospective longitudinal study involving 252 men on ADT for a median of 20.4 months reported lean body mass decreases progressively over 3 years; 1.0% at one year, 2.1% at 2 years, and 2.4% at 3 years which appears more pronounced in men at ≥ 70 years of age [1116].

8.2.4.5 Cardiovascular morbidity

Cardiovascular mortality is a common cause of death in PCa patients [910, 1117, 1118]. Several studies showed that ADT, after only 6 months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1119]. The RTOG 92-02 [1120] and 94-08 [1121] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [1122]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1123, 1124]. Meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease in men treated for PCa e.g. the associations between GnRH agonists and nonfatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI: 1.26-1.94) and RR: 1.51 (95% CI: 1.24-1.84), respectively [1125]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1126] or presenting with a metabolic syndrome [1127]. It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [1128]. However, the methodology used in these studies does not provide convincing evidence to show a clear superiority of these compounds.

These concerns resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [909]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, improved nutrition and smoking cessation [1129].

8.2.4.6 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure. Anaemia may be a cause of fatigue [1098, 1130]. Anaemia requires an aetiological diagnosis (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusions are required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [1131].

8.2.4.7 Neurological side-effects

Castration seems also to be associated with an increased risk of stroke [1132], and is suspect to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1133].

8.3 Overall quality of life in men with PCa

Living longer with PCa, does not necessarily equate to living well [1074, 1075]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa [1134]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1135]. Radical treatment for PCa can negatively impact long-term QoL (e.g. sexual, urinary and bowel dysfunction), as can ADT used in short or long-term treatment, e.g. sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae and increased cardiovascular and bone fracture risk [1089, 1136]. Direct symptoms from advanced or metastatic cancer, e.g. pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1137, 1138]. Men's QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1139, 1140].

The concept of 'quality of life' is subjective and can mean different things to different men, but there are some generally common features across virtually all patients. Drawing from these common features, specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues that affect men after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated systematic reviews around cancer-specific QoL outcomes in men with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

Table 8.3.1: PROMs assessing cancer specific quality of life

Questionnaire	Domains / items
Functional Assessment of Cancer Therapy-General (FACT-G) [1141]	Physical well-being, Social/family well-being, Emotional well-being, and Functional well-being
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1142]	12 cancer site specific items to assess for prostate related symptoms. Can be combined with FACT-G or reported separately.
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1143]	Five functional scales (physical, role, cognitive, emotional, and social); Three symptom scales (fatigue, pain, and nausea and vomiting); Global health status/QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [1144]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [1145]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1146]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1147]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1148]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1149]	Urinary, bowel, and sexual domains.

8.3.1 Long-term (> 12 months) quality of life outcomes in men with localised disease

8.3.1.1 Men undergoing local treatments

The results of the Prostate Testing for Cancer and Treatment (ProtecT) trial (n = 1,643 men) reported no difference in EORTC QLQ-C30 assessed global QoL, up to 5 years of follow-up in men aged 50-69 years with T1-T2 disease randomised for treatment with AM, RP or RT with 6 months of ADT [1085]. However, EPIC urinary summary scores (at 6 years) were worse in men treated with RP compared to AM or RT (88.7 vs. 89.0 vs. 91.4, respectively) as were urinary incontinence (80.9 vs. 85.8 vs. 89.4, respectively) and sexual summary, function and bother scores (32.3 vs. 40.6 vs. 41.3 for sexual summary, 23.7 vs. 32.5 vs. 32.7 for sexual function and 51.4 vs. 57.9 vs. 60.1 for sexual bother, respectively) at 6 years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not available. For men receiving RT with 6 months of ADT, EPIC bowel scores were poorer compared to AM and RP in all domains: function (90.8 vs. 92.3 vs. 92.3, respectively), bother (91.7 vs. 94.2 vs. 93.7, respectively) and summary (91.2 vs. 93.2 vs. 93.0, respectively) at 6 years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies [1079, 1150]. The Prostate Cancer Outcomes Study (PCOS) [1079] studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT. The study reported that at 5 years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at 5 years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at 15 years. More recently, investigators reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance 12 months after treatment [1086]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side-effects in contemporary treatments may be slightly less. This is supported by a contemporary 5-year prospective, population-based cohort study where PROs were compared in men with favourable- and unfavourable-risk localised disease [1150]. In the 1,386 men with favourable risk, comparison between AS and nerve-sparing prostatectomy, EBRT or LDR brachytherapy demonstrates that surgery is associated with worse urinary incontinence at 5 years and sexual dysfunction at 3 years when compared to AS. External beam RT is associated with changes not clinically different from AS, and LDR brachytherapy is associated with worse irritative urinary-, bowel- and sexual symptoms at one year. In 619 men with unfavourable risk disease, comparison between non-nerve sparing RP and EBRT with ADT demonstrates that surgery is associated with worse urinary incontinence and sexual function through 5 years.

With respect to brachytherapy cancer-specific QoL outcomes, one small RCT (n = 200) evaluated bilateral nerve-sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at one year of follow-up. However, there were no significant differences in EORTC QLQ-C30/PR-25 scores at 5 years of follow-up when comparing to pre-treatment values [1151]. It should be noted of this trial within group tests only were reported. In a subsequent study by the same group comparing bilateral nerve-sparing RARP and brachytherapy (n = 165), improved continence was noted with brachytherapy in the first 6 months but lower potency rates up to 2 years [1152]. These data and a synthesis of 18 randomised and non-randomised studies in a systematic review involving 13,604 patients are the foundation of the following recommendations [1153].

8.3.1.2 Guidelines for quality of life in men undergoing local treatments

Recommendations	Strength rating
Advise eligible patients for active surveillance, that global quality of life is equivalent for up to 5 years compared to radical prostatectomy or external beam radiotherapy.	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.	Strong
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after 5 years.	Weak

8.3.2 Improving quality of life in men who have been diagnosed with PCa

Men undergoing local treatments

In men with localised disease, nurse led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues depression, managing bowel and urinary function problems) provided positive short-term effects (4 months) on sexual function (effect size 0.45) and long-term (12 months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1154].

In men with post-surgical urinary incontinence, conservative management options include pelvic floor muscle training with or without biofeedback, electrical stimulation, extra-corporeal magnetic innervation (ExMI), compression devices (penile clamps), lifestyle changes, or a combination of methods. Uncertainty around the effectiveness and value of these conservative interventions remains [1155]. Surgical interventions including sling and artificial urinary sphincter significantly decrease the number of pads used per day and increase the QoL compared with before intervention. The overall cure rate is around 60% and results in improvement in incontinence by about 25% [1156].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single centre, double blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [1157]. However, a multicentre double blind RCT (n = 423) in men aged < 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6: 95% CI: 3.1-16.0) when compared to 20 mg 'on demand' or placebo at 9 months of follow-up [547]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation [1158]. A detailed discussion can be found in the EAU Sexual and reproductive health Guidelines [1159].

Men undergoing systemic treatments

Similar to men treated with a radical approach (see above), in men with T1-T3 disease undergoing RT and ADT, a combined nurse led psychological support and physiotherapist led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5: 95% CI: 0.6-8.4), irritative (adjusted mean 5.8: 95% CI: 1.4-10.3) and hormonal (adjusted mean 4.8: 95% CI: 0.8-8.8) EPIC domains were found up to 22 weeks of follow-up [1160].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8: 95% CI: 6.6-24.9) and cognitive domain outcomes (adjusted mean 11.4: 95% CI: 3.3-19.6) as well as symptom scales for fatigue (adjusted mean 11.0: 95% CI: 20.2-1.7), nausea (adjusted mean 4.0: 95% CI: 7.4-0.25), and dyspnoea (adjusted mean 12.4: 95% CI: 22.5-2.3) up to 3 months in men treated with ADT [1161]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9: 95% CI: 3.7-14.2) in men on long-term ADT [1162, 1163]. These findings are supported by a systematic review which reported improvements up to 12 weeks in cancer-specific QoL in a meta-analysis of high quality trials (SMD 0.33: 95%, CI: 0.08-0.58) [1130].

In case dietary intake is not adequate vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1164].

Bisphosphonates increase BMD in the hip and spine by up to 7% in one year. The optimal regimen for zoledronic acid remains unclear: quarterly [1165] or yearly [1166] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1167]. A quarterly regimen could be considered for a BMD $\leq$ 2.5 as a yearly injection is unlikely to provide sufficient protection [1168].

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [1169]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [1030] without any impact on OS, but with an increase in side-effects. Therefore, this later regimen cannot be recommended.

8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer men on androgen deprivation therapy (ADT), 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men with T1-T3 disease specialist nurse led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Use the WHO FRAX tool to guide monitoring and treatment of bone mineral density in men on long-term ADT.	Strong

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10. CONFLICT OF INTEREST

All members of the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/prostate-cancer/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organization and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Renal Cell Carcinoma

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Renal Cell Carcinoma (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise and judgement when making treatment decisions for individual patients, but rather help to focus decisions whilst also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The RCC Guidelines Panel is an international group of clinicians consisting of urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer care. Since 2015, the Panel has incorporated a patient advocate to provide a consumer perspective for its guidelines.
All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/renalcellcarcinoma/.

1.3 Acknowledgement

The RCC Guidelines Panel is most grateful for the continued methodological and scientific support provided by Prof.Dr. O. Hes (pathologist, Pilzen, Czech Republic) for two sections of this document: Histological diagnosis and Other renal tumours.

1.4 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices, presenting the main findings of the RCC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU RCC Guidelines [1]. All documents can be accessed on the EAU website: http://uroweb.org/guideline/renal-cell-carcinoma/.

1.5 Publication history and summary of changes

*1.5.1 **Publication history***

The EAU RCC Guidelines were first published in 2000. This 2020 RCC Guidelines document presents a limited update of the 2019 publication.

*1.5.2 **Summary of changes***

All chapters of the 2020 RCC Guidelines have been updated, based on the 2019 version of the Guidelines. References have been added throughout the document.

New data have been included in the following sections, resulting in changed recommendations in:

Section 3.4.5 ***Summary of evidence and recommendations for the management of other renal tumours***

Recommendations	Strength rating
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Only offer radical nephrectomy to patients with localised renal medullary carcinoma after a favourable response to systemic therapy.	Weak

7.1.4.3.7 Summary of evidence and recommendation for therapeutic approaches as alternative to surgery

Recommendations	Strength rating
When radiofrequency ablation, cryoablation and active surveillance are offered, inform patients about the higher risk of local recurrence and/or tumour progression.	Weak

7.4.2.5 Summary of evidence and recommendations for immunotherapy of metastatic clear-cell RRC

Summary of evidence	LE
The combination of pembrolizumab and axitinib in treatment-naïve patients with clear-cell-mRCC across all IMDC risk groups demonstrated overall survival and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib can be continued if immune-related adverse events results in cessation of axitinib and pembrolizumab. Re-challenge with combination therapy requires expert support.	4
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4

Recommendations	Strength rating
Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC-risk clear-cell metastatic RCC (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Patients who do not receive the 4 four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Offer axitinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib and pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong*

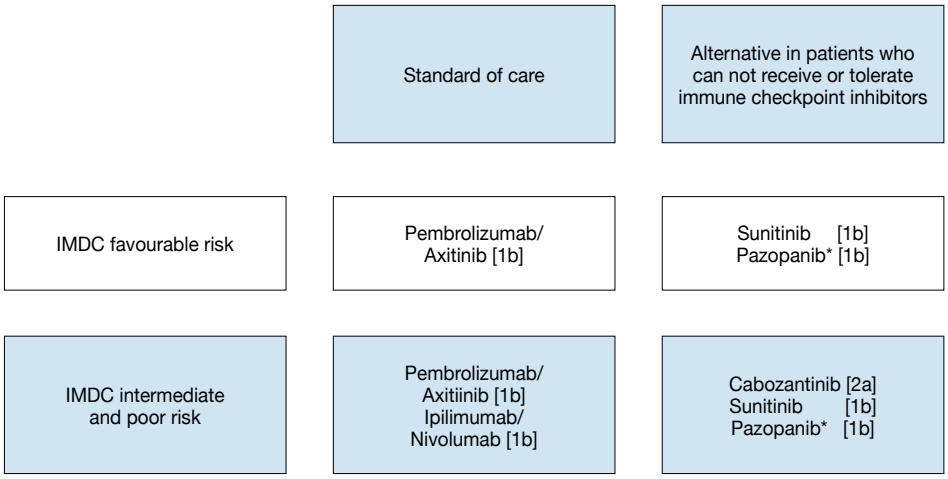
* *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib* in this population*. This justified the same recommendation under exceptional circumstances.*

7.4.7 ***Summary of evidence and recommendations for targeted therapy in metastatic RRC***

Summary of evidence	**LE**
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line metastatic RCC.	1b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-clear cell RCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	**Strength rating**
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in clear-cell-mRCC.	Strong

Figure 7.1: Updated European Association of Urology Guidelines recommendations for the treatment of first-line and following lines in clear-cell metastatic renal cancer



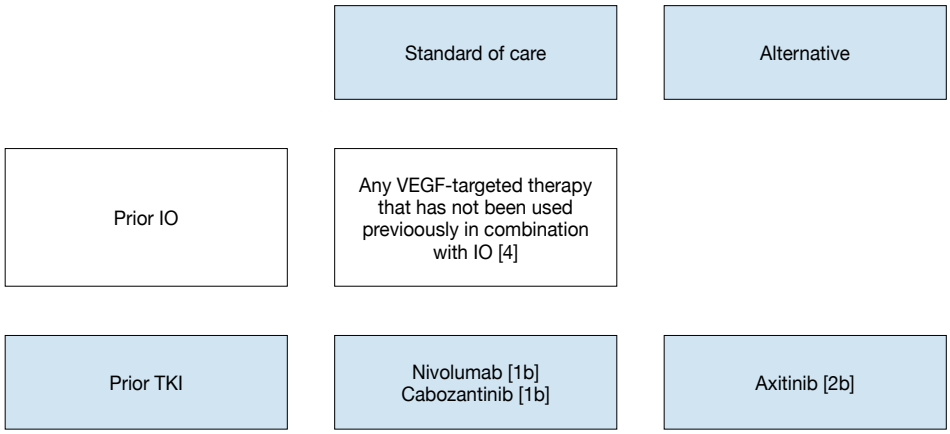
IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium

**pazopanib for intermediate-risk disease only.*

[1b] = based on one randomised controlled phase III trial.

[2a] = based on one randomised controlled phase II trial.

Figure 7.2: Guidelines Recommendations for later-line therapy



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium; IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

2. METHODS

2.1 Data identification

For the 2018 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the chapters as listed in Table 2.1.

A broad and comprehensive scoping search was performed, which was limited to studies representing high levels of evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between June 18th 2018 and April 5th, 2019. Databases covered included Medline, EMBASE, and the Cochrane Library. After deduplication, a total of 2,225 unique records were identified, retrieved and screened for relevance.

A total of 49 new references have been included in the 2020 RCC Guidelines publication. A search strategy is published online: https://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation.

The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Specific chapters were updated by way of SRs, commissioned and undertaken by the Panel, based on

prioritised topics or questions. These reviews were performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/aboutcochranesystematic-reviews.html.

Table 2.1: Description of update and summary of review methodology

Chapter	Brief description of review methodology
1. Introduction	Not applicable.
2. Methods	Not applicable.
3. Epidemiology, aetiology and pathology	This chapter was updated by a narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a narrative review, based on a structured literature assessment. Section 3.3.5 Angiomyolipoma was updated by means of a SR [5].
5. Diagnostic evaluation	Section 5.2 (Diagnostic imaging) was revised based on a SR [6]. The remainder of the chapter was updated by a structured literature assessment.
6. Prognosis	This chapter was updated by a narrative review, based on a structured literature assessment.
7. Treatment (Disease management)	Sections 7.1.2 and 7.2.4 (Treatment of localised and locally advanced disease) were revised based on an updated SR. Section 7.4.6.2 (Non-clear-cell carcinoma) was updated by means of a SR [7]. The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease: this section was updated by a SR.
8. Follow-up in RCC & Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a narrative review, based on a structured literature assessment. The findings of a prospective database set up by the RCC Panel have been included [8, 9].

Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/. A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

All publications ensuring from SRs have been peer reviewed. The 2019 print of the RCC Guidelines was peer-reviewed prior to publication.

2.3 Future goals

For their future updates, the RCC Guideline Panel aims to focus on patient-reported outcomes.

The use of clinical quality indicators is an area of interest for the RCC Panel. A number of key quality indicators for this patient group have been selected:

- thorax computed tomography (CT) for staging of pulmonary metastasis;
- proportion of patients with T1aN0M0 tumours undergoing nephron-sparing surgery (NSS) as first treatment;
- the proportion of patients treated within six weeks after diagnosis;
- the proportion of patients with metastatic RCC (mRCC) offered systemic therapy;
- the proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

The panel have set up a database to investigate current practice in follow-up of RCC patients in a number of European centres. Assessing patterns of recurrence and use of imaging techniques are primary outcomes for this project.

The results of ongoing and new SRs will be included in the 2020 update of the RCC Guidelines:

- Ablative therapy vs. partial nephrectomy (PN) for T1-T2 renal cell carcinoma;
- What is the best treatment option for ≥ T2 tumours?;
- Systematic review and meta-analysis of systemic therapy of renal tumours (Cochrane Review);
- Adjuvant targeted therapy for renal cell carcinoma at high risk for recurrence.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [10]. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe leading to approximately 99,200 new RCC cases and 39,100 kidney cancer-related deaths within the European Union in 2018 [10]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilizing or declining thereafter [11]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [10, 11].

3.2 Aetiology

Aetiological factors include lifestyle factors such as smoking, obesity, and hypertension [12, 13]. In a recent SR also diabetes was found to be detrimental [14]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. A number of other factors have been suggested to be associated with higher or lower risk of RCC, including specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [13, 15]. Moderate alcohol consumption appears to have a protective effect for reasons as yet unknown, while also any physical activity level seems to have a small protective effect [14, 16]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [13].

Renal cell carcinoma is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics [17]. There is a 1.5:1 predominance in men over women, with a peak incidence occurring between 60 and 70 years of age [18].

3.2.1 Summary of evidence and recommendation for epidemiology, aetiology and pathology

Summary of evidence	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

Recommendation	Strength rating
Increase physical activity, eliminate cigarette smoking and in obese patients reduce weight as the primary preventative measures to decrease risk of RCC.	Strong

3.3 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [17]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC- type I and II) and chromophobe (chRCC). The RCC type classification has been confirmed by cytogenetic and genetic analyses [17] (LE: 2b). Collecting duct carcinoma and other rare renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type; evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and peri-renal fat, pT, or even pN categories. The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [17].

3.3.1 ***Clear-cell RCC***

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found, including additional tumour suppressor genes including *SETD2*, *BAP1*, and *PBRM1*; all genes are identified near the VHL gene within a region that is frequently deleted in ccRCC [19]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC [20, 21] even after stratification for stage and grade [22]. The 5-year cancer-specific-survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated between 1987-1998), respectively [23]. For more details, see Section 6.3 - Histological factors.

3.3.2 ***Papillary RCC***

Papillary RCC is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [17]. Type I and II pRCC, which were shown to be clinically and biologically distinct; pRCC type I is associated with activating germline mutations of *MET* and pRCC type II is associated with activation of the NRF2-ARE pathway and at least three subtypes [24]. Future substratification is expected, e.g. oncocytic pRCC [17].

A typical histology of pRCC type I (narrow papillae without any binding, and only microcapillaries in papillae) explains its typical clinical signs. Narrow papillae without any binding and a tough pseudocapsule explain the ideal rounded shape (Pascal's law) and fragility (specimens have a "minced meat" structure). Tumour growth causes necrotisation of papillae, which is a source of hyperosmotic proteins that cause subsequent "growth" of the tumour, fluid inside the tumour, and only a serpiginous, contrast-enhancing margin. Only microcapillaries explain the minimal post-contrast attenuation on CT. Papillary RCC type 1 can imitate a pathologically changed cyst (Bosniak IIF or III). The typical signs of pRCC type 1 are as follows: an ochre colour, more frequently exophytic, extrarenal growth, low grade, and low malignant potential; over 75% of these tumours can be treated by NSS surgery. A substantial risk of renal tumour biopsy tract seeding exists (12.5%), probably due to the fragility of the tumour papillae [25]. Papillary RCC type I is more common and generally considered to have a better prognosis than pRCC type II [17, 26].

3.3.3 ***Chromophobe RCC***

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Chromophobe RCC cannot be graded (by the Fuhrman grading system), because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [17]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [17]. The prognosis is relatively good, with high 5-year recurrence-free survival (RFS), and 10-year CSS [27]. The new WHO/ISUP grading system merges former entity hybrid oncocytic chromophobe tumour with chRCC.

3.4 Other renal tumours

Other renal tumours constitute the remaining renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

3.4.1 ***Renal medullary carcinoma***

Renal medullary carcinoma (RMC) is a very rare tumour, comprising < 0.5% of all RCCs [28], predominantly diagnosed in young adults (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [29, 30] and most patients (~67%) will present with metastatic disease [29, 31]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter; often within a few weeks.

3.4.1.1 Treatment of renal medullary carcinoma

Despite treatment, median OS is 13 months in the most recent series [29]. Due to the infiltrative nature and medullary epicentre of RMC, radical nephrectomy (RN) is favoured over PN even in very early-stage disease. Retrospective data indicate that nephrectomy in localised disease results in superior OS (16.4 vs. 7 months) compared with systemic chemotherapy alone, but deferred treatment seems to be reasonable [29, 32]. There is currently no established role for distant metastasectomy or nephrectomy in the presence of metastases.

Palliative radiation therapy is an option and may achieve regression in the targeted areas but it will not prevent progression outside the radiation field [33, 34]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors [29, 35, 36]. The mainstay systemic treatments for RMC

are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [35]. There are no prospective comparisons between different chemotherapy regimens but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [29, 30]. High-dose-intensity combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has also shown efficacy against RMC [37] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine (CPG) [30]. Single-agent anti-PD-1 (monoclonal antibodies against programmed death-1) immune checkpoint therapy has produced responses in a few case reports, although, as yet, insufficient data are available to determine the response rate to this approach [33, 34]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

*3.4.2 **Carcinoma associated with end-stage renal disease; acquired cystic disease-associated RCC***

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC, are typical features of end-stage renal disease (ESRD). Renal cell carcinomas of native end-stage kidneys are found in approximately 4% of patients. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESRD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [38, 39]. Whether the relatively indolent outcome of tumours in ESRD is due to the mode of diagnosis or a specific ACKD-related molecular pathway still has to be determined [39]. Although the histological spectrum of ESRD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [38-40]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [41] with indolent clinical behaviour, likely due to early detection in patients with ESRD on periodic follow-up [17].

*3.4.3 **Papillary adenoma***

These tumours have a papillary or tubular architecture of low nuclear grade and may be up to 15 mm in diameter, or smaller [42], according to the WHO 2016 classification [17].

*3.4.4 **Hereditary kidney tumours***

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (< 46 years old) of all RCC tumours [43]. Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial nonsyndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [41, 42, 44, 45].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [46, 47]. In most hereditary RCCs nephron-sparing approaches are recommended. The exceptions are HLRCC and SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of these lesions. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter, to reduce interventions [48]. Active surveillance (AS) for VHL, BDH and HPRCC should, in individual patients, follow the growth kinetics, size and location of the tumours, rather than apply a standardised follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes. Multi-disciplinary and co-ordinated care should be offered, where appropriate [49].

Although not hereditary, somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults diagnosed with RCC [50].

*3.4.5 **Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [51]. Overall prevalence is 0.44%, with 0.6% in female and 0.3% in male populations. Only 5% of these patients present with multiple AMLs [52]. Angiomyolipoma belongs to a family of so-called PEComas (perivascular epithelioid cell tumours), characterised by the proliferation of perivascular epithelioid cells. Some PEComas can behave aggressively and can even produce distant metastases. Classic AMLs are completely benign [17, 42, 53]. Ultrasound (US), CT, and magnetic resonance imaging (MRI) often lead to the diagnosis of AMLs due to the presence of adipose tissue, however in fat poor AML, diagnostic imaging cannot

reliably identify these lesions. Percutaneous biopsy is rarely useful. Renal tumours that cannot be clearly identified as benign during the initial diagnostic work-up should be treated according to the recommendations provided for the treatment of RCC in these Guidelines. In tuberous sclerosis, AML can be found in enlarged lymph nodes (LNs), which does not represent metastatic spread but a multicentric spread of AMLs. In rare cases, an extension of a non-malignant thrombus into the renal vein or inferior vena cava can be found, associated with an angiotrophic-type growth of AML. Epithelioid AML, a very rare variant of AML, consists of at least 80% epithelioid cells [42, 53]. Epithelioid AMLs are potentially malignant with a highly variable proportion of cases with aggressive behaviour [54]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2016 [42, 53]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [5].

In some cases, larger AMLs can cause local pain. The main complication of AMLs is spontaneous bleeding in the retroperitoneum or into the collecting system, which can be life threatening. Bleeding is caused by spontaneous rupture of the tumour. Little is known about the risk factors for bleeding, but it is believed to increase with tumour size and may be related to the angiogenic component of the tumour that includes irregular blood vessels [5]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [55, 56].

3.4.5.1 Treatment

Active surveillance is the most appropriate option for most AMLs (48%). In a group of patients on AS, only 11% of AMLs showed growth, spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [5, 57] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4-cm cut-off should not per se trigger active treatment [5]. When surgery is indicated, NSS is the preferred option, if technically feasible. Main disadvantages of less invasive selective arterial embolisation (SAE) are more recurrences and a need for secondary treatment (0.85% for surgery vs. 31% for SAE). For thermal ablation only limited data is available, and this option is used less frequently [5].

Active treatment (SAE, surgery or ablation) should be instigated in case of persistent pain, ruptured AML (acute or repeated bleeding) or in case of a very large AML. Specific patient circumstances may influence the choice to offer active treatment; such as patients at high risk of abdominal trauma, females of childbearing age or patients in whom follow-up or access to emergency care may be inadequate.

In patients diagnosed with tuberous sclerosis, size reduction of often bilateral AMLs can be induced by inhibiting the mTOR pathway using everolimus, as demonstrated in RCTs [58, 59].

*3.4.6 **Renal oncocytoma***

Oncocytoma is a benign tumour representing 3-7% of all solid renal tumours and its incidence increases to 18% when tumours < 4 cm are considered [17, 57]. The diagnostic accuracy of imaging modalities (CT, MRI) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [17, 57]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial- or RN with subsequent histopathological verification. However, due to the inability of modern imaging techniques to differentiate benign from malignant renal masses, there is a renewed interest in renal mass biopsy (RMB) prior to surgical intervention. Accuracy of the biopsy and management of advanced/progressing oncocytomas need to be considered in this context since oncocytic renal neoplasms diagnosed by RMB at histological examination after surgery showed oncocytoma in only 64.6% of cases. The remainder of the tumours were mainly chRCC (18.7% including 6.3% hybrid oncocytic/chromophobe tumours which have now been grouped histologically with chRCC) [17], other RCCs (12.5%), and other benign lesions (4.2%) [60]. The majority of oncocytomas slowly progress in size with an annual growth rate < 14 mm [61-63]. Preliminary data show that AS may be a safe way to manage oncocytoma in appropriately selected patients.

Table 3.1: Other renal cortical tumours, and recommendations for treatment (strength rating: weak) [17]

Entity	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery. Nivolumab and ipilimumab. Sunitinib, gemcitabine plus doxorubicin is also an option [64].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	Surgery, nephron-sparing surgery (NSS).
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The hazard ratio (HR) CSS in comparison with ccRCC is 4.49 [21].	High, very aggressive. Median survival 30 months [65].	Surgery. Response to targeted therapies is poor [66].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [65].	Surgery. Different chemotherapy regimens, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. Less commonly, *TFEB* located on the short arm of chromosome 6 (6p21) [67].	High	Surgery. Vascular endothelial growth factor (VEGF)-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS. VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS.
Acquired cystic disease-associated RCC		Low	Surgery.
Clear-cell papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, new entity in the 2016 WHO classification, caused by a germline mutation of the fumarate hydratase gene [17].	High	Surgery. No data about treatment of metastatic disease.
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Variable	Surgery.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed epithelial and stromal tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS.
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [68, 69].	Benign	Observation (when histologically confirmed) [62, 63, 70]. NSS.

Renal cysts	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Malignant or benign	Treatment or follow-up Recommendation based on Bosniak classification. See table 5.1

*3.4.7 **Cystic renal tumours***

Cystic renal lesions are classified according to the Bosniak classification (see Section 5.2.5). Bosniak I and II cysts are benign lesions which do not require follow up [71]. Bosniak IV cysts are mostly malignant tumours with pseudocystic changes only. Bosniak IIF and III cysts remain challenging for clinicians. The differentiation of benign and malignant tumour in categories IIF/III is based on imaging, mostly CT, with an increasing role of MRI and contrast enhanced ultrasound (CEUS). Computed tomography shows poor sensitivity (36%) and specificity (76%; κ [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity (κ = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS (κ = 0.95) [72]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44-0.58) in Bosniak III and 0.89 (0.83-0.92) in Bosniak IV cysts, respectively. In a SR, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [71]. The updated Bosniak classification strengthens the classification and includes MRI diagnostic criteria [73].

The most common histological type for Bosniak III cysts is ccRCC with pseudocystic changes and low malignant potential [74, 75]; multilocular cystic renal neoplasm of low malignant potential ([MCRNLMP], formerly mcRCC (see Section 3.2 and Table 3.1); pRCC type I (very low malignant potential); benign multilocular cyst; benign group of renal epithelial and stromal tumours (REST); and other rare entities. Surgery in Bosniak III cysts will result in overtreatment in 49% of the tumours which are lesions with a low malignant potential. In view of the excellent outcome of these patients in general, a surveillance approach may also be an alternative to surgical treatment [71, 73, 76, 77].

3.5 Summary of evidence and recommendations for the management of other renal tumours

Summary of evidence	**LE**
A variety of renal tumours exist of which approximately 15% are benign.	1b
Recent histological work up of Bosniak III cysts shows low risk of malignant potential.	2

3.6 Recommendations for the management of other renal tumours

Recommendations	**Strength rating**
Treat Bosniak type III cysts the same as RCC or offer active surveillance.	Weak
Treat Bosniak type IV cysts the same as RCC.	Strong
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Offer systemic therapy to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak
Prior to management, perform pre-operative renal mass biopsies in patients with unclear kidney lesions.	Weak
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak
Only offer radical nephrectomy to patients with localised renal medullary carcinoma after a favourable response to systemic therapy.	Weak
Base systemic therapy for renal medullary carcinoma on chemotherapy regiments containing cisplatinum such as cisplatin plus gemcitabine.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [78], but requires continuous re-assessment [17, 79]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single and multi-institution studies [80, 81]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer.
- The value of size stratification of T2 tumours has been questioned [82].
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion, but, is nevertheless included in the same pT3a stage group [83-85] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [81].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [86, 87] (LE: 4).

Table 4.1: 2017 TNM classification system [78]

T - Primary Tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm or less	
	T1b	Tumour > 4 cm but ≤ 7 cm	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm	
	T2b	Tumours > 10 cm, limited to the kidney	
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia		
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia	
	T3b	Tumour grossly extends into the vena cava below diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava	
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
pTNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.

4.2 Anatomic classification systems

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the description of renal tumours [88-90]. These systems include assessment of tumour size, exophytic/endophytic

properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of PN and tumour ablation series. However, when selecting the most optimal treatment option, anatomic scores must be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [81, 91] (LE: 3). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease [36, 92] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [93] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [94] (LE: 3).

*5.1.1 **Physical examination***

Physical examination has a limited role in RCC diagnosis. However, the following findings should prompt radiological examinations:

- palpable abdominal mass;
- palpable cervical lymphadenopathy;
- non-reducing varicocele and bilateral lower extremity oedema, which suggests venous involvement.

*5.1.2 **Laboratory findings***

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium [95], coagulation study, and urinalysis (LE: 4). For central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment should be considered in order to exclude urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations [96, 97] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased GFR;
- when renal function is clinically important; e.g., in patients with a solitary kidney or multiple or bilateral tumours.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

5.2 maging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [91] (LE: 3). Renal masses are classified as solid or cystic based on imaging findings.

*5.2.1 **Presence of enhancement***

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement [98] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases [99-101] (LE: 3).

*5.2.2 **Computed tomography or magnetic resonance imaging***

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed before, and after, administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before, and after, contrast administration. A change of fifteen, or more, HUs demonstrates enhancement [102] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free

AML from malignant renal neoplasms [68, 103-105] (LE: 3). Abdominal CT provides information on [106]:

- function and morphology of the contralateral kidney [107] (LE: 3);
- primary tumour extension;
- venous involvement;
- enlargement of locoregional LNs;
- condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced CT angiography is useful in selected cases when detailed information on the renal vascular supply is needed [108, 109]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [6] (LE: 1b).

Magnetic resonance imaging may provide additional information on venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [110-113] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [111, 114] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [115].

For the diagnosis of complex renal cysts (Bosniak IIF-III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%; $\kappa = 0.11$); MRI had 71% sensitivity and 91% specificity ($\kappa = 0.64$). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% ($\kappa = 0.95$) [72].

In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative although only limited data exist correlating diagnostic radiation exposure to the development of secondary cancers [116].

*5.2.3 **Other investigations***

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision making [96, 97] (LE: 2a). Positron-emission tomography (PET) is not recommended [6, 117] (LE: 1b).

*5.2.4 **Radiographic investigations to evaluate RCC metastases***

Chest CT is accurate for chest staging [86, 87, 118-120] (LE: 3). There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [118, 121, 122] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [121, 123, 124] (LE: 3).

*5.2.5 **Bosniak classification of renal cystic masses***

This system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [125, 126] (LE: 3), and also advocates treatment for each category (Table 5.1). A new updated Bosniak classification has been proposed that strengthens the classification and includes MRI diagnostic criteria [73].

Table 5.1: Bosniak classification of renal cysts [125]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intra-renal, non-enhancing, high attenuation renal lesions ≥ 3 cm. Generally well-marginated.	Follow-up, up to five years. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance – see Chapter 7. Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

5.3 Renal tumour biopsy

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable medical and surgical treatment strategy in the setting of metastatic disease [127-132] (LE: 3).

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4). A multicentre study assessing 542 surgically removed small renal masses showed that the likelihood of benign findings at pathology is significantly lower in centres where biopsies are performed (5% vs. 16%), suggesting that biopsies can reduce surgery for benign tumours and the potential for short-term and long-term morbidity associated with these procedures [133].

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle aspiration (FNA). Biopsies can be performed under US or CT guidance, with a similar diagnostic yield [130, 134] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [127, 131, 135] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [127, 131] (LE: 3).

Core biopsies are preferred for the characterisation of solid renal masses while a combination with FNA can improve accuracy [136-138] (LE: 2a). An SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel. Fifty-seven articles with a total of 5,228 patients were included in the analysis. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [138]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [127, 130, 134] (LE: 2b).

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy. The above-mentioned meta-analysis showed that sensitivity and specificity of diagnostic core biopsies for the diagnosis of malignancy are 99.1% and 99.7%, respectively [138] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [128-132, 134, 135, 139] (LE: 2a). If a biopsy is non-diagnostic, and radiologic findings are suspicious for malignancy, a further biopsy or surgical exploration should be considered (LE: 4). Repeat biopsies have been reported to be diagnostic in a high proportion of cases (83-100%) [127, 140-142].

Accuracy of renal tumour biopsies for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on renal tumour biopsy and on the surgical specimen of the following PN or RN was 90.3% in the pooled analysis [138].

Assessment of tumour grade on core biopsies is challenging. In the pooled analysis the overall accuracy for nuclear grading was poor (62.5%), but significantly improved (87%) using a simplified two-tier system (high vs. low grade) [138] (LE: 2a).

The ideal number and location of core biopsies are not defined. However, at least two good quality cores should be obtained and necrotic areas should be avoided to maximise diagnostic yield [127, 130, 143, 144] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [145] (LE: 2b). In cT2 or greater renal masses, multiple core biopsies taken from at least four separate solid enhancing areas in the tumour were shown to achieve a higher diagnostic yield and a higher accuracy to identify sarcomatoid features, without increasing the complication rate [146].

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended alone, unless areas with a solid pattern are present (Bosniak IV cysts) [127, 130, 138] (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [131, 139, 140, 147, 148] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [138]. Tumour seeding along the needle tract has been regarded as anecdotal in large series and pooled analyses on renal tumour biopsies. Especially the coaxial technique has been regarded as a safe method to avoid any seeding of tumour cells. However, authors recently reported on 7 patients in whom tumour seeding was identified on histological examination of the resection specimen after surgical resection of RCC following diagnostic percutaneous biopsy [149]. Six of the 7 cases were of the pRCC type. The clinical significance of these findings is still uncertain but only one of these patients developed local tumour recurrence at the site of the previous biopsy [149].

Spontaneously resolving subcapsular/perinephric haematomas are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0-1.4%; 0.7% in the pooled analysis) and generally self-limiting [138].

Percutaneous biopsy of renal hilar masses is technically feasible with a diagnostic yield similar to that of cortical masses, but with significantly higher post-procedural bleeding compared with cortical masses [150].

5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and mRCC.	2
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2
Contrast enhanced ultrasound has a high sensitivity and specificity for characterisation of renal masses.	2
Ultrasound, power-Doppler US and positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Use magnetic resonance imaging to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, mainly contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	Strong
Do not routinely use bone scan and/or positron-emission tomography CT for staging of renal cell carcinoma.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

6. PROGNOSTIC FACTORS

6.1 Classification

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.2 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [151] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system [152, 153]. Fuhrman nuclear grade is the most widely accepted grading system [154]. Although affected by intra- and inter-observer variability, Fuhrman nuclear grade is an independent prognostic factor [155]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [156, 157] (LE: 3). The new WHO/ISUP grading system that will replace the Fuhrman grading, needs to be validated for prognostic systems and nomograms [158].

In a univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [159, 160]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [20, 160] (LE: 3). In a cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were shown, whereas pRCC type I displayed a significantly reduced risk of death compared with ccRCC and pRCC type II [161]. Differences in tumour stage, grade and CSS between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [20, 21, 162]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [163]	CSS (HR)
clear-cell RCC	80-90%	28%	28.5%	Referent
papillary RCC	6-15%	17.6%	28.8%	0.64-0.85
chromophobe RCC	2-5%	16.9%	32.7%*	0.24-0.56

** The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC.*
CSS = cancer-specific survival; HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The 5-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of TKIs [164, 165]. Sarcomatoid changes can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: Cancer-specific survival by stage and histopathological grade in RCCs [21]

Grade	HR (95% CI)
T1N0M0	Referent
T2N0M0	2.71 (2.17-3.39)
T3N0M0	5.20 (4.36-6.21)
T4N0M0	16.88 (12.40-22.98)
N+M0	16.33 (12.89-20.73)
M+	33.23 (28.18-39.18)
Grade 1	Referent
Grade 2	1.16 (0.94-1.42)
Grade 3	1.97 (1.60-2.43)
Grade 4	2.82 (2.08-3.31)

CI = confidential interval. HR = hazard ratio.

Long-term survival in RCC patients treated by RN or PN between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [162] (Table 6.3).

Table 6.3: Cancer-specific survival of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
clear-cell RCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
papillary RCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chromophobe RCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

Two subgroups of pRCC with different outcomes have been identified [166]. Type I have a favourable prognosis. Type II are mostly high-grade tumours with a propensity for metastases (LE: 3). For more details, see Section 3.2 - Histological diagnosis. Renal cell carcinoma with Xp 11.2 translocation has a poor prognosis [167]. Its incidence is low, but it should be systematically addressed in young patients. Renal cell carcinoma type classification has been confirmed by cytogenetic and genetic analyses [163, 168, 169] (LE: 2b).

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil-to-lymphocyte ratio, C-reactive protein (CRP) and albumin [94, 170-174] (LE: 3). Even though obesity is an aetiological factor for RCC, obesity has also been observed to provide prognostic information. In a Korean cohort study, obesity appeared to be a favourable prognostic factor in male, but not in female, patients with non-metastatic RCC [175].

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [176], PTEN (phosphatase and tensin homolog) cell cycle, E-cadherin, osteopontin [177] CD44 (cell adhesion) [178, 179], CXCR4 [180], and other cell cycle and proliferative markers are being investigated [181, 182] (LE: 3). As yet, none of these markers have been shown to improve the predictive accuracy of current prognostic systems and, so far, none have been externally validated. Their routine use in clinical practice is, at present, not recommended. In a pre-diagnostic study, elevated plasma Kidney Injury molecule-1 (KIM-1) concentrations were found to predict RCC up to 5 years prior to diagnosis and were associated with a shorter survival time [183]. KIM-1 is a protein which is expressed at low levels in a healthy kidney.

Several retrospective studies and large molecular screening programs have identified mutated genes in ccRCC with distinct clinical outcomes. The expression of the *BAP1* and *PBRM1* genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [184-186]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [185]. Validated data from surgical series can predict relapse using a 16-gene signature. This signature is likely to be adopted in clinical trials and may be helpful in the clinical setting in due time [187].

The recognition of the potential relevance of immunotherapy as an approach to RCC management is growing. Prognostic information of cytokines and blockade of immune-inhibitory molecules such as PD-L1 have shown promising therapeutic results. A meta-analysis established a correlation between PD-L1 expression, poor prognosis and advanced clinicopathological features of RCC [188]. Emerging evidence of chromosomal alterations, through Genome-Wide Association Studies (GWAS), miRNA, SNPs and gene methylations all contribute to improving diagnostic and prognostic information. A number of studies have confirmed prognostic information based on gain of chromosomal regions 7q, 8q and 20q, and chromosomal losses of regions 9p, 9q and 14q, which are associated with poor survival. CpG-methylation-based assays also independently predict survival in ccRCC [189, 190]. An international collaboration is currently investigating GWAS loci for prognostic information.

6.6 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [191-197]. These may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An advantage of nomograms is their ability to measure predictive accuracy, allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its predictive accuracy is superior to conventional post-operative prognostic schemes [198]. Recently, new pre-operative nomograms with excellent predictive accuracy have been designed [199, 200].

Table 6.4 summarises the current most relevant prognostic systems.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour nuclear grade, and RCC subtype provide important prognostic information [201].	2

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use grading systems and classify renal cell carcinoma type.	Strong
Use prognostic systems in the metastatic setting.	Strong
In localised disease, use integrated prognostic systems or nomograms to assess risk of recurrence.	Strong

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models	Variables													
		TNM Stage [151]	ECOG PS [202]	Karnofsky PS [203]*	RCC related symptoms	Fuhrman grade [154]**	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS [192]***	x	x			x								
	SSIGN [193]	x				x	x	x						
	Post-operative Karakiewicz's nomogram [196]	x			x	x		x						
Metastatic RCC	MSKCC prognostic system [204]****			x					x	x	x	x		
	IMDC [205]			x					x		x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status (see details; Section 7.4.2.1, Table 7.1); IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; SSIGN = Stage Size Grade Necrosis; TNM = Tumour, Node Metastasis (classification); UISS = University of California Los Angeles integrated staging system.

**Karnofsky score calculator: https://www.thecalculator.co/health/Karnofsky-Score-for-Performance-Status-Calculator-961.html*

***Fuhrman nuclear grade: https://www.mdcalc.com/fuhrman-nuclear-grade-clear-cell-renal-carcinoma*

****UISS: https://qxmd.com/calculate/calculator_170/prognosis-in-renal-cell-carcinoma-uiss*

*****MSKCC: https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc*

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

*7.1.1 **Introduction***

Sections 7.1.2 and 7.2.4.2 are underpinned by a SR which includes all relevant published literature comparing surgical management of localised RCC (T1-2N0M0). Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Historically, surgery has been the benchmark for the treatment of localised RCC.

*7.1.2 **Surgical treatment***

7.1.2.1 Nephron-sparing surgery versus radical nephrectomy

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [206]. There is only one prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm), showing comparable CSS for PN vs. RN [207]. Partial nephrectomy demonstrated to preserve kidney function better after surgery, thereby potentially lowering the risk of development of cardiovascular disorders [206, 208-212].

When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [209, 213] as well as improved OS for PN compared to RN. However, in some series this held true only for a younger patient population and/or patients without significant comorbidity at the time of the surgical intervention [214, 215].

A Cochrane review found that PN for clinically localised RCC was associated with a reduced time-to-death of any cause compared to RN, whereas serious adverse event rates, CSS and time-to-recurrence were similar between the two groups [216].

An analysis of the Medicare database [217] could not demonstrate an OS benefit for patients ≥ 75 years of age when RN or PN were compared with non-surgical management. Another series that addressed this question and also included Medicare patients suggested an OS benefit in an older RCC patient population (75-80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.* compared patients who underwent PN for RCC with a non-cancer healthy control group via a retrospective database analysis; showing an OS benefit for the cancer cohort [218]. These conflicting results may be an indication that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries.

In contrast, the only prospectively randomised, but prematurely closed and heavily underpowered, trial did not demonstrate an inferiority of RN vs. PN in terms of OS [207]. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment (either RN or PN), generally present with stable long-term renal function [212]. Adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical chronic kidney disease (CKD) [219]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD which requires haemodialysis.

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN, irrespective of the surgical approach used (open vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general patients' health status deteriorated following both approaches [220, 221].

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, an EORTC randomised trial showed that PN for small, easily resectable, incidentally discovered RCC, in the presence of a normal contralateral kidney, can be performed safely with slightly higher complication rates than after RN [221].

In view of the above, and since oncological safety (CSS and RFS) of PN has been proven to be similar for RN, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term potentially limits the incidence of cardiovascular disorders. Whether decreased mortality from any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment option as it avoids further deterioration of kidney function; the latter being associated with a higher risk of development of ESRD and the need for haemodialysis.

A study compared the survival outcomes in patients with larger (≥ 7 cm) ccRCC treated with PN vs. RN with long-term follow-up (median 102 months). Compared to the RN group, the PN group had a significantly longer

median OS (p = 0.014) and median CSS (p = 0.04) [222]. A SR and meta-analysis of comparative studies of PN vs. RN for cT1b and T2 RCCs observed that the PN group had a lower likelihood of tumour recurrence (OR 0.6, p < 0.001), cancer-specific mortality (OR 0.58, p = 0.001), and all-cause mortality (OR 0.67, p = 0.005) compared to the RN group. For T2 tumours the estimated blood loss was higher for PN (p < 0.001), as was the likelihood of complications (RR: 2.0, p < 0.001). Both the recurrence rate (RR: 0.61, p = 0.004) and cancer-specific mortality (RR: 0.65, p = 0.03) were lower for PN [223].

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN with or without, ipsilateral adrenalectomy [224]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at 5 or 10 years was seen with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 interventions were for benign lesions [224].

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

The indication for LN dissection (LND) together with PN or RN is still controversial [225]. The clinical assessment of LN status is based on the detection of an enlargement of LNs either by CT/MRI or intraoperative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [226]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [227]. For clinically positive LNs (cN+) see Section 7.2.2.

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive LND preferably in patients at high risk for lymphogenic spread. In a large retrospective study, the outcomes of RN with or without LND in patients with high-risk non-metastatic RCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, or cancer-specific or all-cause mortality. Neither eLND nor the extent of LND was associated with improved oncologic outcomes [228]. The number of LN metastases (< / > 4) as well as the intra- and extracapsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [227, 229-231]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extranodal extension. On the basis of a retrospective Surveillance, Epidemiology and End Results (SEER) database analysis of > 9,000 patients no effects of an extended LND on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [232]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of 10 for the number of nodes dissected resulted in a 10% absolute increase in DSS. In addition, in a larger cohort of 1,983 patients, Capitanio *et al.* demonstrated that extended LND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [233]. As to morbidity related to eLND, a recent retrospective propensity score analysis from a large single-centre database showed that eLND is not associated with an increased risk of Clavien grade ≥ 3 complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [234].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of only 4%, the risk of lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to LND [226]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Additionally, only 25% of patients with pT3 tumours underwent a complete LND. The LN template used by the authors was also not clearly stated.

The optimal extent of LND remains controversial. Retrospective studies suggest that an extended LND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [227, 235, 236]. At least 15 LNs should be removed [233, 237]. Sentinel LND is an investigational technique [238, 239].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [240, 241]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [242, 243]. These indications will be revisited in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

7.1.2.2.4 Summary of evidence and recommendations for the treatment of localised RCC

Summary of evidence	LE
The oncological outcome in terms of OS following PN equals that of RN in patients with c/p T1 RCC.	1b
Ipsilateral adrenalectomy during RN or PN has no survival advantage in the absence of clinically evident adrenal involvement.	3
In patients with localised disease without evidence of LN metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	2b
Retrospective studies suggest a clinical benefit associated with lymphadenectomy in high-risk patients.	2b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

*7.1.3 **Radical and partial nephrectomy techniques***

7.1.3.1 Radical nephrectomy techniques

No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A cohort study [244] and retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher stage disease and locally more advanced tumours [245-247]. Based on a SR, less morbidity was found for laparoscopic vs. open RN [206].

Data from one RCT [246] and two NRSs [248, 249] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group as compared with the open group. Convalescence time was also significantly shorter [249]. No difference in the number of patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all 3 studies [246, 248, 249]. Surgical complication rates were low with very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [248].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal tumours ≥ T2. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of hospital stay and convalescence compared to those who underwent open RN [247, 249, 250]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [247, 249, 250] (LE: 2b). Another multi-centre propensity matched analysis compared laparoscopic- and open surgery for pT3a RCC, showing no significant difference in 3-year RFS between groups [251]. The best approach for RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [251, 252] and one quasi-randomised study [253]. Quality of life variables were similar for both approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [253] and one database review and estimated 5-year OS, CSS, and RFS rates were comparable [254]. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN cohort [253, 254]. However, the sample size was small.

A SR reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause cancer-specific mortality [255]. Similar results were seen in observational cohort studies comparing ‘portless’ and 3-port laparoscopic RN, with similar peri-operative outcomes [256, 257].

7.1.3.2 Partial nephrectomy techniques

Studies comparing laparoscopic and open PN found no difference in PFS [258-261] and OS [260, 261] in centres with laparoscopic expertise. However, the oncological safety of laparoscopic vs. open PN has, so far,

only been addressed in studies with relatively limited follow-up. Gill *et al.* suggested comparable oncological efficacy even in case of higher stage tumours (pT1b/pT3a). However, the higher number of patients treated with open surgery in this series might reflect a selection bias by offering laparoscopic surgery in case of a less complex anatomy [262]. The mean estimated blood loss was found to be lower with the laparoscopic approach [258, 260, 263], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [258, 260]. Operative time is generally longer with the laparoscopic approach [259-261] and warm ischaemia time is shorter with the open approach [258, 260, 263, 264]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [261], but not after follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [264]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [265]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [266].

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN than in open PN patients, but there was no significant difference in high Clavien grade complications. Three months after the operation, glomerular filtration rate was lower in the HALPN than in the open PN group [267].

The feasibility of laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm its safety and clinical role [268].

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, with 5 years of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [269].

One study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate- early- and short-term complications, variation in creatinine levels and pathologic margins were similar among the groups [270]. Another study included the 50 last patients having undergone laparoscopic and robotic PN for T1-T2 renal tumours by two different surgeons with an experience of over 200 procedures each in laparoscopic and robotic PN and robotic-assisted partial nephrectomy (RAPN), respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between RAPN and LPN when performed by highly experienced surgeons [271].

A multicentre French prospective database compared the outcomes of 1,800 patients who underwent open PN and robot-assisted PN. Although the follow-up was shorter, there was a decreased morbidity in the robotic-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [272].

A meta-analysis, including a series of NSS with variable methodological quality compared the peri-operative outcomes of robot-assisted- and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of hospital stay. No significant difference was observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins [273].

In a recent analysis of 8,753 patients who underwent PN, an inverse non-linear relationship of hospital volume with morbidity of PN was observed, with a plateauing seen at 35 to 40 cases per year overall, and 18 to 20 cases for the robotic approach [274]. A retrospective study of a U.S. National Cancer Database looked at the prognostic impact of hospital volume and the outcomes of robot-assisted PN, including 18,724 cases. This study shows that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower positive surgical margin rates [275]. A French study, including 1,222 RAPN, has shown that hospital volume is the main predictive factor of Trifecta achievement after adjustment for other variables, including surgeon volume [276].

7.1.3.3 Positive margins on histopathological specimens of resected tumours

A positive surgical margin is encountered in about 2-8% of PNs [273]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [277, 278]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite positive surgical margins [279]. A positive surgical margin status occurs more frequently in cases in which surgery is imperative (solitary kidneys and bilateral tumours) and in patients with adverse pathological features (pT2a, pT3a, grade III-IV) [280-283]. The potential negative impact of a positive margin status on the oncologic outcome is still controversial [277].

The majority of retrospective analyses reported so far indicated that positive surgical margins do not translate into a higher risk of metastases or a decreased CSS [281, 282]. On the other hand, another retrospective study of a large single institutional series showed that positive surgical margins are an independent predictor of PFS due to a higher incidence of distant and local relapses [284].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy [285]. Local tumour bed recurrences were found in 16% in patients with positive surgical margins compared with 3% in those with negative margins [280], Therefore, RN or re-resection of margins can result in overtreatment in many cases. Patients with positive surgical margins should be informed that they will need a more intense surveillance (imaging) follow-up and that they are at increased risk of secondary local therapies [281, 286]. On the other hand, protection from recurrence is not ensured by negative surgical margins [287].

7.1.3.4 Summary of evidence and recommendations for radical and partial nephrectomy techniques

Summary of evidence	**LE**
Laparoscopic radical nephrectomy (RN) has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.	3

Recommendations	**Strength rating**
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological-, functional- and peri-operative outcomes.	Strong

*7.1.4 **Therapeutic approaches as alternatives to surgery***

7.1.4.1 Surgical versus non-surgical treatment

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality in patients treated with surgery [217, 288, 289]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable for surgery. Other-cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [288]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [290-292].

7.1.4.2 Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [293, 294]. Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [295]. The concept of AS differs from the concept of watchful waiting; watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and do not require follow-up imaging, unless clinically indicated.

In the largest reported series of AS the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [296, 297].

A single-institutional comparative study evaluating patients aged > 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours. However, a multi-variate analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [293]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [298].

Results from the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published [299]. This prospective NRS enrolled 497 patients with solid renal masses < 4 cm who selected either AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often had multiple and bilateral lesions. In patients who elected AS in this study the overall median small renal mass growth rate was

0.09 cm/year with a median follow-up of 1.83 years. The growth rate and variability decreased with longer follow-up. No patients developed metastatic disease or died of RCC [300].

Overall survival for primary intervention and AS was 98% and 96% at 2 years, and 92% and 75% at 5 years, respectively (p = 0.06). At 5 years, CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow up [299]. Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate for initially monitoring small renal masses, followed, if required, by treatment for progression [295-297, 301-304].

A multicentre study assessed QoL of patients undergoing immediate intervention vs. AS. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least one year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on AS [305].

7.1.4.3 Ablative therapies

7.1.4.3.1 Cryoablation

Cryoablation is performed using either a percutaneous or a laparoscopic-assisted approach. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [306-308]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow up compared with 118 patients treated percutaneously with a shorter follow up [307]. A shorter average length of hospital stay was found with the percutaneous technique [307-309].

A recent systematic review including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [310]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

7.1.4.3.2 Cryoablation versus partial nephrectomy

Studies compared open-, laparoscopic- or robotic PN with percutaneous or laparoscopic cryoablation. Oncological outcomes were mixed, with some studies showing no difference in OS, CSS, RFS, disease-free survival (DFS), local recurrence or progression to metastatic disease [311, 312], with some showing significant benefit for the PN techniques for some or all of these outcomes [313-316]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed an oncological benefit for cryoablation over PN.

Peri-operative outcomes, complication rates and other QoL measures were mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [311-313], whilst also finding no differences in other peri-operative outcomes such as recovery times, complication rates or post-operative serum creatinine levels. Two studies [315, 316] reported specific Clavien rates, with mostly non-significant differences, which were mixed for intra-operative vs. post-operative complications. Estimated GFRs were not significantly different in two of the studies, but in favour of cryoablation in a third [314-316]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [314], another strongly in favour of PN [315], and the third showing no difference [316]. One study compared PN with ablation therapy, either cryoablation or RFA [317], and showed significantly improved DSS at both 5 and 10 years for PN.

A study compared 1,057 patients treated by PN to 180 treated by RFA and 187 treated by cryoablation for a cT1 tumour and found no difference regarding RFS between the three techniques. Metastasis-free survival was superior after PN and cryoablation compared to RFA for cT1a patients. However, follow-up of patients treated by thermal ablations was shorter [214].

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Four studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [318-321]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously.

One study with a limited number of patients found a higher rate of incomplete ablation in patients treated by percutaneous RFA [320]. However, no differences in recurrence or CSS were found in the three comparative studies.

7.1.4.3.4 Radiofrequency ablation versus partial nephrectomy

Most publications about RFA are retrospective cohort studies with a low number of patients and limited follow up. Some studies retrospectively compared RFA to surgery in patients with T1a tumours [322-324].

One study compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS [298]. Another study retrospectively reviewed 105 T1a patients treated

by percutaneous RFA or RN. Cancer-specific survival was 100% in both groups [322]. Overall survival was lower in the RFA group but patients treated with surgery were younger [322].

A retrospective evaluation comparing RFA with LPN concluded after a median follow-up time of 27.5 months that both methods achieved equivalent secondary efficacy rates. Radiofrequency ablation included several treatment sessions, but session and hospitalisation times were shorter, and complications were less frequent than for LPN. The differences remained after adjustment for renal tumour complexity [325].

A meta-analysis reported comparable complication rates and post-operative estimated glomerular filtration rates (eGFR) between RFA and PN [326]. The local tumour recurrence rate was higher in the RFA group than in the PN group (OR = 1.81) but there was no difference regarding the occurrence of distant metastasis.

A retrospective analysis of 264 patients treated with either percutaneous RFA or PN and a median follow up of 78 months showed that T1b ccRCC patients have less favourable outcomes for percutaneous RFA as compared to PN. However, percutaneous RFA provides comparable oncological outcomes to PN in patients with T1b non-ccRCC. The authors conclude that it may be necessary to take RCC subtypes into consideration when selecting either PN or percutaneous RFA as a surgical approach to treat T1b RCC [327].

A recent large systematic review and meta-analysis including 3,974 patients who had undergone an ablative procedure (RFA or cryoablation) or PN showed higher all-cause mortality and cancer-specific mortality rates for ablation than for PN (HR: 2.11 and 3.84, respectively). No statistically significant difference in local recurrence rates or risk of metastasis was seen. Complication rates were lower for ablation than for PN (13% vs. 17.6%, $p < 0.05$). A significantly greater decrease in eGFR was observed after PN vs. ablation therapy [328].

7.1.4.3.5 Cryoablation and thermal ablation versus deferred therapy

An analysis of the SEER registry included 733 patients with histopathologically confirmed localised T1a ccRCC who either received cryosurgery (n = 315) or thermal ablation (n = 155), as well as patients who had deferred therapy (n = 263) [329]. Patients treated with cryosurgery and thermal ablation had a statistically significant CSS benefit compared to those who had deferred therapy (cryosurgery HR: 0.25, 95% CI: 0.14–0.45, $p < 0.001$; thermal ablation HR: 0.27, 95% CI: 0.13–0.55, $p < 0.001$, after adjustment for age at diagnosis, tumour grade, and size).

However, in a systematic review and meta-analysis of 99 studies representing 6,471 small renal lesions, no statistical differences were detected in the incidence of metastatic progression regardless of whether the lesions were excised, ablated with cryotherapy or radiofrequency or observed [330].

7.1.4.3.6 Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [331, 332]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study [331] reported improvement with RFA, while the other [332] reported a benefit with cryoablation. One study [331] reported no differences in Clavien complication rates between the techniques.

A recent retrospective series including 384 patients (mean age 71 years; range 22-88 years) evaluated the peri-operative outcomes of thermal ablation with microwave, RFA, and cryoablation for stage T1c RCC. Complication rates and immediate renal function changes were similar among the three ablation modalities. Microwave ablation was associated with a significantly decreased ablation time ($p < 0.05$), procedural time ($p < 0.05$), and dosage of sedative medication ($p < 0.05$) compared with RF ablation and cryoablation. The authors conclude that CT-guided percutaneous microwave ablation is comparable to RF ablation or cryoablation for the treatment of stage T1N0M0 RCC with regard to treatment response and is associated with shorter treatment times and less sedation than RF ablation or cryoablation [333].

7.1.4.3.7 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, laser ablation, high-intensity focused US ablation and irreversible electroporation. However, these techniques are considered experimental.

7.1.4.3.8 Summary of evidence and recommendation for therapeutic approaches as alternative to surgery

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for thermal ablation therapies compared to partial nephrectomy.	3

Recommendation	Strength rating
Offer active surveillance, radiofrequency ablation or cryoablation to frail and/or comorbid patients with small renal masses.	Weak
When radiofrequency ablation, cryoablation and active surveillance are offered, inform patients about the higher risk of local recurrence and/or tumour progression.	Weak

7.2 Treatment of locally advanced RCC

*7.2.1 **Introduction***

In addition to the summary of evidence and recommendations outlined in Section 7.1 for localised RCC, certain therapeutic strategies arise in specific situations for locally advanced disease.

*7.2.2 **Management of clinically positive lymph nodes (cN+)***

In the presence of clinically positive LNs (cN+), LND is always justified [23]. However, the extent of LND remains controversial [227]. A systematic review and meta-analysis attempted to evaluate the role of retroperitoneal LND in non-metastatic and mRCC [334]. The review included several studies which recruited patients at high risk of LN metastases, including cN1 patients. Lymph node dissection was not associated with any survival benefit.

However, LND may provide additional staging information. A recent analysis also indicates that LND is not associated with improved oncologic outcomes in patients with radiographic lymphadenopathy (cN1) and across increasing probability thresholds of pN1 disease [228].

*7.2.3 **Management of locally advanced unresectable RCC***

In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [242, 243, 335]. The use of systemic therapy to downsize tumours is experimental and cannot be recommended outside clinical trials.

*7.2.4 **Management of RCC with venous tumour thrombus***

Tumour thrombus formation in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [336-344]. However, uncertainties remain as to the best approach for surgical treatment of these patients.

7.2.4.1 The evidence base for surgery in patients with venous tumour thrombus

Data whether patients with venous tumour thrombus should undergo surgery is derived from case series only. In one of the largest published studies a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis [341]. Thus, all patients with non-metastatic disease and venous tumour thrombus, and an acceptable PS, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation. The surgical technique and approach for each case should be selected based on the extent of tumour thrombus.

7.2.4.2 The evidence base for different surgical strategies

A systematic review was undertaken which included only comparative studies on the management of venous tumour thrombus in non-metastatic RCC [345, 346]. Only 5 studies were eligible for final inclusion, with high risk of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [347, 348]. Pre-operative embolisation was associated with increased operating time,

blood loss, hospital stay and peri-operative mortality in patients with T3 RCC [349]. No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support [350].

No surgical method was shown to be superior for the excision of venous tumour thrombus. The surgical method selected depended on the level of tumour thrombus and the grade of occlusion of the IVC [345, 347, 348, 350]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 Summary of evidence and recommendations for the management of RCC with venous tumour thrombus

Summary of evidence	**LE**
In patients with locally advanced disease due to clinically enlarged lymph nodes (LNs), the survival benefit of LN dissection is unproven but LN dissection adds staging information.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3
Tumour embolisation or inferior vena cava filter do not appear to offer any benefits.	3

Recommendations	**Strength rating**
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong

*7.2.5 **Adjuvant therapy***

There is currently no evidence from randomised phase III trials that adjuvant therapy offers a survival benefit. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [351-355] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) did not show a survival benefit [356]. Heat shock protein-peptide complex-96 (vitespen) may have a benefit in a subgroup of patients but the overall data from phase III trials were negative [357]. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [358]. No difference in DFS was observed in the overall trial analysis, but a subgroup evaluation of patients with high CAIX expression suggests a potential benefit of girentuximab in this population. Several trials investigating adjuvant sunitinib, sorafenib or pazopanib have reported whilst studies investigating sorafenib, axitinib and everolimus have completed accrual and are expected to report in the next years.

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, three RCTs comparing VEGFR-TKI vs. placebo have been published. One of the largest adjuvant trials compared sunitinib vs. sorafenib vs. placebo (ASSURE). Its interim results published in 2015 demonstrated no significant differences in DFS or OS between the experimental arms and placebo [359]. The study published its updated analysis on a subset of high-risk patients in 2018, which demonstrated 5-year DFS rates of 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo (HR: 0.94 for sunitinib vs. placebo; and HR: 0.90, 97.5% CI: 0.71-1.14 for sorafenib vs. placebo), and 5-year OS of 75.2%, 80.2%, and 76.5% (HR: 1.06, 97.5% CI: 0.78-1.45, p = 0.66, sunitinib vs. placebo; and HR: 0.80; 97.5% CI: 0.58-1.11, p = 0.12 for sorafenib vs. placebo). The results indicated that adjuvant therapy with sunitinib or sorafenib should not be given [360].

The PROTECT study included 1,135 patients between pazopanib (n = 571) and placebo (n = 564) in a 1:1 randomisation [361]. The primary endpoint was amended after 403 patients were included on pazopanib 800 mg vs. placebo, to DFS with pazopanib 600 mg. The primary analysis results of DFS in the intention to treat (ITT) pazopanib 600 mg arm were not significant (HR: 0.86; 95% CI: 0.7-1.06, p = 0.16). Disease-free survival in the ITT pazopanib 800 mg population was improved (HR: 0.69; 95% CI: 0.61 0.94, 1.06, p = 0.02). No benefit in OS was seen in the ITT pazopanib 600 mg population (HR: 0.79 [0.57-1.09, p = 0.16]). A subset analysis of these studies suggests that full-dose therapy is associated with improved DFS. Furthermore, no strong association of DFS with OS has been established for RCC [362, 363].

In contrast, the S-TRAC study included 615 patients randomised to either sunitinib or placebo [364]. The results showed a benefit of sunitinib over placebo for DFS (HR: 0.76; 95% CI: 0.59-0.98, p = 0.03) but data for OS remained immature. Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in QoL for loss of appetite and diarrhoea. The study published its updated

results in 2018; the results for DFS had not changed significantly (HR: 0.74; 95% CI: 0.55-0.99, p = 0.04) and median OS was not reached in either arm (HR: 0.92, 95% CI: 0.66-1.28, p = 0.6).

In summary, there is conflicting data in the three available studies of adjuvant therapy. A recent systematic review and meta-analysis combined the results of all three RCTs [365]. The pooled analysis of VEGFR-TKIs vs. placebo demonstrated that VEGFR-targeted therapy was not statistically significantly associated with improved DFS (HR: 0.92, 95% CI: 0.82-1.03, p = 0.16) nor OS (HR: 0.98, 95% CI: 0.84-1.15, p = 0.84) compared with placebo. The adjuvant therapy group experienced significantly higher odds of grade 3-4 adverse events (OR: 5.89, 95% CI: 4.85-7.15, p < 0.001).

In summary, there is currently a lack of proven benefits of adjuvant therapy with VEGFR-TKIs for patients with high-risk RCC after nephrectomy.

The European Medicines Agency (EMA) has not approved sunitinib for adjuvant treatment of high-risk RCC in adult patients after nephrectomy.

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
After nephrectomy in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) in one of the two available studies, but not overall survival (OS).	1b
Adjuvant sorafenib, pazopanib or axitinib does not improve DFS or OS after nephrectomy.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma.	Weak

7.3 Advanced/metastatic RCC

*7.3.1 **Local therapy of advanced/metastatic RCC***

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN+ INF-based immunotherapy vs. INF-based immunotherapy only, increased long-term survival was found in patients treated with CN [366]. However, INF-based immunotherapy is no longer relevant in contemporary clinical practice. In order to investigate the role and sequence of CN in the era of targeted therapy, a structured literature assessment was performed to identify relevant RCTs and systematic reviews published between July 1st - June 30th 2019. Two RCTs [367, 368] and a narrative systematic review were identified [369]. The narrative systematic review included both RCTs and 10 NRSs. CARMENA, a phase III non-inferiority RCT investigating immediate CN followed by sunitinib vs. sunitinib alone, showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS [370]. The trial included 450 patients with metastatic ccRCC of intermediate- and MSKCC poor risk of whom 226 were randomised to immediate CN followed by sunitinib and 224 to sunitinib alone. Patients in both arms had a median of two metastatic sites. Patients in both arms had a tumour burden of a median/mean of 140 mL of measurable disease by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, of which 80 mL accounted for the primary tumour. The study did not reach the full accrual of 576 patients and the Independent Data Monitoring Commission (IDMC) advised the trial steering committee to close the study. In an ITT analysis after a median follow-up of 50.9 months, median OS with CN was 13.9 months vs. 18.4 months with sunitinib alone (HR: 0.89; 95% CI: 0.71-1.10). This was found in both risk groups. For MSKCC intermediate-risk patients (n = 256) median OS was 19.0 months with CN and 23.4 months with sunitinib alone (HR: 0.92; 95% CI: 0.60-1.24) and for MSKCC poor risk (n = 193) 10.2 months and 13.3 months, respectively (HR: 0.86; 95% CI: 0.62-1.17). Non-inferiority was also found in two per-protocol analyses accounting for patients in the CN arm who either did not undergo surgery (n = 16) or did not receive sunitinib (n = 40), and patients in the sunitinib-only arm who did not receive the study drug (n = 11). Median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82; 95% CI: 0.67-1.00). The clinical benefit rate, defined as disease control beyond 12 weeks was 36.6% with CN and 47.9% with sunitinib alone (p = 0.022). Of note, 38 patients in the sunitinib-only arm required secondary CN due to acute symptoms or for complete or near-complete response. The median time from randomisation to secondary CN was 11.1 months.

The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS (HR: [95% CI: 0.88 [0.59-1.37], p = 0.569). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 (range 14.5-65.3) months in the deferred CN arm vs. 15.0 (9.3-29.5) months in the immediate CN arm (HR: [95% CI] 0.57 [0.34-0.95], p = 0.032). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy. This confirms previous findings from single-arm phase II studies [371]. Moreover, deferred CN and surgery appears safe after sunitinib which supports the findings, with some caution, of the only available RCT.

In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended [372]. These data are confirmed by CARMENA [370].

7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery or with non-resectable disease, embolisation can control symptoms including visible haematuria or flank pain [242, 243, 335] (see recommendations Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic RCC

Summary of evidence	**LE**
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Recommendations	**Strength rating**
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

*7.3.2 **Local therapy of metastases in metastatic RCC***

A SR of the local treatment of metastases from RCC in any organ was undertaken [373]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [374]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [375-382]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [383-385], two in the brain [386, 387] and one each in the liver [388] lung [389] and pancreas [390]. Three studies were published as abstracts only [378, 380, 389]. Data were too heterogeneous to meta-analyse. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 Complete versus no/incomplete metastasectomy

An systematic review, including only 8 studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [375-382]. In one study complete resection was achieved in only 45%

of the metastasectomy cohort, which was compared with no metastasectomy [382]. Non-surgical modalities were not applied. Six studies [376-378, 380-382] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [375] showed no significant difference in CSS between complete and no metastasectomy, and one [379] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [389], liver [388], and pancreas [390], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and 5-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [385]. Single-dose IGRT (≥ 24 Gy) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [383]. A significantly higher 5-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multi-variate analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases to the spine [384]. Pain, objective response rate (ORR), time-to-pain relief and duration of pain relief were similar.

7.3.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study [386] compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus WBRT.

Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS and WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [387]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and 3-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better 2-year local control rate compared with metastasectomy plus conventional radiotherapy.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [391]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [392] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	**LE**
All studies included in the Panel systematic review were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	Strength rating
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone- or brain metastases for local control and symptom relief.	Weak

7.4 Systemic therapy for advanced/metastatic RCC

*7.4.1 **Chemotherapy***

Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered in rare patients, with the exception of collecting duct and medullary carcinoma [393].

7.4.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong

*7.4.2 **Immunotherapy***

7.4.2.1 IFN-α monotherapy and combined with bevacizumab

All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab plus IFN-α, and temsirolimus [394-397]. Interferon-α has been superseded by targeted therapy in clear-cell-mRCC (cc-mRCC).

Table 7.1: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [398]*

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

**The MSKCC (Motzer) criteria are also widely used in this setting [204].*

***Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three to six risk factors.*

7.4.2.2 Interleukin-2

Interleukin-2 has been used to treat mRCC since 1985 with response rates ranging from 7-27% [397, 399, 400]. Complete and durable responses have been achieved with high-dose bolus IL-2, however, this can be achieved at less toxicity with immune checkpoint inhibitor combination therapy and IL-2 is no longer widely used.

7.4.2.3 Immune checkpoint blockade

7.4.2.3.1 Immuno-oncology monotherapy

Immune checkpoint blockade with monoclonal antibodies targets and blocks the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-signalling to restore tumour-specific T-cell immunity [401]. Immune checkpoint inhibitor monotherapy has been investigated as second- and third-line therapy. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [182]. Nivolumab has superior OS to everolimus (HR: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus (LE: 1b). Patients who had failed multiple lines of VEGF-targeted therapy were included in this trial making the results broadly applicable. The trial included 15% MSKCC poor-risk patients. There was no PFS advantage with nivolumab despite the OS advantage. Progression-free survival does not appear to be a reliable surrogate of outcome for PD-1 therapy in RCC. Currently PD-L1 biomarkers are not used to select patients for this therapy.

There are no RCTs supporting the use of single-agent immune checkpoint blockade in treatment-naïve patients. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95% CI: 0.82-1.71)

which did not justify further assessment of atezolizumab as single agent as first-line treatment option in this group of patients, despite high complete response rates in the biomarker-positive population [402]. Single-arm phase II data for pembrolizumab from the Keynote-427 trial show high response rates of 38% (up to 50% in PD-L1+ patients), but a PFS of 8.7 months (95% CI: 6.7-12.2) [403]. Based on these results and in the absence of randomised phase III data, single-agent checkpoint inhibitor therapy is not recommended as an alternative in a first-line therapy setting.

7.4.2.4 Immunotherapy/combination therapy

The phase III trial CheckMate 214 (NCT 02231749) showed a superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint population focused on the IMDC intermediate- and poor-risk population where the combination demonstrated an OS benefit (HR 0.63 95% CI: 0.44-0.89) which led to regulatory approval [404] and a paradigm shift in the treatment of mRCC [1]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete response rates (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve the predefined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29-0.41). Frequency of grade 3-4 adverse events and QoL data favoured the immune combination.

Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity including 1.5% treatment-related deaths. It should therefore be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4). PD-L1 biomarker is currently not used to select patients for therapy.

The frequency of steroid use has generated controversy and further analysis, as well as real world data, are required.

A recent update with 32-month data shows ongoing benefits for the immune combination with investigator-assessed CR rates of 11% and an OS HR in the IMDC intermediate- and poor-risk group of 0.66 (95% CI 0.54-0.80) [406]. The IMDC good-risk group continues to perform well with sunitinib although this appears less marked than in earlier analyses (HR for OS 1.22 [95% CI: 0.73-2.04]). For these reasons the Guidelines Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The Keynote-426 trial (NCT02853331) has recently reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naïve cc-mRCC patients [407]. Overall survival and PFS assessed by central independent review in the ITT population were the co-primary endpoints. Response rates and assessment in the PD-L1-positive patient population were secondary endpoints. With a median follow-up of 12.8 months, at first interim analysis both primary endpoints were reached, The median PFS in the pembrolizumab plus axitinib arm was 15.1 months vs. 11.1 in the sunitinib arm (HR 0.69; 95% CI: 0.57-0.84, $p < 0.001$). Median OS has not been reached in either arm, but the risk of death was 47% lower in the axitinib plus pembrolizumab arm when compared to the sunitinib arm (OS HR: 0.53; 95% CI: 0.38–0.74, $p < 0.0001$). Response rates were also higher in the experimental arm (59.3% vs. 35.7%). Efficacy occurred irrespective of IMDC group and PD-L1 status. Treatment-related AEs (≥ grade 3) occurred in 63% of patients receiving axitinib and pembrolizumab vs. 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [408]. It met one of its co-primary endpoints (PFS in the PD-L1-positive population at first interim analysis [median follow up 11.5 months]). Progression-free survival and OS in the ITT population was HR 0.69 (95% CI: 0.56-0.84) and 0.78 (95% CI: 0.55-1.08), respectively. The same applies to the atezolizumab/bevacizumab combination which also achieved a PFS advantage over sunitinib in the PD-L1-positive population at interim analysis and ITT (HR: 0.74 [95% CI: 0.57-0.96]), but has not yet shown a significant OS advantage (HR: 0.81 [95% CI: 0.63-1.03]) [409]. Results are awaited and the combination cannot currently be recommended.

Table 7.2: Cross trial comparison is not recommended and should occur with caution

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS Median (95% CI) HR
KEYNOTE-426 **NCT02853331** [407]	861	Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BID vs. sunitinib 50 mg PO QD 4/2 weeks	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI 15.1 (12.6-17.7) SUN 11.1 (8.7-12.5) HR: 0.69 (95% CI: 0.57, 0.84) p = < 0.0001
JAVELIN 101 **NCT02684006** [408]	886	Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID vs. sunitinib 50 mg PO QD 4/2 weeks	PFS in the PD-L1+ population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI 13.8 (11.1-NE) SUN 7.2 (5.7-9.7) HR: 0.61 (95% CI: 0.475, 0.790) p < .0001
Immotion 151 **NCT02420821** [409]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs. sunitinib 50 mg. PO QD 4/2 weeks	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 70% POOR 10%	(PD-L1+) ATEZO + BEV 11.2 (8.9-15.0) SUN 7.7 (6.8-9.7) HR: 0.74 (95% CI: 0.57, 0.96) p = 0.02
Checkmate 214 **NCT02231749** [405, 410]	1096	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs. sunitinib 50 mg. PO QD 4/2 weeks	PFS and OS in the IMDC intermediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC intermediate/poor) NIVO + IPI 11.8 (8.7-15.5) SUN 8.4 (7.0-10.8) HR: 0.82 (99.1% CI: 0.64, 1.05) p = 0.03

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO QD = by mouth, once a day; SUN = sunitinib.

Whilst this table gives a broad overview of the available, data direct cross trial comparisons should be avoided.

Patients who stop nivolumab plus ipilimumab because of toxicity require expert guidance and support from a multidisciplinary team before re-challenge occurs (LE: 1). Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible (LE: 4). Treatment past progression with nivolumab plus ipilimumab can be justified but requires close scrutiny and the support of an expert multidisciplinary team [405, 410] (LE: 1).

Patients who stop axitinib and pembrolizumab due to immune-related toxicity can receive single-agent axitinib once the adverse event has resolved (LE: 1). Adverse event management, including transaminitis and diarrhoea, require particular attention as both agents may be causative. Expert advice should be sought on re-challenge of immune checkpoint inhibitors after significant toxicity (LE: 4). Treatment past progression on axitinib and pembrolizumab requires careful consideration as it is biologically distinct from treatment past progression on ipilimumab and nivolumab.

Generally, the Panel is of the opinion that nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4).

7.4.2.5 Summary of evidence and recommendations for immunotherapy in metastatic RCC

Summary of evidence	**LE**
Interferon-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b
The combination of nivolumab and ipilimumab in treatment-naïve patients with clear-cell-mRCC (cc-mRCC) of IMDC intermediate and poor risk demonstrated overall survival (OS) and objective response rate (ORR) benefits compared to sunitinib.	1b
The combination of pembrolizumab and axitinib in treatment-naïve patients with cc-mRCC across all IMDC risk groups demonstrated OS and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib can be continued if immune-related adverse events results in cessation of axitinib and pembrolizumab. Re-challenge with immunotherapy requires expert support.	4
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
The combination of nivolumab and ipilimumab in the ITT population of treatment-naïve unselected patients with cc-mRCC leads to superior survival compared to sunitinib.	2b
Due to the exploratory nature of PD-L1 tumour expression, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn relative to the usefulness of PD-L1 expression.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

Recommendations	Strength rating
Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC-risk clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab and pembrolizumab plus axitinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Offer axitinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib and pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in mRCC.	Strong
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong[a]

[a] While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.

*7.4.3 **Targeted therapies***

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL-inactivation results in over-expression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [411-413]. This process substantially contributes to the development and progression of RCC. Several targeting drugs for the treatment of mRCC are approved in both the USA and Europe.

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes.

In major trials leading to registration of the approved targeted agents, patients were stratified according to the IMDC risk model (Table 7.1) [205].

Table 7.3: Median OS and percentage of patients surviving two years treated in the era of targeted therapy per IMDC risk group*,**

IMDC Model	Patients**		Median OS* (months)	2-yr OS (95% CI)**
	n	%		
Favourable	157	18	43.2	75% (65-82%)
Intermediate	440	52	22.5	53% (46-59%)
Poor	252	30	7.8	7% (2-16%)

** Based on [205]; ** based on [398].*
CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; n = number of patients; OS = overall survival; yr = year.

7.4.3.1 Tyrosine kinase inhibitors

7.4.3.1.1 Sorafenib

Sorafenib is an oral multi-kinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS (HR: 0.44; 95% CI: 0.35-0.55, $p < 0.01$) [414]. Overall survival improved in patients initially assigned to placebo who were censored at crossover [415]. In patients with previously untreated mRCC sorafenib was not superior to IFN-α (phase II study). A number of studies have used sorafenib as the control arm in sunitinib-refractory disease vs. axitinib, dovitinib and temsirolimus. None showed superior survival for the study drug compared to sorafenib.

7.4.3.1.2 Sunitinib

Sunitinib is an oral TKI inhibitor and has anti-tumour and anti-angiogenic activity. First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4 months) vs. INF-α (21.8 months) despite crossover [417].

In the EFFECT trial, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [418]. No significant differences in OS were seen (23.1 vs. 23.5 months, p = 0.615). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer time to progression with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (2 weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [419, 420].

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [421].

A non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as an alternative to sunitinib. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles, and QoL was better with pazopanib [422]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, $p < 0.05$) due to symptomatic toxicity [423]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial, axitinib was compared to sorafenib in patients who had previously failed cytokine treatment or targeted agents (mainly sunitinib) [424].

The overall median PFS was greater for axitinib than sorafenib. Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months) after progression on sunitinib. Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [425, 426]. In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naïve cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated, although the study was underpowered, raising the possibility of a type II error [427]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.3.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinase, including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to VEGFR and mTOR inhibitors demonstrating objective responses and disease control [180]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [181, 428]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58 95% CI: 0.45-0.75) [181] (LE: 1b). The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI: 14.7-18.8) with everolimus in VEGF-resistant RCC. The HR for death was 0.66 (95% CI: 0.53-0.83, p = 0.0003) [428]. Grade 3 or 4 adverse events were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib.

The Alliance A031203 CABOSUN randomised phase II trial comparing cabozatinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [429, 430]. Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66; 95% CI: 0.46 to 0.95; one-sided p = 0.012). Objective response rate was 46% (95% CI: 34-57) for cabozantinib vs. 18% (95% CI: 10-28) for sunitinib. All-causality grade 3 or 4 adverse events were similar for cabozantinib and sunitinib. No difference in OS was seen. Due to limitations of the statistical analyses within this trial the evidence is inferior over existing choices.

7.4.3.1.6 Lenvatinib

Lenvatinib is an oral multi-target TKI of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), platelet growth factor receptor [(PDGFR-α), re-arranged during transfection (RET) and receptor for stem cell factor (KIT). It has recently been investigated in a randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.6.1.1.5 for discussion of results) [431].

7.4.3.1.7 Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1, VEGFR2, and VEGFR3 and was compared in two phase III trials with sorafenib in patients with mRCC [432, 433]. Tivozanib was approved by the EMA in front-line mRCC. While it is associated with a PFS advantage in both studies, no OS advantage was seen. In view of the choice of sorafenib as the control arm in the front-line trial, the Panel feels there is too much uncertainty, and too many attractive alternatives, to support its use in this setting.

*7.4.4 **Monoclonal antibody against circulating VEGF***

7.4.4.1 Bevacizumab monotherapy and bevacizumab plus IFN-α

Bevacizumab is a humanised monoclonal antibody.

The double-blind AVOREN study compared bevacizumab plus IFN-α with INF-α monotherapy in mRCC. Overall response was higher in the bevacizumab plus IFN-α group. Median PFS increased from 5.4 months with IFN-α to 10.2 months with bevacizumab plus IFN-α. No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab/IFN-α group (23.3 vs. 21.3 months) [434].

An open-label trial (CALGB 90206) of bevacizumab plus IFN-α vs. IFN-α showed a higher median PFS for the combination group [435, 436]. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab plus IFN-α, with significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria.

Bevacizumab, alone, or in combinations, is not widely recommended or used in mRCC due to more attractive alternatives.

*7.4.5 **mTOR inhibitors***

7.4.5.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [437]. Its use has been superseded as front-line treatment option.

7.4.5.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus plus best supportive care (BSC) vs. placebo plus BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [438]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [438].

The RCC Guidelines Panel consider, even in the absence of conclusive data, that everolimus may present a therapeutic option in patients who were intolerant to, or previously failed, immune- and VEGFR-targeted therapies (LE: 4). Recent phase II data suggest adding levantinib is attractive.

*7.4.6 **Therapeutic strategies***

7.4.6.1 Therapy for treatment-naïve patients with clear-cell metastatic RCC

The combination of pembrolizumab and axitinib as well as nivolumab and ipilimumab is the standard of care in all IMDC and IMDC intermediate- and poor-risk patients (Figure 7.1). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease), remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Figure 7.1).

7.4.6.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [181, 182, 431]. Pembrolizumab plus axitinib and nivolumab plus ipilimumab are the new standard of care for front-line therapy. The impact of front-line immune checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or pembrolizumab plus axitinib in a first-line setting are lacking, and available cohorts are limited [439]. Prospective data on cabozantinib and axitinib are available for patients progressing on immune therapy, but these studies do not focus solely on the front-line setting, involve subset analysis, and are too small for definitive conclusions [181, 440].

Retrospective data on VEGFR-TKI therapy after progression on front-line immune combinations exist but have significant limitations. When considering this data in totality, there is some activity but it is still too early to recommend one VEGFR-TKI above another after immunotherapy-immunotherapy or immunotherapy-VEGFR combination (Figure 7.2). After the axitinib plus pembrolizumab combination, changing the VEGFR-TKI at progression is recommended which may be cabozantinib or any other TKI not previously used.

The Panel do not favour the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated as they have been outperformed by other VEGF-targeted therapies in mRCC [441]. Drug choice in the third-line setting, after immune checkpoint inhibitor combinations and subsequent VEGF-targeted therapy, is unknown. The Panel recommends a subsequent agent which is approved in VEGF-refractory disease, with the exception of re-challenge with immune checkpoint blockade. Cabozantinib is the only agent in VEGF-refractory disease with a survival advantage in an RCT and should be used preferentially [424]. Axitinib has positive PFS data in VEGF-refractory disease. Both sorafenib and everolimus have been outperformed by other agents in VEGF-refractory disease and are therefore less attractive [441]. The Lenvatinib and everolimus combination appears superior to everolimus alone and has been granted EMA regulatory approval based on randomised phase II data. This is an alternative despite the availability of phase II data only [431]. Tivozinib has PFS superiority to sorafenib in VEGF-refractory disease as shown in a study which also included patients on immune checkpoint inhibitors [442].

7.4.6.2 Non-clear-cell metastatic RCC

No phase III trials of patients with non-cc-mRCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib and pembrolizomab [396, 443-445].

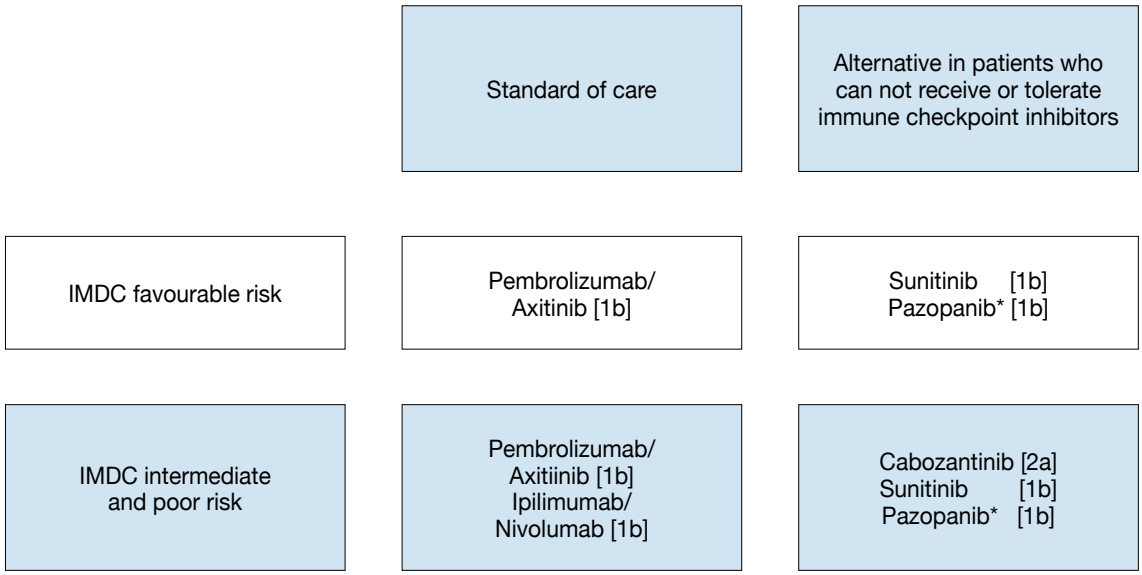
The most common non-clear-cell subtypes are papillary type I and non-type I papillary RCCs. There are small single-arm trials for sunitinib and everolimus [445-448]. A trial of both types of pRCC treated with everolimus (RAPTOR) [448], showed a median PFS of 3.7 months per central review in the ITT population with a median OS of 21.0 months.

However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-cc-mRCC including 73 patients (27 with pRCC) was stopped after a futility analysis for PFS and OS [449]. The final results showed a non-significant trend favouring sunitinib (6.1 vs. 4.1 months). Based on a systematic review including subgroup analysis of the ESPN, RECORD-3 and another phase II trial (ASPEN), sunitinib and everolimus remain options in this population, with a preference for sunitinib [7, 139, 450]. Patients with non-cc-mRCC should be referred to a clinical trial, where appropriate. Efficacy for pembrolizumab (n = 165; response rates of 24%, PFS 4.1 months [95% CI: 2.8-5.6 months] 72% one-year OS) was noted but these results are based on a single-arm phase II study [403]. Pembrolizumab can be conceded in this setting due to the high unmet need.

Subset analysis has shown impressive results for PD-L1 inhibitors combined with CTLA4 or VEGF-targeted therapy in renal tumours with sarcomatoid features. Bevacizumab/atezolizumab, ipilimumab/nivolumab, axitinib/pembrolizumab and avelumab/axitinib can all be recommended instead of VEFG-targeted therapy alone. These options have impressive OS advantages over sunitinib and superseded VEGF-targeted therapy.

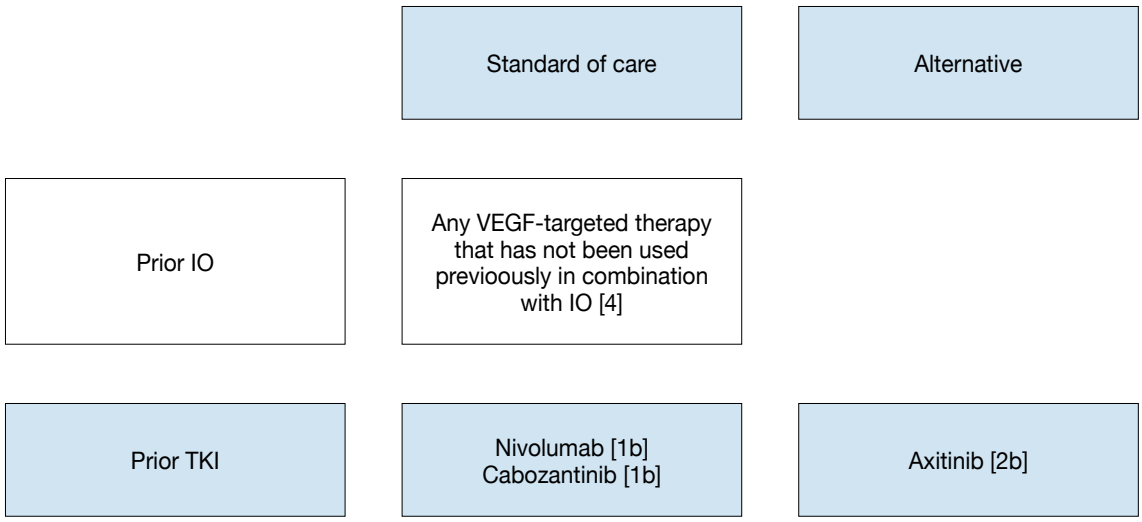
Collecting-duct cancers and renal medullary cancers are highly resistant to systemic therapy. Only case reports have been published for a spectrum of treatment options so far and no clear recommendations can be provided until data from international registries (RARECARE) or clinical trials become available.

Figure 7.1: Updated European Association of Urology Guidelines recommendations for the treatment of first-line and following lines in clear-cell metastatic renal cancer



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on one randomised controlled phase II trial.

Figure 7.2: Guidelines Recommendations for later-line therapy



IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

7.4.7 Summary of evidence and recommendations for targeted therapy in metastatic RCC

Summary of evidence	LE
Single agent VEGF-targeted therapy has been superseded by immune checkpoint based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naïve clear-cell RCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	Strength rating
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong

7.5 Recurrent RCC

Locally recurrent disease can either affect the tumour-bearing kidney after PN, or focal ablative therapy such as RFA and cryotherapy, or occur outside the kidney following PN or RN for RCC.

After NSS for pT1 disease, recurrences within the remaining kidney occur in about 1.8-2.2% of patients [451, 452]. Although the impact of positive margins on the clinical prognosis is still unclear [287, 452, 453] the preferred management, when technically feasible, is repeat surgical intervention to avoid the potential risk of tumour recurrence.

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [454]. Whereas repeat ablation is still recommended as the preferred therapeutic option after treatment failure, the most effective salvage procedure as an alternative to complete nephrectomy has not yet been defined.

Most studies reporting on the oncological efficacy of surgery for recurrent disease after removal of the kidney, have not considered the traditional definition of local recurrence after RN, PN and thermal ablation, which is: “tumour growth exclusively confined to the true renal fossa”. Instead, recurrences within the renal vein, the ipsilateral adrenal gland or the regional LNs were included under this term. Isolated tumour recurrence within the true renal fossa only is a rare event. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3).

Only retrospective and non-comparative data on the frequency and efficacy of available therapeutic options have been reported. One of the largest series including 2,945 patients treated with RN reported on 54 patients with recurrent disease localised in the renal fossa, the ipsilateral adrenal gland or the regional LNs as sole metastatic sites [455]. Another recent series identified 33 local recurrences within a cohort of 2,502 surgically treated patients, confirming the efficacy of surgical treatment vs. conservative approaches (observation, medical therapy). In a series of 1,955 patients with clinical T1 RCCs treated with PN, 95 patients (4.9%) had a pT3a upstaging, indicating a high risk for local and intra-renal recurrence and reduced survival

[456]. These data were further confirmed by an analysis of the SEER database showing that up-staging to pT3a with worse CSS occurred in 4.2% of cT1a tumours and in 9.5% of cT1b tumours [457].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally recurrent disease can induce durable tumour control. Since local recurrences develop early, with a median time interval of 10-20 months after treatment of the primary tumour [458], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up). Data show that both adequate pre-operative assessment and careful surgical technique are crucial in reducing local recurrence risk.

Adverse prognostic parameters are a short time interval (< 3-12 months) since treatment of the primary tumour [459], sarcomatoid differentiation of the recurrent lesion and an incomplete surgical resection [455]. In case complete surgical removal is unlikely to be performed or when significant comorbidities are present (especially when combined with poor prognostic tumour features), palliative therapeutic approaches including radiation therapy aimed at symptom control and prevention of local complications should be considered (see Sections 7.3 and 7.4).

*7.5.1 **Summary of evidence and recommendation for advanced/metastatic RCC***

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
In the absence of adverse prognostic factors such as sarcomatoid features or median time interval of < 12 months since treatment of the primary tumour, resection of local recurrences can induce durable tumour local control.	3
Most local recurrences develop within the first two years following treatment of the primary tumour. A guideline-adapted follow-up regimen is advised for early detection.	3

Recommendation	Strength rating
Offer surgical resection of locally recurrent disease when a complete resection is possible and significant comorbidities are absent.	Weak

8. FOLLOW-UP IN RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- development of metastases.

There is no consensus on surveillance after RCC treatment, and there is no evidence that early vs. later diagnosis of recurrences improves survival. Intensive radiological surveillance for all patients is not necessary. However, follow-up is important to increase the available information on RCC and should be performed by a urologist who should record the time to recurrence or the development of metastases. The outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify follow up, taking into account the risk of developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods [20, 460, 461] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol vs. patients who were not [462]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [462].

An individualised, risk-based, approach to RCC surveillance was recently proposed. The authors use competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [463]. For patients with low-stage disease but with a Charlson comorbidity index > 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age. The RECUR database consortium initiated by this Panel collects similar data with the aim to provide comparators for guideline

recommendations. Preliminary data support a risk-based approach. In the near future, genetic profiles may refine the existing prognostic scores and external validation in datasets from adjuvant trials were promising [8, 464].

Renal function is assessed by the measurement of serum creatinine and eGFR. Repeated long-term monitoring of eGFR is indicated in case of impaired renal function before, or after, surgery. Renal function [465, 466] and non-cancer survival [208, 209, 467] can be optimised by performing NSS, whenever possible, for T1 and T2 tumours [468] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is surgery [469, 470]. Recurrence in the contralateral kidney is also rare (1-2%), can occur late (median 5-6 years), and might be related to positive margins, multifocality, and grade [471] (LE: 3). Surveillance can identify local recurrences or metastases at an early stage. In metastatic disease, extended tumour growth can limit the opportunity for surgical resection which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

- The sensitivity of chest radiography and US for small metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in histology controlled comparative trials [472-474].
- Surveillance with these imaging modalities are less sensitive [475].
- In low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used outside the thorax.
- When the risk of relapse is intermediate or high, CT of the chest, abdomen and pelvis should be performed.
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to their limited specificity and sensitivity.
- After injection of contrast medium, the risk of acute renal failure seems to be negligible in patients with a GFR > 20 mL/min and chronic renal impairment [476].

Controversy exists on the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after five years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with NSS if the tumours are detected early. For tumours < 4 cm, there is no difference between PN and RN with regard to recurrences during follow up [477] (LE: 3). Several authors have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death [194, 196, 478, 479]. These systems have been compared and validated [480] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed but none include ablative therapies [481, 482]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [191]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [200] (LE: 3).

A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk profile, but also efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the surveillance schedule according to suspected risk of recurrence. The most suitable approach to define high-risk patients is the utilisation of nomograms.

Data from adjuvant trials are generally based on the University of California Los Angeles integrated staging system (UISS) risk stratification which makes it the most widely used and validated system [360, 483].

Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (based on expert opinion [LE: 4])

Risk profile	Surveillance				
	6 mo	**1 y**	**2 y**	**3 y**	**> 3 y**
Low	US	CT	US	CT	CT once every 2 years; Counsel about recurrence risk of ~10%
Intermediate / High	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; US = ultrasound of abdomen, kidneys and renal bed.

8.3 Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing surveillance have a better overall survival than patients not undergoing surveillance.	3
Repeated CT scans do not reduce renal function in chronic kidney disease patients.	3

Recommendations	Strength rating
Base follow-up after RCC on the risk of recurrence.	Strong
Intensify follow-up in patients after nephron-sparing surgery for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Base risk stratification on pre-existing classification systems such as the University of California Los Angeles integrated staging system: http://urology.ucla.edu/body.cfm?id=443 or the SSIGN score.	Strong

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Further information should be sought at what time point restaging has the highest chance to detect recurrence. Prognostic markers at surgery should be investigated to determine the risk of relapse over time.

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10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/renalcell-carcinoma/?type=panel/.

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11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Testicular Cancer

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1. INTRODUCTION

1.1 Aim and objectives

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer (TC) represents 5% of urological tumours affecting mostly younger males. This document addresses germ-cell tumours (GCTs) and sex cord/gonadal stromal tumours.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions which should also take personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, oncologists, a radio-oncologist and a pathologist. Members of this Panel have been selected, based on their expertise, to represent the professionals treating patients suspected of having TC. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents are accessible through the EAU website: http://www.uroweb.org/guideline/testicularcancer/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The European Association of Urology (EAU) published the first guidelines on TC in 2001. Since 2008, the Testicular Cancer Guidelines contains a separate chapter on testicular stromal tumours. This document presents a limited update of the 2019 publication. Review papers have been published in the society's scientific journal European Urology, the latest version dating to 2015 [1].

*1.4.2 **Summary of changes***

For the 2020 Testicular Cancer Guidelines, new references have been added throughout the document. Key changes in this publication include:

- A table on minimal sets for pathology reports of neoplasia of the testis has been included in the 2020 version.
- Citations relating to a number of low quality papers (SEER database on epidemiology retrospective biased fluorodeoxyglucose-positron emission tomography [FDG-PET] scan and non-validated prognostic models) have been removed from the text. As per previous versions of the text, some small phase II studies in the relevant text section on second relapse are included since there are few publications addressing this rare and desperate clinical scenario.
- Several old citations have been replaced with newer reports.
- Beyond the Scope search, a few relevant articles identified in the months after the search have been included.
- Text and tables throughout the guideline have been rephrased and revised.
- The panel is aware that a new International Germ Cell Cancer Collaborative Group (IGCCCG) classification for metastatic tumours has recently been presented. This new classification stratifies more accurately the population of patients with metastatic TC than the one proposed in 1997 and used in these guidelines. However, as of December 2019, there is no "peer reviewed" publication or external validation of the proposed new classification. Once published, these will be incorporated into the 2021 version of the guideline.
- Recommendations on abdominal, thorax and brain imaging at diagnostic and staging have been reviewed by a consultant radiologist.

2. METHODS

For the GCT section, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between June 2018 and April 2019 and included testicular stromal tumours. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,256 unique records were identified, retrieved and screened for relevance. Fifty-four new references have been included in the 2020 print. A detailed search strategy is available online: http://uroweb.org/guideline/testicular-cancer/?type=appendices-publications

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2, 3]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; www.uroweb.org/guidelines.
A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Review

This document was subjected to peer review prior to publication in 2015. The 2020 guidelines will be peer-reviewed following publication with reviewer comments forming the basis for the 2021 revision.

2.2 Future goals

- A new chapter on "Incidentally diagnosed testicular masses" will be included in the 2021 revision of the Guidelines.
- A systematic review on the topic of "Quality of care of testicular cancer" will be explored by the panel. The main research question will investigate the quality of care for patients undergoing post-chemotherapy retroperitoneal lymph node dissection (RPLND).
- A preliminary literature search will be performed to explore the evidence on minimally invasive RPLND.
- An Individual Patient Data (IPD) prognostic factor study on the value of pathological factors in clinical stage I seminoma testis patients under active surveillance has been approved by the Guidelines Office Methods Committee. Five international centres are collaborating on the study. Data analysis and outcomes are expected in 2021.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [6]. Its incidence has increased during recent decades particularly in industrialised countries [7, 8]. At diagnosis, 1-2% of cases are bilateral and the predominant

histology is GCT (90-95% of cases) [6]. Peak incidence is in the third decade of life for non-seminoma and mixed GCTs, and fourth decade for pure seminoma.

Genetic changes have been described in patients with TC. A specific genetic marker – an isochromosome of the short arm of chromosome *12 – (i12p)* – is pathognomonic of all types of adult GCTs [9] as well as germ cell neoplasia *in situ* (GCNIS). Alterations in the *p53* locus have been identified in 66% of cases of GCNIS [10] and an association between genetic polymorphism in the PTEN tumour suppressor gene and the risk of TC have recently been described [11]. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, *M2A, C-KIT* and *OCT4/NANOG*) is likely to be responsible for the development of GCNIS and germ cell neoplasia. In line with this, genome-wide association studies (GWAS) have revealed several single nucleotide polymorphisms (SNPs) markers associated with an increased risk of developing TC, in particular at 15q21.3 [12]. That said, current genomic studies do not show evidence for a major single high-penetrance TC susceptibility gene [13]. There is overlap in the development to seminoma and embryonal carcinoma, as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma [14, 15].

Epidemiological risk factors for the development of TC are components of the testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadia, decreased spermatogenesis evidenced by sub- or infertility [16, 17], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or GCNIS [9, 16, 18-22].

3.2 Histological classification

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [23].

1. **Germ cell tumours**
   - Germ cell neoplasia *in situ* (GCNIS)
2. **Derived from germ cell neoplasia *in situ* (GCNIS)**
   - Seminoma
   - Embryonal carcinoma
   - Yolk sac tumour, post-pubertal type
   - Trophoblastic tumours
   - Teratoma, post-pubertal type
   - Teratoma with somatic-type malignancies
   - Mixed germ cell tumours
3. **Germ cell tumours unrelated to GCNIS**
   - Spermatocytic tumour
   - Yolk sac tumour, pre-pubertal type
   - Mixed germ cell tumour, pre-pubertal type
4. **Sex cord/stromal tumours**
   - Leydig cell tumour
     - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - Malignant Sertoli cell tumour
     - Large cell calcifying Sertoli cell tumour
     - Intratubular large cell hyalinising Sertoli cell neoplasia
   - Granulosa cell tumour
     - Adult type
     - Juvenile type
   - Thecoma/fibroma group of tumours
   - Other sex cord/gonadal stromal tumours
     - Mixed
     - Unclassified
   - Tumours containing both germ cell and sex cord/gonadal stromal
     - Gonadoblastoma
5. **Miscellaneous non-specific stromal tumours**
   - Ovarian epithelial tumours
   - Tumours of the collecting ducts and rete testis
     - Adenoma
     - Carcinoma

- Tumours of paratesticular structures
  - Adenomatoid tumour
  - Mesothelioma (epithelioid, biphasic)
  - Epididymal tumours
- Cystadenoma of the epididymis
- Papillary cystadenoma
- Adenocarcinoma of the epididymis
- Mesenchymal tumours of the spermatic cord and testicular adnexae

4. STAGING & CLASSIFICATION SYSTEMS

4.1 Staging

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 4.1) [24].

Table 4.1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [24]

pT - Primary Tumour[1]	
pTX	Primary tumour cannot be assessed (see note 1)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)+
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis**
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion**
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N - Regional Lymph Nodes – Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn - Regional Lymph Nodes – Pathological	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis **
	M1a Non-regional lymph node(s) or lung metastasis
	M1b Distant metastasis other than non-regional lymph nodes and lung

S - Serum Tumour Markers (Pre chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal.
LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.
[1] Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.
+The current "Carcinoma in situ" nomenclature is replaced by GCNIS.
**AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [25].*
*** AJCC eighth edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [25].*

4.2 UICC Prognostic groups

According to the 2016 TNM classification, the following prognostic groups are defined:

Table 4.2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) [24]

Stage grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Stage IA: Patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchidectomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.

Stage IB: Patients have a more locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: Patients have persistently elevated (and usually increasing) serum tumour marker levels after orchidectomy, indicating subclinical metastatic disease (or possibly a second GCT in the remaining testis).

In population-based patient series of developed countries, 75-80% of seminoma patients, and about 55%-64% of non-seminomatous germ cell tumour (NSGCT) patients have stage I disease at diagnosis [26, 27]. True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients [26].

4.3 The International Germ Cell Cancer Collaborative Classification for metastatic Testicular Cancer

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system for metastatic TC based on identification of clinically independent adverse factors. This widely-used classification uses histology, location of the primary tumour, location of metastases and pre-chemotherapy serum tumour marker levels as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 4.3) [28].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [26]*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*

PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

5. DIAGNOSTIC EVALUATION

5.1 Physical examination

Testicular cancer usually presents as a unilateral testicular scrotal mass detected by the patient, or as an incidental ultrasound (US) finding. Scrotal pain may be present in 27% of patients [29, 30] and might be a reason for delayed diagnosis in 10% of cases [29]. Around 1% of patients presenting with gynecomastia have a germ cell or sex cord/gonadal tumour of the testes [31] and 11% present with back and flank pain [30]. As such, when there is suspicion of TC, physical exploration must include abdominal and supraclavicular exploration.

5.2 Imaging

5.2.1 ***Ultrasonography of the testes***

High-frequency (>10 MHz) testicular US should be used to confirm a testicular tumour even in the presence of a clinically evident testicular lesion [30, 32].

The use of testicular US can:
(1) determine whether a mass is intra- or extra-testicular;
(2) determine the volume and anatomical location of the testicular lesion;
(3) be used to characterise the contralateral testicle – to exclude other lesions and identify risk factors for GCNIS (see section 5.4.4).

Testicular US is also recommended for all men with retroperitoneal or visceral masses and/or without elevated serum Human chorionic gonadotropin (hCG) or AFP in the absence of a palpable testicular mass; and for fertility work-up evaluation [30, 32-34].

In order to distinguish between benign and malignant lesions, diverse modalities of US have been used (B-mode, dynamic contrast enhanced, real time elastography, and shear wave elastography) in an investigational mode in small cohorts [35-38]. So far, the results are preliminary and not sufficiently mature to provide clinical recommendations.

5.2.2 ***Computerised tomography (CT)***

Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen and pelvis for TC staging [39]. Contrast enhanced CT is recommended in all patients for staging before orchidectomy but may be postponed until histopathological confirmation of malignancy.

The size of metastases should be described in three dimensions, or at least by the greatest axial diameter. For abdominal staging a recent systematic review reports a median sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of 66.7% (range 37-100%), 95.2% (range 58-100%, 87.4% (60-100%), 73.4% (67-100%) and 83% (range 71-100%), respectively [39].

Sensitivity decreases and specificity increases with increasing lymph node size. As such, pooled sensitivity decreases to 37% and specificity increases to 100% for nodes ≥ 10 mm. For nodes ≥ 4 mm pooled sensitivity is 93% and specificity 58% [39]. Using a 10 mm short-axis lymph node diameter as a cut-off yielded a high specificity (97%), a moderate sensitivity (59%) and false-negative rate of 20% in the retroperitoneum [40]. Note should be taken of the expected patterns of nodal spread in TC when evaluating small and borderline nodes.

Chest CT was evaluated in three studies in the systematic review by Pierorazio *et al.* [39]. It presents a median sensitivity, specificity, PPV, NPV and accuracy of 100% (range 95-100%), 92.7% (range 89-97%), 67.7% (range 25-84%), 100% (range 99-100%) and 93% (range 91-97%), respectively. Computerised tomography of the chest is more sensitive but less specific than chest X-ray (CXR) in thoracic staging. Nevertheless, potential harms of chest CT imaging in low-stage seminoma should be taken into consideration [39].

In patients with equivocal masses (< 2 cm) in the retroperitoneum (doubts on stage I) or chest and negative tumour markers, restaging after 6-8 weeks rather than treatment initiation is advisable.

Brain imaging by CECT is recommended in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCCG risk group (for patients with hCG values > 5,000 UI/L), or if clinical symptoms are present [41].

5.2.3 ***Magnetic resonance imaging (MRI)***

Magnetic resonance imaging of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis [42-44]. It may however, be helpful to distinguish between an intra- and extra-testicular mass when this cannot be confirmed clinically or with US [42, 43].

Magnetic resonance imaging for abdominal staging purposes has been shown to have similar accuracy to CECT in the detection of retroperitoneal nodal enlargement [39, 45]. The above mentioned systematic review, however, only identified one study providing granular data of the use of MRI in abdominal staging with a reported sensitivity of 78-96% among three radiologists [39]. Magnetic resonance imaging is subject to greater artefacts and is not routinely indicated. If CT is contraindicated because of allergy to iodine based contrast media, non-contrast CT may be performed to evaluate nodal size. Currently, there are no indications for routine use of MRI for TC staging.

Magnetic resonance imaging has a primary role in the detection of brain metastasis. Whilst both CECT and MRI are key image modalities for the detection of brain metastasis, MRI is far more sensitive than CECT, though it does requires some expertise [39, 46, 47]. In the absence of specific reports on comparative accuracy of TC brain metastasis by CECT or MRI, extrapolation of data from other cancer-related brain metastases indicates that if available, or when CECT is contraindicated (e.g. iodine contrast allergy), MRI should be used to screen for brain metastases [46].

Magnetic resonance imaging of spine is advisable in patients with symptoms or equivocal staging on CT [47].

*5.2.4 **Fluorodeoxyglucose-positron mission tomography (FDG-PET)***

There is no evidence to support the use of FDG-PET for initial staging and follow-up of TC [39, 48-50].

Fluorodeoxyglucose-positron emission tomography is only recommended for seminoma patients with post-chemotherapy residual masses > 3 cm (largest diameter) to assess FDG activity [51]. However, it should not be performed before two months after completion of the last cycle of chemotherapy. The NPV for active tumours is > 90% [52, 53]; however, the PPV ranges from 23% to 69% [52-54]. Thus, for a positive FDG-PET the possibility of residual seminoma is of the order of 20%, and false-positive results are common (up to 80% of lesions are only-necrotic tissue) [52, 54]. Given the low PPV (necrosis, fibrosis, inflammation and benign tumours were also associated with positive FDG activity) caution is advised on initiating active therapy driven by positive findings in FDG-PET-CT [54].

*5.2.5 **Bone scan***

There is no evidence to support the use of bone scan for staging of TC.

5.3 Serum tumour markers

*5.3.1 **Pre-operative serum tumour markers***

Alphafetoprotein, beta subunit of human Chorionic Gonadotropin (β-hCG) and lactate dehydrogenase LDH should be determined before and after orchidectomy as they predict germ cell cancer histology supporting the diagnosis of TC [55]. Alphafetoprotein and β-hCG are increased in 50-70% and in 40-60% of patients with NSGCT, respectively, and about 90% of NSGCT present with a rise in either AFP or β-hCG at diagnosis [29, 56]. Only 30% of pure seminomas can present or develop an elevated β-hCG level during the course of the disease [55]. Overall serum tumour markers have a low sensitivity and high false positive rates and normal marker levels do not exclude the diagnosis of GCT [56]. Lactate dehydrogenase is a less specific marker, its serum level being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [56].

Recent interest has been given to miRNAs as potential new biomarkers for TC diagnosis. The preliminary evidence revealed higher discriminatory accuracy than conventional markers [57-60]. Before miRNAs can be considered for use in routine clinical practice, issues around laboratory standardisation and availability of the test need to be resolved.

*5.3.2 **Serum tumour markers after orchidectomy***

Serum levels of AFP, β-hCG and LDH are used for TC prognostic stratification after orchidectomy [28]. As the serum half-life of AFP and β-hCG are five to seven days and one to three days respectively, it may take several weeks until normalisation occurs [55, 56] The persistence or increase of elevated serum tumour markers following orchidectomy indicates the likely presence of metastatic disease. Whilst normalisation of marker levels after orchidectomy is a favourable indicator, it does not exclude the possibility of metastatic disease. With metastatic TC, risk stratification is based on serum tumour markers levels immediately before initiation of systemic treatment [28].

Tumour markers should be routinely used for follow-up as indicators of recurrence, although the precise frequency of testing is unclear [61].

Following orchiectomy, preliminary results suggest that miRNAs may indicate metastatic disease. Further studies are required to verify its value in the detection of occult metastases [59, 62, 63].

5.4 Inguinal exploration and initial management

*5.4.1 **Orchidectomy***

orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care in patients with TC.

*5.4.2 **Testis-sparing surgery***

Testis sparing surgery (TSS) may be attempted in patients with a solitary testis and is often used to preserve fertility and hormonal function. Testis sparing surgery should only be offered together with frozen section examination (FSE) because FSE has shown to be reliable and highly concordant with final histopathology [64, 65]. Nevertheless, patients should be informed about the risk of completion orchidectomy in case of incorrect FSE. Patients should be aware that only limited data about the oncological safety of TSS is available when TC is present [66].

In cases of small or indeterminate testicular masses with negative tumour markers, where possible patients should be offered TSS when feasible, to avoid overtreatment of potentially benign lesions and to preserve testicular function. Currently, there is no evidence supporting any size cut-off for a testicular lesion to be safely followed-up. Patients should be informed and the physician must be aware that cancer can be found even in sub-centimetre masses [67, 68], thus obtaining histology is mandatory.

*5.4.3 **Insertion of testicular prosthesis***

Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchiectomy [69]. The prosthesis can be inserted during the follow-up or at orchidectomy without adverse consequences, including infection [70].

*5.4.4 **Contralateral biopsy***

Contralateral biopsy has been advocated to rule out the presence of GCNIS [71].

Whilst routine policy in some countries [72], the low incidence of GCNIS and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [73, 74], the morbidity of GCNIS treatment, and the fact that most metachronous tumours are low stage at presentation, it is controversial to recommend routine contralateral biopsy in all patients [75, 76]. Nevertheless, the risks and benefits of biopsy of the contralateral testis should be discussed with TC patients at high risk for contralateral GCNIS, i.e. testicular volume < 12 mL, and/or a history of cryptorchidism. Contralateral biopsy is not necessary in patients older than 40 years without risk factors [77-79]. Patients should be informed that a testicular tumour may arise despite a negative biopsy [80]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [79].

5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasia are based on the recommendations of the International Society of Urological Pathology (ISUP) [81-84].

Mandatory pathological requirements:

- *Macroscopic features:* It must indicate radical or partial orchidectomy, side, testis size, number of tumours, and macroscopic features of the epididymis, cord length, and tunica vaginalis.
- *Sampling:* At least a 1 cm^2 section for every centimetre of maximum tumour diameter including normal macroscopic parenchyma (if present), tunica albuginea and epididymis, with selection of suspicious areas. If the tumour is < 20 mm it should be completely sampled.
- At least one proximal (base of the cord) and one distal section of spermatic cord plus any suspicious area. Cord blocks should preferably be taken prior to tumour sections to avoid contamination.
- *Microscopic features and diagnosis:* histological types (specify individual components and estimate amount as percentage) according to WHO 2016 [81]:
  - Presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - Presence or absence of GCNIS in non-tumour parenchyma;
  - In case of rete testis invasion attention should be paid to distinguishing between pagetoid involvement and stromal invasion [82].
- If microscopic findings are not concordant with serum markers further block samples should be taken.
- pT category according to TNM 2016 [24]. In a multifocal seminoma the largest nodule should be used to determinate pT category.

Advisable immunohistochemical markers in cases of doubt are:

- Seminoma: CD-117 (c-kit), OCT ¾, Sall 4, PLAP
- GCNIS: CD-117 (c-kit), OCT ¾, Sall 4, PLAP
- Syncytiotrophoblast: β-hCG
- Embryonal carcinoma: CD30
- Yolk sac tumour: Glypican 3
- Sex cord gonadal tumours: Inhibin, calretinin

In order to facilitate consistent and accurate data collection, promote research, and improve patient care, the International Collaboration on Cancer Reporting has constructed a dataset for the reporting of urological neoplasms. The dataset for testicular tumours encompasses the updated 2016 WHO classification of urological tumours, the ISUP consultation and staging with the 8th edition AJCC [84].

The dataset includes those elements unanimously agreed by the expert panel as "required" (mandatory) and those "recommended" (non-mandatory) that would ideally be included but are either non-validated or not regularly used in patient management [84]. The dataset for handling pathological assessment of TC is shown in table 5.5.

Table 5.5: Recommended data set for reporting of neoplasia of the testis (modified from the International Collaboration on Cancer Reporting [84]**.**

Elements	Required	Recommended*	Content	Remarks
Clinical information		√	- Not provided - Previous history of testicular cancer - Previous therapy - Other	Specify each
Serum tumour markers		√	- Not provided - If provided within normal limits or - Specify serum tumour markers used - Specify levels - Specify date markers were drawn	Select all that apply Serum tumour markers: LDH (IU/L), AFP (ug/L), b-hCG (IU/L)
Operative procedure	√		- Not specified - Orchidectomy partial - Orchidectomy radical - Other	Specify side for partial or radical orchidectomy Specify other
Tumour focality	√		- Cannot be assessed - Indeterminate - Unifocal - Multifocal	If multifocal specify number of tumours in specimen
Maximum tumour dimension	√		- Cannot be assessed - Dimensions largest tumour (mm) - Dimensions additional tumour nodules#	Specify at least maximun diameter of largest tumour Preferably specified 3 dimensions axes#
Macroscopic extent of invasion	√		- Cannot be assessed - Confined to testis - Invades epididymis - Invades tunica vaginalis - Invades hilar structures - Invades spermatic cord - Invades scrotum - Other	Select all that apply If other specify
Block identification key		√	N/A	List overleaf or separately with indication of nature and origin of all tissue blocks
Histological tumour type	√		- Germ cell tumour: type and percentage - Other	- Use WHO classification (2016) - If other specify

Microscopic extent of invasion	√		- Rete testis of stromal/ interstitial type - Epididymis - Hilar fat - Tunica albuginea# - Tunica vaginalis - Spermatic cord - Scrotal wall	For all: - not submitted - not involved - involved
Lymphovascular extension	√		- Not identified - Present	If present specify type#
Intratubular lesions (GCNIS)	√		- Not identified - Present - Other intratubular lesions#	If other intratubular lesions present identify type#
Margin status	√		- Partial orchidectomy . cannot be assessed . involved . not involved - Radical orchidectomy . cannot be assessed . spermatic cord margin involved . spermatic cord margin not involved - Other margin involved	In partial orchidectomy if margin not involved, distance of tumour from closest margin (mm)# If other margin involved specify
Coexisting pathology		√	- None identified - Hemosiderin-laden macrophages - Atrophy - Other	If other specify
Ancillary studies		√	- Not performed - Performed	If performed specify
Response to neoadjuvant therapy		√	- Present - Absent, - No prior treatment, - Cannot be assessed	Explain reasons if cannot be assessed
Pathologic staging*	√		T classification according to TNM 8th edition (UICC)**	m-multiple primary tumours r-recurrent y- post-therapy

** Not mandatory. Ideally to be included but either non-validated or no regularly used in patient management.*

*** TNM 8th edition (AJCC) used in the original publication*

 # Recommended

5.6 Screening

There are no high-level evidence studies supporting screening programs. It has not been shown that screening asymptomatic patients has greater accuracy for detecting TC at more curable stages; stage and prognosis have been shown to be directly related to early diagnosis [85, 86].

In the presence of clinical risk factors, and especially in patients with a family history of TC, family members and the patient should be informed about the importance of physical self-examination [87].

5.7 Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy [88, 89]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozoospermic) before treatment [89].

Treatment for TC, including orchidectomy, may have a negative impact on the reproductive function [90]. Chemotherapy and radiation treatment can both impair fertility; although, long-term infertility is rare after radiation therapy and is dose-cumulative-dependent after chemotherapy [91-93]. Spermatogenesis usually recovers one to four years after chemotherapy [94]. In CSI, adjuvant treatment (BEP [cisplatin, etoposide,

bleomycin] x1; Carbo x1) does not appear to significantly affect testicular function compared to surveillance, with full recovery after one year [95].

All patients should be offered semen preservation as the most cost-effective strategy for fertility preservation, and pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) is advised [96].

If cryopreservation is desired, sperm banking should be offered before orchidectomy, maximising the chances of fertilisation and avoiding the risk of having a non-functioning remaining testicle after surgery. If not offered before orchidectomy, it should be undertaken prior to chemotherapy or RT [91-93, 96-98].

In patients with bilateral orchidectomy or low testosterone levels after treatment of GCNIS, life-long testosterone supplementation is necessary [99].

Chemotherapy and radiation therapy are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [100].

For more detailed information, the reader is referred to the EAU Guidelines on Sexual Reproductive Health [101].

5.8 Guidelines for the diagnosis and staging of testicular cancer

Recommendations	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.	Strong
Perform physical examination including supraclavicular, cervical, axillary and inguinal lymph nodes, breast and testicles.	Strong
Measure serum tumour markers both before and after orchiectomy taking into account half-life kinetics.	Strong
Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, commence chemotherapy prior to orchidectomy.	Strong
Perform contrast enhanced computerised tomography (CT) scan (chest, abdomen and pelvis) in patients with a diagnosis of TC. If iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
Perform MRI of the brain (or brain CT if not available) in patients with multiple lung metastases, or high beta subunit of human Chorionic Gonadotropin (β-Hcg) values, or those in the poor-prognosis International Germ Cell Cancer Collaborative Group (IGCCCG) risk group.	Strong
Do not use positron emission tomography–computed tomography or bone scan for staging.	Strong
Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Strong
Discuss testis-sparing surgery with frozen section examination in patients with a high-likelihood of having a benign testicular tumour which are suitable for enucleation.	Strong
Offer biopsy of the contralateral testis to patients with TC and at high-risk for contralateral germ cell neoplasia *in situ*.	Strong

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I

With stage 1 seminoma, tumour size and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis of retrospective data [102]. Absence of both factors indicates a low risk of recurrence (6%) [103]. Whilst the original analysis was not supported by a further retrospective report [104], some prospective series [105-107] support the prognostic significance of tumour size and stromal invasion of the rete testis. Two systematic reviews have assessed the prognostic value of these risk factors [108, 109]. While tumour size (continuous or dichotomised) and rete testis invasion are associated with a higher risk of relapse, both systematic reviews highlighted the low quality of the studies included and that the level of evidence is too low to recommend the use of these pathological risk factors to drive adjuvant treatment decisions [108, 109].

For non-seminoma stage I, invasion of the primary tumour into blood or lymphatic vessels (LVI) is the most reliable single predictor of occult metastatic disease [82, 110]. The percentage of embryonal carcinoma within a tumour may enhance the positive- and negative predictive value of LVI [110]. Risk of relapse at five years with LVI is 50% compared to 15% without LVI. The significant prognostic pathological risk factors for stage I TC are listed in Table 6.1.

Table 6.1: Pathological risk-factors for occult metastatic disease in Stage I testicular cancer

Histological type	**Seminoma** [108]	**Non-seminoma** [82]
• Pathological risk-factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoral tissue

7. DISEASE MANAGEMENT

Chemotherapy results in excellent cure rates in TC due to their chemosensitivity, particularly with cisplatin based regimens [111]. Careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach, rigorous follow-up and adequate initiation of salvage therapies are critical to successful outcomes. Whilst early stages can be successfully treated in a non-specialist centre, relapse rates are higher than in specialist centres [112, 113]. In clinical trials poor prognosis patients, overall survival (OS) relates to the number of patients treated at the participating centre (worse if < 5 patients enrolled) [114]. Treatment at high-volume specialist centres is thus strongly encouraged. Establishment of second-opinion clinics for TC patients as well as collaboratively working with specialist centres may also help prevent over- and under-treatment [115].

Initiation of treatment before histopathological confirmation
In cases of life-threatening disseminated disease, chemotherapy should commence immediately, particularly when the clinical picture strongly supports TC, and/or tumour markers are increased. Orchidectomy in these circumstances can be delayed until clinical stabilisation occurs or subsequently in combination with resection of residual lesions.

7.1 Stage I Germ cell tumours

7.1.1 ***GCNIS***

If GCNIS is diagnosed, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be offered in the case of a solitary testis [93, 116-118]. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [93]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [79]. Chemotherapy is significantly less effective and the cure rates are dose-dependent [116].

If GCNIS is diagnosed and the contralateral testis is healthy, the options for management are orchidectomy or close observation, as the five-year risk of developing TC is 50% [119].

7.1.2 ***Seminoma clinical Stage***

Despite modern staging procedures, approximately 15% of clinical stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone [104, 107, 120, 121].

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.1.2.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted over the past decade. Previous analysis from four studies showed an actuarial five-year relapse-free rate of 82.3% [122]. The largest series (> 1500 patients) reported an overall relapse rate in unselected patients of 16.8% [122]. The conditional risk of relapse is of the order of 12.2% - 20.3% at five years, with most relapses occurring in retroperitoneal lymph nodes during the first two years [123-125].

Very low recurrence rates of 6% have been described in patients with low-risk features, including tumours size < 4 cm and no stromal rete testis invasion. In contrast, others report a five year conditional risk of relapse of 12.2% with tumours < 3 cm in size [106, 125].

The cancer-specific survival (CSS) rate reported with surveillance performed by specialist centres is over 95% for clinical stage I seminoma [122-124, 126]. The principal limitation of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.1.2.2 Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC), which compared one cycle of carboplatin area under curve (AUC) 7 with adjuvant RT, showed no significant difference in recurrence rate, time to recurrence and survival after a median follow-up of four years [127-129]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to RT or surveillance in clinical stage I seminoma [123, 127, 128]. Retrospective data on patients who relapsed after adjuvant treatment with carboplatin showed that these seem to be later than those with active surveillance [130]. Median time to relapse was reported to be 19 months, with 15% occurring later than three years after adjuvant treatment. The majority of patients relapsing after adjuvant carboplatin can be successfully treated with a standard cisplatin-based chemotherapy regimen appropriate to their disease stage [130].

7.1.2.3 Adjuvant radiotherapy

Seminomas are extremely radiosensitive tumours. Adjuvant radiotherapy to a para-aortic (PA) field or to a PA and ipsilateral field (PA and ipsilateral iliac nodes), with a total dose of 20-24 Gy, reduced the relapse rate to 1-3% [131-133]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

With regard to the irradiation dose, a large MRC RCT of 20 Gy versus 30 Gy PA radiation in clinical stage I seminoma showed non-inferiority in terms of recurrence rates [132]. The rate of severe radiation induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects were seen in about 5% of patients with moderate acute GI toxicity in about 60% [131]. The main concern with adjuvant radiotherapy is the increased long term risk of radiation-induced secondary non-germ cell malignancies [134-137].

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [134].

7.1.2.4 Risk-adapted treatment

Using testicular tumour size > 4 cm and stromal rete testis invasion, patients with clinical stage I seminoma may be subdivided into low- and high-risk groups for relapse following radical orchidectomy. Patients with and without both risk factors have a 32% and 6% risk of relapse, respectively. These risk factors were introduced based on an analysis of retrospective trials [88], and then confirmed in subsequent prospective studies [106, 107]. Two prospective trials based on these risk factors demonstrated the feasibility of a risk-adapted approach. In a Spanish study including 227 men, patients without or with one risk factor were managed with surveillance, whilst the group with both risk factors present received two adjuvant courses of carboplatin, AUC 7 [106]. Although the median follow up was relatively short (34 months), the relapse rate with adjuvant treatment was reported at 1.4% [106].

A SWENOTECA trial included 897 patients [107]. Patients with no or one risk factor were offered surveillance, patients with both risk factors were offered one course of carboplatin, AUC 7. The final decision regarding adjuvant treatment was made by the individual patient. At a median follow up of 5.6 years patients without risk factors had a relapse rate of 4% with surveillance compared to 2.2% with adjuvant carboplatin. Overall, when one or both risk factors were present, 15.5% of the patients under surveillance relapsed whereas 9.3% of those receiving adjuvant carboplatin relapsed. Thirty-three per cent of relapses in patients who received adjuvant treatment occurred more than three years after orchidectomy and 3% more than five years [107].

With a risk reduction of 60% in patients with tumours with both risk factors present, the efficacy of one cycle of adjuvant carboplatin seems rather low, although the comparison with two adjuvant cycles of carboplatin is difficult because of small sample size and limited follow up in the Spanish study [106]. A currently recruiting SWENOTECA ABC trial compares the efficacy of one cycle of adjuvant carboplatin with one cycle of adjuvant cisplatin, etoposide, bleomycin (BEP) [138].

7.1.2.5 Guidelines for the treatment of stage I seminoma

Recommendations	Strength rating
Fully inform the patient about all available management options, including surveillance or adjuvant therapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as a management option if facilities are available and the patient is compliant.	Strong

Offer one course at area under curve 7, if carboplatin chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low risk of recurrence (no risk factors).	Strong
Do not routinely perform adjuvant radiotherapy. This option should be reserved for selected patients not suitable for surveillance and with contraindications to chemotherapy.	Strong

*7.1.3 **NSGCT clinical stage I***

Depending on risk factors, up to 50% of NSGCT patients with CS1 disease have subclinical metastases and will relapse during surveillance [110, 121, 125, 139]. This raises the issue of adjuvant chemotherapy, which should be considered on the basis of discussion with each patient about advantages and disadvantages of the options, as well as their individual circumstances and concerns.

7.1.3.1 Surveillance

Improvements in clinical staging and follow-up methods, as well as the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of close surveillance only after orchiectomy in CS1 NSGCT patients.

Overall, 14-48% of CS1-NSGCT patients undergoing surveillance recur within two years of orchidectomy. The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS1-NSGCT (five-year conditional risk of relapse 42.4% and 17.3 for high- and low-risk CS1-NSGCT respectively) [121, 122]. Of these, 92% present within the first two years [121, 122].

Approximately 35% of patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite rigorous follow-up, 11% of relapsing patients will present with large-volume metastatic recurrent disease [121, 139].

The somewhat lower relapse rates reported from surveillance studies, compared with some series of patients staged by RPLND [140], may relate to selection bias with exclusion of high-risk cases or very early marker relapse prior to surveillance re-imaging. Based on the overall CSS data, surveillance within a rigorous protocol can safely be offered to patients with non-risk stratified CSI non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [139, 141, 142].

7.1.3.2 Adjuvant chemotherapy

Adjuvant chemotherapy with two courses of BEP was evaluated in a prospective MRC trial reported in 1996 [143]. Subsequently, adjuvant chemotherapy was mainly given to high-risk patients (LVI present) [143-145]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [143], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [146].

More recently, use of one cycle of adjuvant BEP has also resulted in low recurrence rates (2-3%) [147, 148]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. In light of equivalent CSS rates, including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is now the recommended strategy if adjuvant chemotherapy is considered [147, 148]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined which should be taken into consideration with decision making [149, 150].

7.1.3.3 Retroperitoneal lymph node dissection

In view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary RPLND has diminished.

A randomised phase III trial compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND favoured chemotherapy with recurrence free survival of 99.5% versus 91% [151]. The hazard ratio to experience a tumour recurrence with surgery compared to BEP x 1 was 8 [151]. No clinically relevant differences in quality of life (QoL) were detected [152].

In a multicentre setting, higher rates of in-field recurrences and complications have been reported with nerve sparing RPLND [151, 153]. This suggests that primary RPLND, when indicated or chosen, should be performed by an experienced surgeon in a specialist centre.

If retroperitoneal metastases are not found at RPLND (PS1), approximately 10% of patients will relapse at distant sites [110, 154], although more recent series report lower figures of pN+ cases and relapse [155]. Following RPLND about 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease [153, 154]. In patients with active malignancy who are not treated with adjuvant chemotherapy, approximately 31% will experience recurrence [154].

Presence of LVI, predominant embryonal carcinoma, pT category and extranodal extensions of involved nodes all appear associated with an increased risk of recurrence with PS2 disease without adjuvant chemotherapy. The use of these further parameters, however, has yet to be clearly defined in clinical practice [154, 156].

Follow-up after RPLND is less demanding and costly than with surveillance due to the reduced need for CECT [157]. With primary RPLND, laparoscopic or robot-assisted RPLND appears feasible but cannot be recommended outside of a high-volume RPLND centres with appropriate minimally invasive expertise [158].

7.1.3.4 Risk-adapted treatment

A risk-adapted strategy is an alternative to universal surveillance patients with CS1 NSGCT. Risk-stratification is based on the presence of LVI. If a risk-adapted policy is applied, patients with LVI receive adjuvant chemotherapy with BEP whereas patients without LVI are recommended surveillance. A community based prospective study of 490 patients that received BEP x 1, showed a five-year relapse rate of 3.2% for LVI+ patients and 1.6% for LVI- patients. After a median follow up of 8.1 years the relapse rate was 2.3%, 3.4% and 1.3% for all, LVI+, and LVI-, respectively [147, 148]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no relapses were observed later than 3.3 years.

It is, however, critical to remain aware of the possibility of slow-growing retroperitoneal teratomas after adjuvant chemotherapy [159].

Cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up protocols [160]. With low-frequency follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow up can be considerably reduced [161].

7.1.3.5 Teratoma with somatic-type malignancy

According to a multi-institutional study analysing retrospective datasets of patients with teratoma with somatic-type malignancy (TSTM), patients with clinical stage I disease and TSTM had an approximately 10% shorter five-year OS than GCT stage I patients. Moreover, the proportion of those stage I patients undergoing primary RPLND who had nodal metastases (PSII) of TSTM was higher than expected (37.5%). Despite the limitations of this study, this represents the strongest evidence on this issue and supports primary RPLND in clinical stage I patients diagnosed with TSTM in the testis [162].

7.1.3.6 Guidelines for the treatment of clinical stage I non-seminomatous germ cell tumour

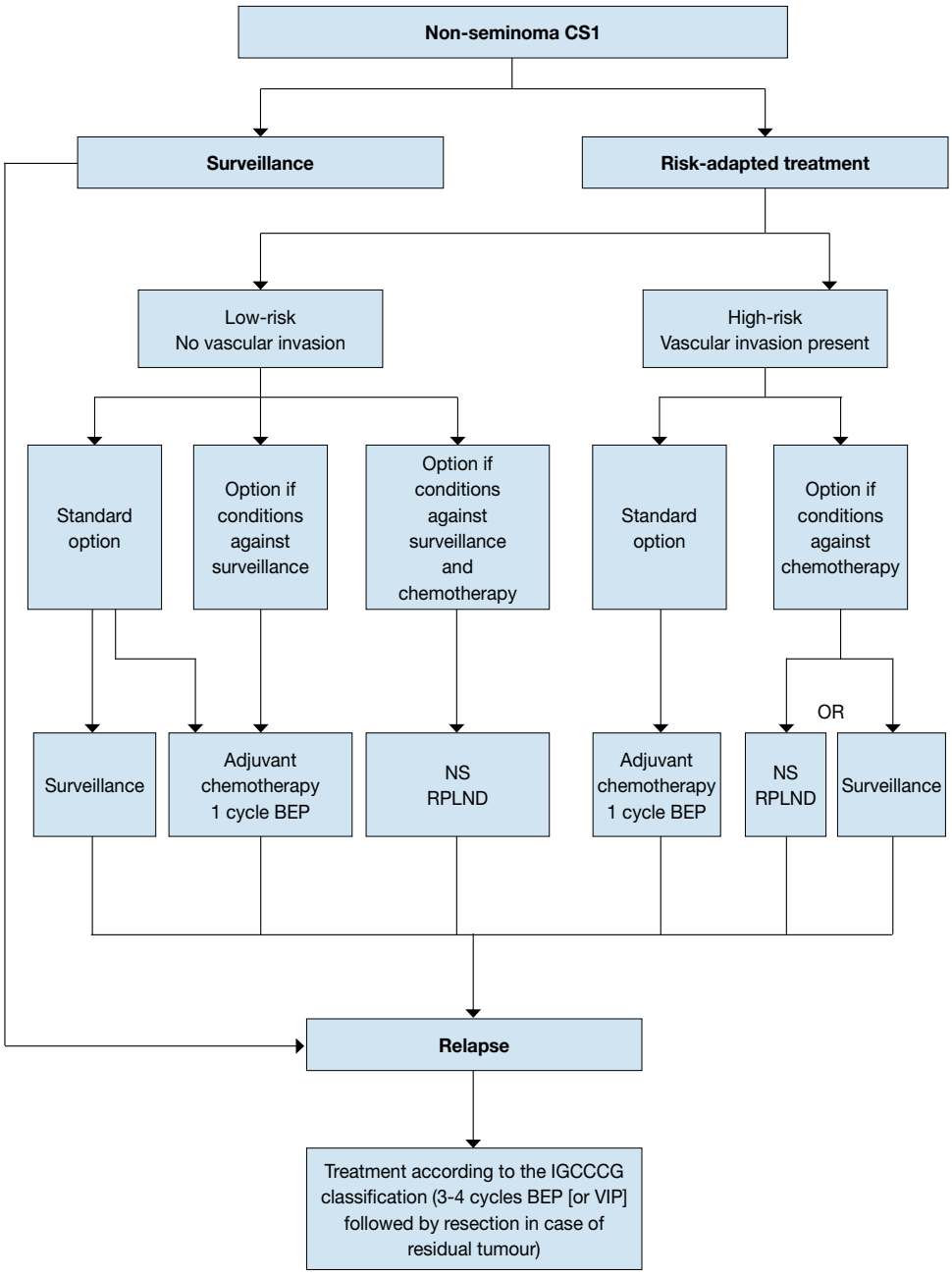
Recommendations	**Strength rating**
Inform patients with stage 1 non-seminomatous germ cell tumour (NSGCT) about all management options after orchiectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
If patients are not willing to undergo or comply with surveillance, offer one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	Strong

7.1.3.7 Risk-adapted treatment for clinical stage I non-seminomatous germ cell tumour based on vascular invasion

Recommendations	**Strength rating**
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	Strong
Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong

Offer nerve-sparing retroperitoneal lymph node dissection (RPLND) to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary RPLND should be advised in men with teratoma with somatic-type malignancy.	Strong

Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT [163]*



**Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*

BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.2 Metastatic germ cell tumours

The first-line treatment of metastatic GCTs depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG (Table 4.3) [28];
- marker decline during the first cycle of chemotherapy in “poor-prognosis” patients.

In relapsed patients, a prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy [164].

*7.2.1 **CS1S with (persistently) elevated serum tumour markers***

Serum tumour markers should be followed closely until levels fall into the reference ranges based on the expected half-lives for AFP and hCG. The clinical significance of persistently elevated LDH after orchidectomy in clinical stage I disease is unclear. If AFP or hCG increase or fail to return to normal levels after orchidectomy, US examination of the contralateral testicle must be performed.

Although some patients may have a persistent, slightly elevated but stable AFP or HCG, those with rising markers only after orchidectomy, require repeated imaging including extra-abdominal sites in order to detect and define sites of metastasis and to individually tailor treatment [163].

The treatment of true CS1S-NSGT should be the same as other good-prognosis metastatic non-seminoma (stage IIA/B). With this five and ten years disease-free survival of 87% and 85% have been recently reported [165].

*7.2.2 **Metastatic disease (stage IIA/B)***

7.2.2.1 Stage IIA/B seminoma

Patients with enlarged retroperitoneal lymph nodes < 2 cm and normal markers represent a clinical dilemma. These nodes may be benign or indicate true metastatic disease. In this situation observation for six to eight weeks with repeat staging imaging is recommended. Treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise [163, 166].

Standard treatment option for stage IIA/B seminoma has been radiotherapy, with reported relapse rates of 9-24% [167, 168]. Accumulating data on long-term morbidity, such as an increased risk of cardiovascular events and second malignancies following radiotherapy has raised concerns. One study with a follow up of 19 years reported a 7-fold higher all-cause mortality rate than mortality due to seminoma [169].

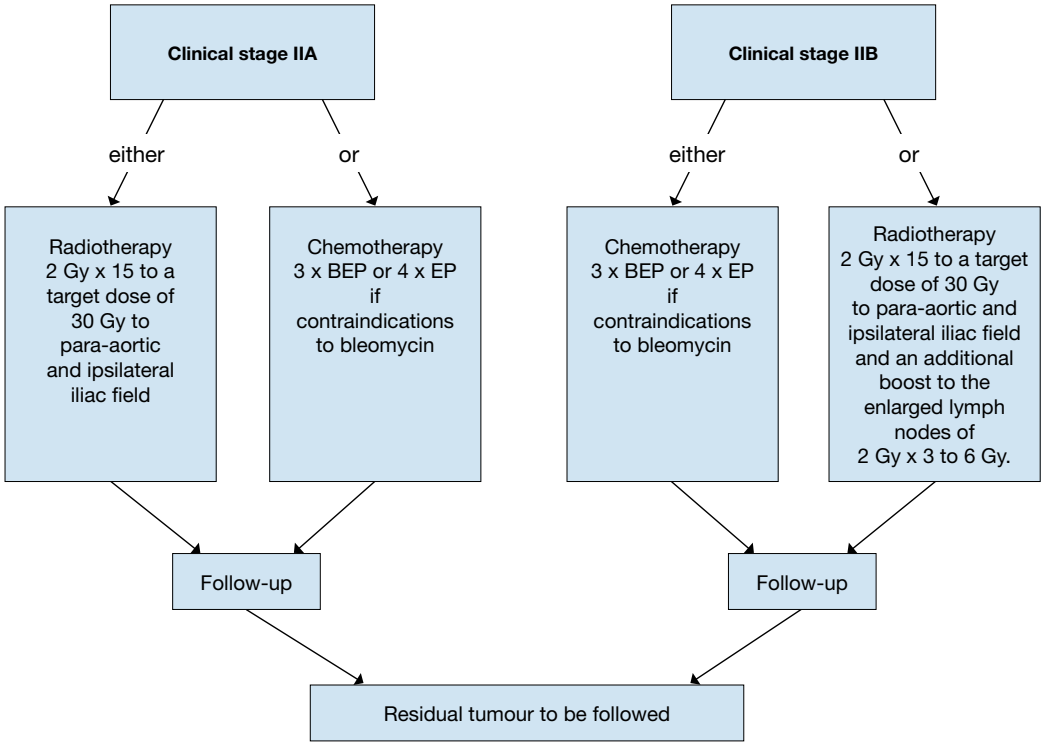
Most reports encompass patients irradiated with larger target volumes and higher doses, although recent studies with more limited radiotherapy fields report similar rates of relapse [170]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively, with the standard field encompassing the PA and ipsilateral iliac nodes. In stage IIB, the lateral borders should include the metastatic lymph nodes with a surrounding margin of 1.0-1.5 cm. This technique yields relapse-free survival rates in stage IIA and IIB of 92% and 90%, respectively [167, 168]. Dose reduction in stage IIA to 27 Gy has been associated with relapse rates of 11% [124, 170].

Currently, chemotherapy is the preferred alternative to radiotherapy for stage IIA/B. This entails three cycles BEP or four cycles of etoposide and cisplatin (EP) as an alternative in case of contraindications to bleomycin or for older patients. There are no randomised studies comparing radiotherapy and chemotherapy. A recent meta-analysis of thirteen high-quality studies, comparing efficacy and toxicity of radiotherapy and chemotherapy in stage IIA/IIB patients [171], shows that radiotherapy and chemotherapy appeared to be similarly effective in both stages, with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [171]. Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent following radiotherapy, mainly comprising bowel toxicity and secondary cancers, generally in the irradiated field [171].

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease, with the risk of failure or relapse at the site of initial nodal disease [172].

Specific trials (e.g. including RPLND or involved field radiation combined with a single course of carboplatin chemotherapy) are addressing the role of treatment options with potentially lower toxicity compared to standard options of either radiotherapy or chemotherapy with three cycles of BEP.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B



BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.2.2.2 Stage IIA/B non-seminoma

There is a general consensus that initial treatment should be chemotherapy in all advanced cases of NSGCT with the exception of stage IIA/B NSGCT disease consisting of post-pubertal teratoma without elevated tumour markers, which can be managed by primary RPLND [159, 173]. A recent large retrospective series reported 73% of long-lasting remissions following RPLND alone in selected patients who relapsed as stage II following surveillance for stage I non-seminoma [139].

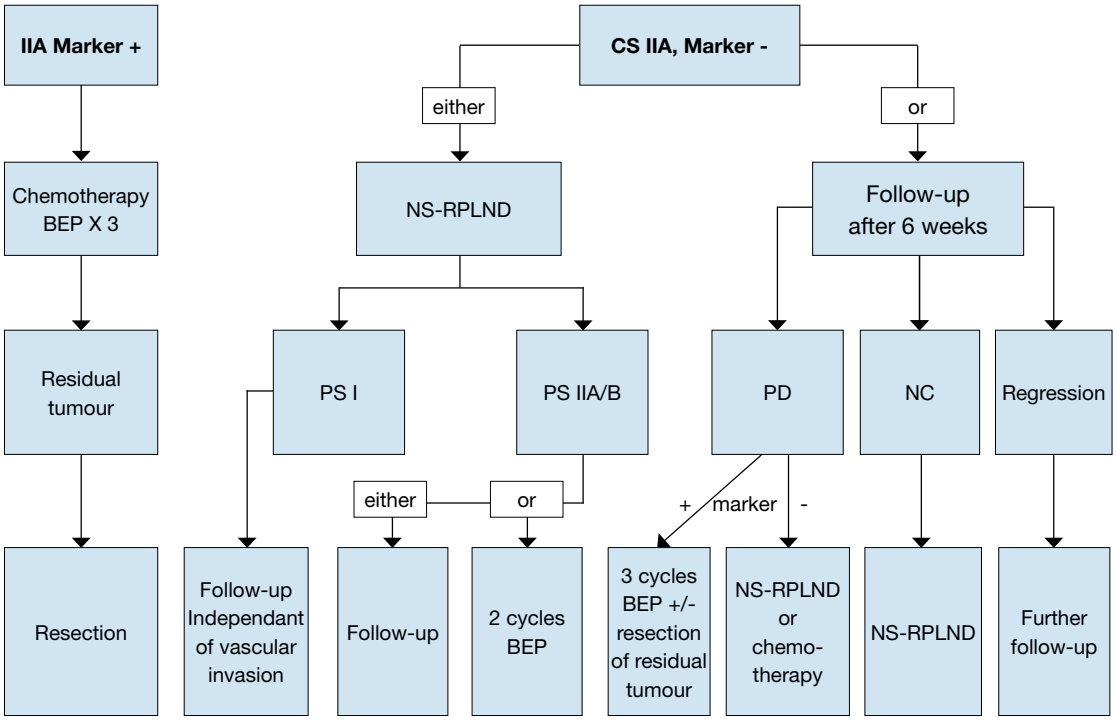
Initial surveillance may be considered in patients with “equivocal” (i.e. less than 2 cm, non-nodular shape) nodal disease and normal markers with early re-evaluation at six weeks. A shrinking lesion may be observed further. If the lesion is growing without a corresponding increase in the tumour markers AFP or β-hCG, teratoma should be considered. In this case nerve-sparing RPLND represents the first treatment option which should be performed by an experienced surgeon [173].

Patients with a growing lesion and a concomitant increase in the tumour markers AFP or β-hCG require primary chemotherapy according to the treatment algorithm for patients with metastatic disease and according to IGCCCG risk-group (See section 7.2.3).

When a marker negative stage IIA/B relapse is diagnosed two or more years following initial diagnosis, a CT- or US-guided biopsy should be advised to confirm the diagnosis of GCT relapse. A RPLND may be an alternative option. There is insufficient published data on PET scans in this situation to provide recommendations.

Primary chemotherapy and primary ‘nerve-sparing’ RPLND are comparable options in terms of oncological outcome, but early and long-term side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [174]. Following RPLND, PS-IIA or B, patients can be followed or receive two cycles of BEP. The cure rate with either approach will be close to 98% [175-177].

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA



BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

*7.2.3 **Metastatic disease (stage IIC and III)***

7.2.3.1 Primary chemotherapy

7.2.3.1.1 Good prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, only very limited data is available from RCTs, although studies suggest that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [178]. As data from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) S99 trial indicates that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [179], this regimen can also be used. Therefore, standard treatment in good-prognosis seminoma should be, BEP x 3 or EP x 4. In the case of contraindications to bleomycin, EP x 4 should be given [180].

Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.2.3.1.2 Intermediate prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) when contraindications to bleomycin, are recommended options, although no RCT has focused specifically on this group of rare patients. A risk-adapted approach with EP x 4 for patients with good prognosis and VIP x 4 for patients with intermediate-prognosis metastatic seminoma yielded an OS of 99% and 87% for good- and intermediate-prognosis patients, respectively [179].

7.2.3.1.3 Good prognosis risk group - non-seminomatous germ cell tumour

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good-prognosis disease, according to the IGCCCG risk classification, is BEP x 3 (Table 7.1) [28]. This regimen is superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [181, 182]. The available randomised controlled data support the equivalence of three and four cycles of BEP x 4 and of three-day and five-day for projected two-years PFS. However, the three-days regimes experienced increased GI toxicity at three months and increased two-years risk of tinnitus (see section 8.3.9. The difference in toxicity between the three and five days regimes reached clinical relevance when BEP x 4 was given [183, 184]. Based on these data the BEP x 3 and 5-day regimen is recommended in the good prognosis risk group.

Table 7.1: cisplatin, etoposide, bleomycin (BEP) regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

**Plus hydration.*

Patients with a clear contraindication to bleomycin may receive EP x 4 [183]. In all other cases omission of bleomycin is not recommended. Two RCTs support the superiority of 3 x BEP over other regimes or schedules/ intensities [185, 186]. Additionally, the GETUG T93BP RCT suggested that when EP is used the mortality rate is twice that of BEP, although the difference did not reach statistical significance [186]. Furthermore, the incidence of residual active cancer in the post-chemotherapy RPLND was significantly higher in patients who received EP x 4 as compared to BEP x 3 (31.9% versus 7.8%, p. < 0.0.01) [187]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could thereby offset the anticipated advantage of reduced toxicity.

A randomised study using 72 hour infusion versus bolus bleomycin in order to reduce pulmonary toxicity did not show any significant difference in efficacy or in pulmonary side effects [188].

Therapy should be given without reduction of the doses at 21-day intervals. Delaying a chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1,000/mm^3 or thrombocytopenia < 100,000/ IU. Neutropenia without fever alone is not a reason to delay the next cycle. As Granulocyte colony-stimulating factor (GCS-F) lowers the risk of neutropenic sepsis, one may consider up-front administration. Granulocyte colony-stimulating factor must be given if infectious complications have occurred during or after chemotherapy, or when a treatment interval is delayed due to myelotoxicity [189].

7.2.3.1.4 Intermediate prognosis risk group - non-seminomatous germ cell tumour

The 'intermediate-prognosis' group in the IGCCCG is defined as patients with a five-year survival rate of the order of 80%. With this group the available data support BEP x 4 as standard treatment [190]. A RCT showed no significant improvement in OS with BEP x 4 plus paclitaxel (T-BEP) compared to BEP x 4 alone [191]. The overall toxicity with T-BEP was higher than with BEP; therefore, it cannot be recommended as a standard approach.

Patients with intermediate prognosis treated in recent years (after 1997) are more likely to have a five year survival of near 90% [192, 193].

7.2.3.1.5 Poor prognosis risk group - non-seminomatous germ cell tumour

For patients with a 'poor-prognosis' non-seminoma as defined by the IGCCCG, standard treatment consists of BEP x 4 with five-year PFS of 45%-50%. Four cycles of cisplatin, etoposide and ifosfamide (PEI) has similar efficacy, but is more myelotoxic [194]. Several RCTs have shown no advantage in OS for high-dose chemotherapy (HDCT) in the overall 'poor-prognosis' patients group [186, 195, 196]. Patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [196, 197]. There are several ways to calculate slow tumour marker decline with an example available at https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [198]. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive chemotherapy regimen [198]. Further prospective trials/registries are planned to validate this approach.

Additional patient groups that may benefit from up-front dose intensification are those with mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [199, 200].

As a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [201], poor-prognosis patients should still be treated in ongoing prospective trials or registries, whenever possible. Patients meeting 'poor-prognosis' criteria should be transferred to a specialist centre, as better outcomes are reported for intermediate- and poor-prognosis patients treated within a clinical trial at a high volume centre [114, 202]. There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small reports indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [203, 204].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome. Omitting bleomycin with the first-cycle of chemotherapy (with inclusion for subsequent cycles) has been suggested to reduce the risk of early death in this setting [204]. Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [205].

7.3 Treatment evaluation and further treatment

*7.3.1 **Treatment evaluation***

Response to treatment is assessed after the initial induction cycle by repeat imagining and re-evaluation of tumour markers. With marker decline and stable or regressive tumour features, radiologically chemotherapy should be completed (three or four cycles, depending on the initial prognostic category) [206, 207]. If markers decline, but metastases progress on imaging, these should be immediately resected where feasible after completion of induction therapy. [208].

Patients with initial disease progression following induction (primary cisplatin refractory) should be switched to experimental new drug trials [209]. Patients with slow marker decline with the first one to two cycles of chemotherapy are candidates for dose intensification (see Section 7.2.3.1.5). Patients with a low-level β-hCG marker plateau post-treatment should be observed to determine whether complete normalisation occurs. In patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only [210, 211].

*7.3.2 **Residual tumour resection***

7.3.2.1 Seminoma

A residual mass of seminoma should be monitored with imaging and tumour markers and not primarily resected, irrespective of size [212-215].

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > two months after chemotherapy. In patients with residual masses > 3 cm, FDG-PET should be performed in order to provide more information on disease viability. In patients with residual masses < 3 cm, the use of FDG-PET is optional [52, 53].

When a post-chemotherapy mass remains positive at reclassification FDG-PET with no volume increase, repeat FDG-PET should be performed six weeks later. A recent publication shows a low PPV for vital tumours in residual lesions (generally > 3 cm) after chemotherapy in metastatic seminoma (11 to 38% depending on subgroup). Therefore, caution is recommended with FDG-PET and single parameters driving clinical decisions in a persistent mass [54]. In patients with progressive disease on radiological criteria (i.e. a growing mass which enhances with CECT or is FDG-PET avid), salvage therapy is indicated (usually chemotherapy or radiotherapy) [216-218].

Patients with persistent and progressing β-hCG elevation after first-line chemotherapy should immediately proceed to salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e.g. by percutaneous or surgical biopsy) before salvage chemotherapy is given.

When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be extremely difficult to remove due to intense fibrosis [217]. Ejaculation may be preserved in some of these cases [219].

7.3.2.2 Non-seminoma

Following first-line BEP chemotherapy, only 6-10% of residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only [220]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients after chemotherapy [48-50]. With complete remission after first-line chemotherapy (no visible tumour), tumour resection is not indicated [221, 222].

No diagnostic or risk calculator can accurately predict histology of the residual masses. Thus resection is mandatory in all patients with a residual mass > 1 cm at cross-sectional CECT imaging until novel predictive models are externally validated [223-226].

The role of surgery is uncertain in patients with retroperitoneal residual lesions < 1 cm. There is still a risk of cancer or teratoma, although in the vast majority of patients (> 70%) these contain only fibro-necrotic tissue [227]. Proponents of post-chemotherapy RPLND for all patients refer to the fact that both teratoma and malignant GCTs may still be present despite remission in lesions < 10 mm [228]. The alternative for patients with a residual mass < 1 cm is an observation protocol with recurrence risk of 6-9% depending on the follow-up duration [221, 222]. In the series with the longest follow-up of 15.5 years, twelve (9%) of 141 patients

relapsed despite a complete response following primary treatment [222]. Eight of the twelve relapsing patients were cured with subsequent treatment. Patients after salvage chemotherapy or HDCT in first or subsequent salvage situations harbour vital tumour at a much higher rate [229]. Surgery is therefore indicated in salvage patients even with residual masses < 1 cm [221, 222].

When surgery is indicated, all areas of primary metastatic sites should be completely resected within six weeks of completion of chemotherapy, when feasible. Bilateral nerve-sparing RPLND has been the standard option. Ipsilateral template resection with contralateral preservation of nerves in selected patients has been reported to yield equivalent long-term results compared to bilateral systematic resections. The mere resection of the residual tumour (so called lumpectomy) should not be performed [222, 226, 227, 229-232].

Laparoscopic RPLND may yield comparable outcomes to the open procedure in selected cases with low residual disease and when undertaken by very-experienced hands, but it is not recommended outside a specialised laparoscopic centre with specific expertise in TC. In that setting, up to 30% of post-chemotherapy RPLND may be performed via a laparoscopic approach [233-235]. Experience with robot-assisted laparoscopic RPLND in this setting is still limited [236] and atypical recurrences have been reported, and occur more often, after the robotic approach [237].

*7.3.3 **Sequencing of surgery in the case of multiple sites***

In general, residual surgery should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites [223]. In cases of retroperitoneal and lung residual masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [238].

Resection of contralateral pulmonary lesions is not mandatory in cases where pathologic examination of the lesions from the first lung show complete necrosis. However, discordant histology between both lungs may occur in up to 20% of patients [239, 240].

7.3.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Whilst most post-chemotherapy RPLNDs do not require resection of major vessels or organs, a proportion of patients may require an intervention in which organs affected by the disease are removed (e.g. kidney, psoas muscle or gross vessels), and may potentially also require *ad hoc* reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses). Patients undergoing adjunctive complex surgery benefit from disease control but have a greater risk of complications [241, 242]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [243]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [244]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [245]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [246].

7.3.3.2 Salvage and desperation surgery

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [247]. Also, even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [248, 249].

Desperation surgery refers to resection of non-responsive or progressive (e.g. rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term [250].

7.3.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or post-pubertal teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. 'poor-prognosis' patients) [230]. However, caution is required with cumulative doses of bleomycin. After complete resection of 'vital' tumour < 10% of the total volume, particularly in patients who were initially good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [251]. The prognosis is worse if malignant disease is present in masses resected after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated [252].

7.3.4 ***Systemic salvage treatment for relapse or refractory disease***

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients who relapse after first-line chemotherapy. These results are highly dependent on several prognostic factors [253]. The regimens of choice are four cycles of a three agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [254, 255]. No RCT has compared these regimens. Due to their potential risk of lethal haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available RCT comparing standard-dose and HDCT plus transplantation in the salvage setting showed no benefit in OS in patients treated with three cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus one cycle of consolidation HDCT, compared with VeIP x 4 [256]. For methodological reasons this trial design can no longer be considered state of the art.

Table 7.2: Standard PEI/VIP, TIP and GIP salvage chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	Cisplatin*	20 mg/m^2	Days 1-5
	Etoposide	75-100 mg/m^2	Days 1-5
	Ifosfamide†	1.2 g/m^2	Days 1-5
TIP	Paclitaxel	250 mg/m^2 [xx]	24 hour continuous infusion day 1
	Ifosfamide†	1.5 g/ m^2	Days 2-5
	Cisplatin*	25 mg/m^2	Days 2-5
	Alternative schedule		
	Paclitaxel	175 mg/m^2	Day 1, 3 hour infusion
	Ifosfamide†	1.2 g/m^2	Days 1-5
	Cisplatin*	20 mg/m^2	Days 1-5
GIP	Gemcitabine	1000 mg/m^2	Day 1 + 5
	Ifosfamide	1200 mg/m^2	Days 1-5
	Cisplatin	20 mg/m^2	Days 1-5

** Plus hydration.*

† Plus mesna protection.

[xx] An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion [255].

There is clear evidence from retrospective analyses that there are different prognostic groups at risk in the case of relapse after first-line chemotherapy. The International Prognostic Factors Study Group (IPFSG) score for patients with metastatic germ cell tumours who experienced treatment failure with first-line cisplatin-based chemotherapy is based on seven variables: histology, primary tumour location, response, progression-free interval after first-line and level of α-feto protein, hCG and the presence of liver, bone or brain metastasis at salvage treatment [164]. Using these factors, five risk-groups: *very low risk* = -1 points; *low risk* = 0 points; *intermediate-risk* = 1-2 points, *high risk* = 3-4 points; and *very high risk* > 5 points were identified with significant differences in PFS and OS. Table 7.3 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [164].

Several recent trials have validated this scoring system [257-260]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [261]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [262].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed an improvement of about 10-15% in OS in all prognostic subgroups when treated with high-dose salvage therapy compared to standard-dose therapy. To prospectively confirm this finding, an international RCT of high-dose versus conventional-dose chemotherapy in patients with first-line relapse has commenced (Tiger trial). When HDCT is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide (HD-CE) should be preferred to a single high-dose regimen as the former is associated with less toxicity-related deaths [263]. A recent systematic review confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [264]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 7.3: The International Prognostic Factors Study Group Score for Seminoma and Non-seminoma that relapse after Cisplatin-based First line chemotherapy [164]

Points	**-1**	**0**	**1**	**2**	**3**
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	≤ 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; CR = complete remission; PRm- = partial remission, negative markers; PRm+ = partial remission, positive markers; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval; SD = stable disease.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG prognostic score for Seminoma and Non-seminoma that relapse after Cisplatin-based First line chemotherapy [165]

Score (n = 1,435)	**N**	**%**	**HR**	**2-years PFS**	**3-year OS**
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159	-	-	-	-

HR = hazard ratio; PFS – progression-free survival; n = number of patients; OS = overall survival.

*7.3.5 **Second relapse***

No RCTs have been reported for patients with second relapse and conventional therapy does not appear to be very effective. For patients who have received two series of conventionally-dosed therapy (first-line and first-salvage), high-dose (HD) chemotherapy with autologous stem cell support should be used [258]. Even with HD-therapy the prospect of cure is only 20-25%.

Refractory disease: Patients relapsing within four to eight weeks after platinum-based therapy, or who are progressing despite platinum-based therapy, as well as those relapsing shortly after HD- chemotherapy, are considered cisplatin refractory. For these patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [265]. For patients with a second relapse not responding to the combination of Oxaliplatin and gemcitabine or the triple combination, inclusion in clinical trials is encouraged.

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [248, 266].

Various targeted agents have generally failed in refractory disease [267-270]. Limited responses with rapid development of resistance have been observed for Brentuximab Vedotin in CD30-expressing germ cell tumours [271, 272]. Most GCT series report a substantial expression of PDL-1 in approximately 50% of tumour cells or tumour infiltrating cells [273, 274]. Despite this, single-agent treatments with immune checkpoint inhibitors did not yield any meaningful responses [275, 276]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing.

7.3.5.1 Late relapse (> two years after end of first-line treatment)

Late relapse is defined as recurrence more than two years following cure after chemotherapy for metastatic TC, with, or without, residual tumour surgery [51]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [277]. When feasible, all lesions of late-relapsing non-seminoma patients should be removed by radical surgery.

Patients with rapidly rising β-hCG may benefit from induction salvage chemotherapy before complete resection is attempted. In general, however, surgery should be performed in most patients when feasible irrespective of the level of their tumour markers in order to completely resect all viable GCT, post-

pubertal teratoma or TSTM [159, 278].

Survival strongly relates to the histology of the removed lesions rather than the initial presenting tumour. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [279].

If the lesions are not completely resectable, biopsies should be obtained for histological assessment, and salvage chemotherapy should be initiated based on the histological phenotype. In these cases, consultation of an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of germ cell malignancy [280]. If the patient responds to salvage chemotherapy, secondary surgery should be conducted, whenever possible. In the case of unresectable, but localised, refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [281].

*7.3.6 **Treatment of brain metastases***

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30-50%) and even poorer when a site of recurrent disease (the five-year survival-rate is 2-5%) [282, 283]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnosis and 27% three-year OS rates for patients with brain metastases at relapse [41]. Chemotherapy as initial treatment proved effective in a first-line setting (potentially even as dose-intensified therapy upfront) with data also supporting the use of multimodal treatment particularly in relapsed disease [41]. Consolidation RT, even with total response after chemotherapy, should thus be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [284]. Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic disease status, histology of the primary tumour and the location of the metastasis.

7.3.6.1 Guidelines for the treatment of metastatic germ cell tumours

Recommendations	**Strength rating**
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like ‘good- or intermediate-prognosis’ advanced NSGCT, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection or biopsy. If not possible, repeat staging after six weeks before making a final decision on further treatment.	Strong
In metastatic NSGCT with an intermediate prognosis, treat with four cycles of standard BEP.	Strong
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, (or cisplatin, etoposide and ifosfamide [PEI], in case of poor lung function), followed by tumour marker assessment after three weeks. In case of favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of visible residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
In clinical stage IIA seminoma, offer radiotherapy or chemotherapy and inform the patient of potential long-term side effects of both treatment options.	Strong
Offer initial chemotherapy in seminoma stage IIB (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	Strong
Treat seminoma stage IIC and higher, with primary chemotherapy based on the same principles used for NSGCT.	Strong

8. FOLLOW UP AFTER CURATIVE THERAPY

8.1 Rationale for follow-up

The primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to enable treatment with curative intent using the least aggressive therapy [51]. An adequate follow-up relies on profound knowledge about TC with regards to histology, stage, primary treatment and treatment success. Follow-up must be tailored to the individual patient with a schedule acceptable to the patient, the clinician, and the healthcare system. The interval of follow-up visits and the clinical investigations to be performed at each visit should depend on the risk of relapse, in general, as well as the likely sites of relapse in an individual patient [285]. Only one RCT addresses the implication of different follow-up schedules and the use of imaging and tumour markers [161]. Several recent publications have provided valuable information and recommendations [105, 107, 121, 127, 129, 148, 286-289] contributing to the development of consensus recommendations by the European Society for Medical Oncology Testicular Cancer Consensus Committee [290].

To minimise ionising radiation exposure risks associated with repeated CT scanning [291] a reduction in the number of follow up CT scans advised has occurred in the past few years [1, 292].

8.2 Minimal recommendations for Follow up

Based on different risks of relapse depending on diagnosis and initial treatment, three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for good- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually by specialised centres. Tables 8.1-8.3 show the minimal recommendations for follow up of the three different groups based on recommendations developed at an ESMO consensus conference [290].

Generally, MRI of the abdomen can be used as an alternative to CECT in experienced centres. Regarding the use of US of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [290].

Follow-up for relapse beyond five years is generally not recommended. A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients based on a population-based analysis [279]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment.

Most patients with VLR are diagnosed due to symptoms, although in up to 50% elevated tumour markers are present in both seminoma and NSGCTs [279, 293]. Patient education regarding relapse symptoms and clinician awareness are important elements of survivorship management. Early use of imaging and tumour markers with suspicion of relapse is encouraged.

Table 8.1: Recommended minimal follow-up for seminoma clinical stage I on active surveillance or after adjuvant treatment (Carboplatin or Radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 8.2: Recommended minimal follow-up for non-seminoma clinical stage I on Active Surveillance

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times***	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+*	At 60 months if LVI+*	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	At 24 months****	Once at 36 months**	Once at 60 months**	

* *LVI+: Lymphovascular invasion present*

** *Recommended by 50% of the consensus group members.*

*** *In case of high-risk (LVI+) a minority of the consensus group members recommended six times.*

**** *In case of high-risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

Table 8.3: Recommended minimal follow up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

* *Same time points as abdominopelvic CT/MRI in case of pulmonary metastases at diagnosis.*

** *In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

8.3 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured with five-year relative survival rates of approximately 95% in Western Europe. Testicular cancer patients are usually between 18 and 40 years of age at diagnosis and life expectancy after cure extends over several decades [294]. Patients should be informed before treatment of common long-term toxicities, which are avoided or minimised by adherence to international guidelines.

Treatment of stage I TC is controversial, with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [142], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [295]. Unfortunately, it is not known which treatment spares most patients from long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy [144, 150, 296].

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia and testosterone deficiency. When follow-up by the TC clinician is terminated, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up may be helpful [51, 297]. Whilst the following overview is not complete those interested may consider review articles on this topic [294, 297, 298].

*8.3.1 **Second malignant neoplasms (SMN)***

Treatment-induced SMN usually occurs after the first ten years [297]. Testicular cancer belongs to the group of cancers commonly diagnosed in adolescents and young adults (AYA), which have a higher absolute risk of developing a subsequent primary neoplasm than survivors of childhood or adult cancer [299]. In a comprehensive study on second cancers in AYA cancer survivors (aged 15-39 years at AYA cancer diagnosis) 24,309 TC survivors with 1,435 second cancers were registered as opposed to 808 expected second cancers, yielding a standardised incidence ratio of 1.8. The second cancer incidence increased with time resulting in remarkably high and accelerating 35 year cumulative incidence rate of 20.2% (95% CI: 18·9–21·5) [299].

The risk for solid SMN increases with younger age at radio- or chemotherapy [297]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (colon, stomach, pancreas, bladder and the

urinary tract) [297]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [300].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [301]. A relationship between cumulative dose of Cisplatin and 2nd SMN, especially in the GI tract has been noted [302]. As few studies have observation times beyond 25 years, the cumulative incidence of SMN may be underestimated. An increase from 6.5% after 25 years to 20.2% after 35 years has been reported [299]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [303]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [303].

The European Society for Blood and Marrow Transplantation (EBMT) reported SMN in 59 of the 5,295 TC patients registered after receiving HDCT within a median follow-up of 3.8 years. Of them, 39% developed a hematologic SMN and 58% a solid SMN. Twenty year cumulative incidence of solid and hematologic SMN was 4.2% and 1.4% respectively, with median OS shorter after diagnosis of hematologic versus solid SMN (8.6 versus 34.4. months). Age ≥ 40 years at the time of HDCT was significantly associated with hematologic, but not with solid SMNs [304].

*8.3.2 **Leukaemia***

In a series of 40,576 TC survivors, the observed ratio for developing leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [305]. The risk of AML seems to be related to both the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [306]. The majority of TC patients receive much lower doses of etoposide than this so that the absolute risk of AML after three to four courses of BEP is very low. In patients requiring HDCT with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to develop AML. There is a cumulative dose-disease risk relationship with cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a poor prognosis [307].

*8.3.3 **Infections***

Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the general population (standard mortality ratio 2.48, 95% CI: 1.70-3.5) [308]. This is possibly due to long-term bone-marrow suppression, as well as complications of subsequent salvage treatment (which was not reliably registered). Alternatively, extensive or subsequent surgical treatment may be contributory. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to respiratory infections long after treatment.

*8.3.4 **Pulmonary complications***

Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [308]. Bleomycin-induced lung toxicity may affect 7-21% of patients in the long term, resulting in death in 1-3% [309]. Chemotherapy-treated TC survivors treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [299]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not the dose of bleomycin [310]. The data contrasts with a meta-analysis on chemotherapy for TC including 6,498 patients showing a significant effect of bleomycin administration on all-grade pulmonary toxicity [311]. In a Danish cohort of 565 TC survivors, Lauritsen *et al*. found pulmonary function recovered with repeated assessments over five years in almost all patients [312]. Pulmonary function was not associated with reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, but rather pulmonary embolism, lung surgery, and poor IGCCCG risk group [312]. In 234 good risk TCSs patients the inclusion of bleomycin did not seem to influence pulmonary morbidity, operative difficulty, or non-pulmonary post-operative complications after post-chemotherapy RPLND [313].

A Canadian study on 212 TC patients receiving bleomycin-containing chemotherapy revealed bleomycin-induced pneumonitis (BIP) in 73 patients (34%) with the majority of these (75%) asymptomatic [314]. Granulocyte colony stimulating factor use was not associated with increased risk of BIP in multivariable analyses nor was it associated with increased severity of symptomatic BIP. There was a non-statistically significant trend towards greater risk of BIP in patients that developed renal impairment during chemotherapy treatment [314].

*8.3.5 **Cardiovascular toxicity***

Thromboembolic events (mostly venous) occur more frequently in patients with GCT receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [315]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [316], though

level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR 5) [308, 317, 318]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [149, 319]. Feldman *et al.* applied the Framingham Risk Score (FRS) on 787 TC survivors and compared the results with controls [320]: FRS did not differ by chemotherapy regimen (BEP 3 versus EP 4) nor between control and TCSs, although the latter were three times less likely to smoke and generally more physically active. However, less educated and less vigorously active TCSs had higher FRS representing a high-risk subgroup for intense follow-up and counselling [320].

Metabolic syndrome, a strong risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR 9.8) [318, 321, 322]. Hypogonadism increases the risk of insulin resistance, a proxy for metabolic syndrome, and an inherent risk of CVD. Bogefors *et al*. showed, however, that most associations between TC treatment and metabolic parameters became statistically non-significant after adjustment for hypogonadism, indicating that hypogonadism might be the mediator of several toxicities which are usually attributed to the applied TC treatment [323]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [324]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, and hypercholesterolaemia as well as major vascular events [316].

Physical activity reduces the risk of metabolic syndrome and CVD. High-intensity aerobic interval training (HIIT) for twelve weeks improved cardiorespiratory fitness, multiple pathways of CVD risk, and surrogate markers of mortality in TCSs as compared to standard care, i.e. no supervised training [325]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [326]. Two patients developed a pulmonary embolism (respectively at days seven and nine of BEP cycle 2) and the remainder a myocardial infarction (at day seven of BEP cycle 3). It is difficult to draw firm conclusions from such small patient numbers but the observed CVD was well above the expected 5% risk of thromboembolic complications during or shortly after cisplatin-based chemotherapy such that the authors discourage HIIT during cisplatin-based chemotherapy for TC.

8.3.6 ***Raynaud-like phenomena***

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually attributed to bleomycin [327, 328]. Cisplatin is believed to contribute to cold-induced vasospasms. Vogelzang *et al*. reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than with vinblastine and bleomycin only, 41% versus 21%, respectively [329].

8.3.7 ***Neurotoxicity***

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesias, affects 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchiectomy alone [318, 330]. Treatment with five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three to seven days following its administration. Platinum is measurable in the serum of TCSs many years after its application with the intensity of paraesthesias more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [324]. Patients who experience a larger decline in circulating residual serum platinum during follow-up are at reduced risk of worsening of tinnitus or hand paraesthesia [331].

8.3.8 ***Cognitive function***

There are concerns that chemotherapy may reduce the cognitive function leading to "chemo-brain". Amidi *et al.* could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [332]. Impaired brain networks may underlie poorer performance over time on both specific and nonspecific cognitive functions in TC survivors following chemotherapy.

8.3.9 ***Ototoxicity***

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [318, 333-335]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m^2 cisplatin over two days as compared to 20 mg/m^2 over five days (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [330]. A significant association between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [336, 337]. Understanding the pathogenesis of, and susceptibility to, this complication will lead to more individualised treatment in the future.

8.3.10 ***Nephrotoxicity***

Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20-30% of TCSs [316, 319, 321]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [338, 339]. A comprehensive assessment of 1,206 Danish TCSs, however, did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [317]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [322]. The estimation of glomerular filtration rate (eGFR) depends on whether creatinine or cystatin is applied, with the latter substance leading to an overestimation of eGFR in cisplatin treated TCSs, whereas this discrepancy was not found in patients with chronic kidney failure due to medical disease [340].

8.3.11 ***Hypogonadism***

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased LH levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [296, 318, 338, 341]. Compensated Leydig cell dysfunction in TCSs (testosterone within normal limits & increased LH values) was not associated with symptoms of depression, anxiety, sexual dysfunction, fatigue or impaired overall self-evaluated QoL, such that testosterone substitution seems not to be indicated in these patients [342].

Hypogonadism increases the risk of insulin resistance and hence the risk of metabolic syndrome, which, in turn, might lead to CVD in the long term [323]. Wiechno *et al*. could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [343]. Although there are clear indications of hypogonadism-related complications, and despite an established association between low testosterone and metabolic syndrome, no clear association between Leydig cell dysfunction and the risk of metabolic syndrome during a median ten-year follow-up could be established [344]. Furthermore, the clinical benefits of testosterone substitution are not well established. An ongoing Danish RCT might yield level 1 evidence [345].

Erectile dysfunction (OR 4.2) has been significantly associated with chemotherapy in a recent multicentre study [318].

Of 481 North American TCSs treated with modern cisplatin-based chemotherapy, 38% were hypogonadal (defined as on testosterone substitution or serum testosterone level ≤ 3.0 ng/mL) [346]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [347].

8.3.12 ***Fatigue***

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest, and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [346]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [184]. Of note, the prevalence of CF increased from 15% to 27% during a ten year period in long-term TCSs [348].

8.3.13 ***Quality of life***

Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [184]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [183]. After one and two years, one-third of patients reported an improvement in global QoL after chemotherapy, while one-fifth of patients reported deterioration, with no difference between treatment groups. After adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (five years) QoL between RPLND, or one course of BEP [152]. Anxiety, depression, fear of cancer recurrence (FCR), and distress may impair the health-related quality of life (HRQoL) in TCSs. A recent review identified a considerable variation in both severity and prevalence of each of these issues, probably due to use of different questionnaires and also cultural variations [349]. Clinically significant anxiety is reported in approximately 1 out of 5 TCSs and distress in 1 out of 7, and is therefore more frequent among TCS than in the general population. Depression was not uniformly found to be more frequent, whereas every third TCSs reported fearing recurrence. Importantly, poorer psychological outcomes were more common among single, unemployed TCSs with a low socio-economic status and co-morbidities, as well as those experiencing worse symptoms/side effects, and those using passive coping strategies. These findings are mostly in line with an earlier reported survivorship study on HRQoL among 486 TCSs revealing a greater prevalence of moderate- to extremely severe anxiety (19%) and depression (20%); and significant deficits to mostly mental aspects of HRQoL. The authors found that again, helpless/hopeless coping style was correlated with psychological distress and impaired generic HRQoL [350].

A German study found clinically significant anxiety in 6.1% and depression present in 7.9% of TC patients, with both a higher number of physical symptoms and having children being related to higher levels of anxiety and depression [351].

Among 2,479 Danish long-term TCSs higher anxiety was reported by those who experienced bilateral TC as compared to unilateral TC [352] .

For a subset of approximately 11% of TSCs, the diagnosis of TC was traumatic. This subset was found to suffer from post-traumatic stress disorder in the long term, which resulted in significant QoL reduction [353]. The authors recommend that healthcare professionals explore stress symptoms at follow-up visits in order to timely identify TSCs requiring support.

Sexual function and satisfaction was assessed in 2,260 Danish TCSs. Erectile dysfunction was found in men who underwent radiotherapy, BEP chemotherapy with subsequent surgical resection of residual masses, or more than one line of treatment. The latter group also reported orgasmic dysfunction. After radiotherapy, significantly more men reported overall decreased sexual satisfaction, whereas all other groups reported no difference in overall satisfaction, intercourse satisfaction, and sexual desire [354].

9. TESTICULAR STROMAL TUMOURS

9.1 Classification

Non-germ-cell tumours of the testicle include sex cord/gonadal stromal tumours and miscellaneous nonspecific stromal tumours. The different histological subtypes of testicular tumours are defined according to the 2016 WHO classification [23].

*9.1.1 **Epidemiology and prognosis***

Sex cord stromal tumours comprise less than 5% of testicular neoplasms. Recent population-based US registries (National Cancer Data Base and Surveillance Epidemiology and End Results) show that 0.39 to 0.59% of all testis neoplasm patients are diagnosed with a primary malignant Leydig or Sertoli cell tumour. Of these, 71-79% are malignant Leydig cell tumours and 21-29% malignant Sertoli tumours [355, 356].

Median ages at diagnosis are 39 and 47 years for malignant Sertoli and Leydig cell tumours, respectively [356]. At diagnosis approximately 96% of the malignant Leydig cell tumours are CSI, whilst 22-35% of Sertoli cell tumours are CS II-III [356].

Overall survival at one and five years for CSI Leydig cell tumours is 98% (95% CI: 96-100) and 91% (95% CI: 85-96), respectively, and for CSI Sertoli cell tumours OS is 93% (95% CI: 83-100) and 77% (95% CI: 62-95), respectively ($p = 0.015$). Overall, five-year survival estimates of stage I Leydig and Sertoli cell tumours are significantly lower compared to those of stage I GCTs, with Sertoli cell tumours significantly worse than Leydig cell tumours [355]. Presentation with metastatic disease is the only variable associated with worse CSS [357].

Only limited evidence is available for local and systemic treatment of testicular stromal tumours. After TSS, local recurrence rates up to 9.5% have been reported [358]. A systematic review [359] analysing the impact of previously identified pathologic risk factors on harbouring occult metastatic disease (OMD) in patients with CS I testicular stromal tumours showed an increased risk of occult metastatic disease for each additional risk factor ($p < .001$). Five-year OMD-free survival was 98.1% for those with < 2 risk factors versus 44.9% for those with ≥ 2 risk factors ($p < .001$). Whilst the existing literature does not support making firm recommendations, TTS instead of radical orchidectomy might be offered in patients with localised disease and risk stratification might improve clinical decision making regarding adjuvant treatment options [360].

These data support the importance of large databases to evaluate the efficacy of treatment in rare neoplasms.

9.2 Leydig cell tumours

*9.2.1 **Epidemiology***

Leydig cell tumours comprise about 1-3% of adult testicular tumours [361, 362] and 3% of testicular tumours in infants and children [362]. These tumours are most common in the third to sixth decade in adults, with a similar incidence observed in each decade. Another peak incidence is seen in children aged between three and nine years. Only 3% of Leydig cell tumours are bilateral [361]. These tumours occur in about 8% of patients with Klinefelter's syndrome [362].

*9.2.2 **Pathology of Leydig cell tumours***

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well delineated and usually up to 5 cm in diameter. They are solid, yellow to tan in colour, with haemorrhage and/or necrosis in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm and occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) [81].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [363, 364]:

- large size (> 5 cm);
- older age;
- increased mitotic activity (> 3 per 10 high-power field [HPF]);
- vascular invasion;
- cytological atypia;
- increased MIB-1 expression;
- necrosis;
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy.

*9.2.3 **Diagnosis***

Patients either present with a painless enlarged testis or a tumour is found incidentally on US. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels, low testosterone, and increased levels of LH and FSH are reported [365, 366], while negative results are always obtained for the testicular GCT-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [366, 367].

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation; however, the appearance is variable and is indistinguishable from GCTs [37]. Contrast-enhanced US [36] or contrast-enhanced MRI [44] may improve the diagnosis. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long-term follow-up, eighteen metastatic tumours were found in a total of 83 cases (21.7%) [361, 363, 368]; while five recently published studies with long-term follow-up reported only two metastatic tumours in 156 patients (1.3%) [355, 366, 367, 369, 370].

Metastases are most frequently found in retroperitoneal lymph nodes (60%), lungs (38%) or liver (29%). A recent analysis of published case series data showed that older age, larger tumour size and the presence of any adverse factor are risk factors [371].

9.3 Sertoli cell tumours

*9.3.1 **Epidemiology***

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with sporadic cases under 20 years of age [372, 373]. On rare occasions, these occur in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome [374].

*9.3.2 **Pathology of Sertoli cell tumours***

These tumours are well circumscribed, yellow, tan or white in colour, with an average diameter of 3.5 cm [372]. Microscopically, the cells are eosinophilic to pale with a vacuolated cytoplasm. The nuclei are regular with grooves and inclusions may be present. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine with capillaries, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) [372]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [375, 376]:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis;
- vascular invasion.

9.3.2.1 Classification

Three subtypes have been described [373]:

- classic Sertoli cell tumour [373];
- large cell calcifying form with characteristic calcifications [377, 378];
- sclerosing form [379, 380].

*9.3.3 **Diagnosis***

Patients present either with an enlarged testis, or the tumour is found incidentally on US. Most classic Sertoli cell tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia may be present [381]. The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative. Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and abdomen. Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and thus cannot be safely distinguished from GCTs [382]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [381]. Metastatic disease of 12% in classic Sertoli cell tumour has been reported. In general, affected patients are older, tumours are nearly always palpable, and show more than one sign of malignancy [382].

The large cell calcifying form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [382] and Peutz-Jeghers syndrome [374]) or, in about 40% of cases, endocrine disorders. Forty-four percent of cases are bilateral, either synchronous or metachronous, and 28% show multifocality with good prognosis [378].

Up to 20% of the large cell calcifying forms are malignant. It has been suggested that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared to 23%) [373].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [380].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as GCTs and inguinal orchidectomy is performed. An organ-sparing procedure for small US-detected, non-palpable intraparenchymal lesions is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [383]. When a non-GCT is suggested by frozen section immediate orchidectomy may be avoided. In cases with GCT in either frozen section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

When diagnosed and treated early, long-term favourable outcomes are seen at follow up in Leydig cell tumours, even with its potential metastatic behaviour. In stromal tumours with histological signs of malignancy, especially in older patients, orchidectomy and early RPLND may be an option to prevent metastases [355, 384] or to achieve long-term cure in stage IIA cases [385]. Prophylactic RPLND is unjustified for patients with CS I disease without high-risk features [386].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [355, 384]. No recommendations are available for the treatment of these patients.

9.5 Granulosa cell tumour

This is a rare tumour with two variants: juvenile and adult. Less than 100 cases are reported with a predominance of the juvenile type.

- The juvenile type is benign. It is the most frequent congenital testicular tumour and represents about 1-5% of all pre-pubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [387, 388].
- The average age of the adult type at presentation is 45 years. The typical morphology is a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements [389].

Only 20% of granulosa tumours appear malignant. Lymphovascular invasion, necrosis, infiltrative borders and size > 4 cm may help in identifying cases with aggressive behaviour. Mitotic counts vary and do not appear to be of prognostic significance [390].

9.6 Thecoma/fibroma group of tumours

These tumours are rare with variable histology such as minimal invasion into surrounding testis, high cellularity, and increased mitotic rate. Their immunoprofile is variable and typically not diagnostic. These tumours seem to be uniformly benign [391].

9.7 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or in mixed forms. There is limited

experience with incompletely differentiated sex cord/gonadal stromal tumours and no reported cases of metastasis. In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour most likely reflects the predominant pattern or the most aggressive component of the tumour [392].

9.8 Tumours containing germ cell and sex cord/gonadal stroma (gonadoblastoma)

Some patients with disorders of sex development (DSDs) have abnormal gonadal development with ambiguous genitalia and an increased risk of GCTs. If the arrangement of the germ cells is in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component [393, 394].

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider these to be entrapped rather than neoplastic [395].

9.9 Miscellaneous tumours of the testis

*9.9.1 **Tumours of ovarian epithelial types***

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types are malignant [81].

*9.9.2 **Tumours of the collecting ducts and rete testis***

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) variants have been reported, with malignant tumours showing local growth with a mortality rate of 40% within one year [396].

*9.9.3 **Tumours (benign and malignant) of non-specific stroma***

These are very uncommon and have similar criteria, prognosis and treatment to soft tissue sarcomas.

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11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

12. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Penile Cancer

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European
Association
of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines on Penile Cancer provides up-to-date information on the diagnosis and management of penile squamous cell carcinoma (SCC).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Penile Cancer Guidelines Panel consists of an international multi-disciplinary group of clinicians, including a pathologist and an oncologist. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of having penile cancer. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the most recent dating back to 2014 [1], as are a number of translations of all versions of the Penile Cancer Guidelines. All documents are available through the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

1.4 Publication history

The EAU Penile Cancer Guidelines were first published in 2000; the current publication presents a limited update of the 2017 print.

1.5 Summary of changes

Key changes for the 2018 print:

Chapter 3 - Epidemiology, aetiology and pathology. New information has been added on the various histological subtypes of penile carcinomas, risk factors and human papilloma virus (HPV) association.

New and changed recommendations can be found in sections:

3.4.8 Guidelines for the pathological assessment of tumour specimens

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

4.2 Guidelines on staging and classification

Recommendation	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade.	Strong

5.4 Guidelines for the diagnosis and staging of penile cancer

Recommendations	Strength rating
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong

Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

6.2.6 ***Guidelines for treatment strategies for nodal metastases***

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
Radiotherapy Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphade-nectomy in responders.	Weak
Pelvic Lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

6.3.6 ***Guidelines for chemotherapy***

Recommendations	**Strength rating**
Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide).	Strong
Offer palliative chemotherapy to patients with systemic disease.	Weak

A systematic review (SR) was performed by the Panel on 'Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer' [2]. Even though not fully published, the review findings support the information presented in Section 6.2.2.3 Adjuvant treatment.

This review was performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html

2. METHODS

2.1 Data identification

For the 2018 Penile Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Penile Cancer Guidelines, was performed. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering the period between November 1st 2013 and September 20th 2016. All articles relating to penile cancer (n = 838) in the relevant literature databases were reviewed resulting in the inclusion of 29 new publication in this print.

Fully revised Guidelines were produced using the updated research base, together with several national and international guidelines on penile cancer (National Comprehensive Cancer Network [3], French Association of Urology [4] and the European Society of Medical Oncology [5]).

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [6, 7]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation which is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

Penile carcinoma is usually a SCC and there are several recognised subtypes of penile SCC with different clinical features and natural history (see Table 1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans.

Table 1: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common squamous cell carcinoma (SCC)	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [10]
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group
Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential [11] (higher than in warty, lower than in basaloid SCC)

Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [12]

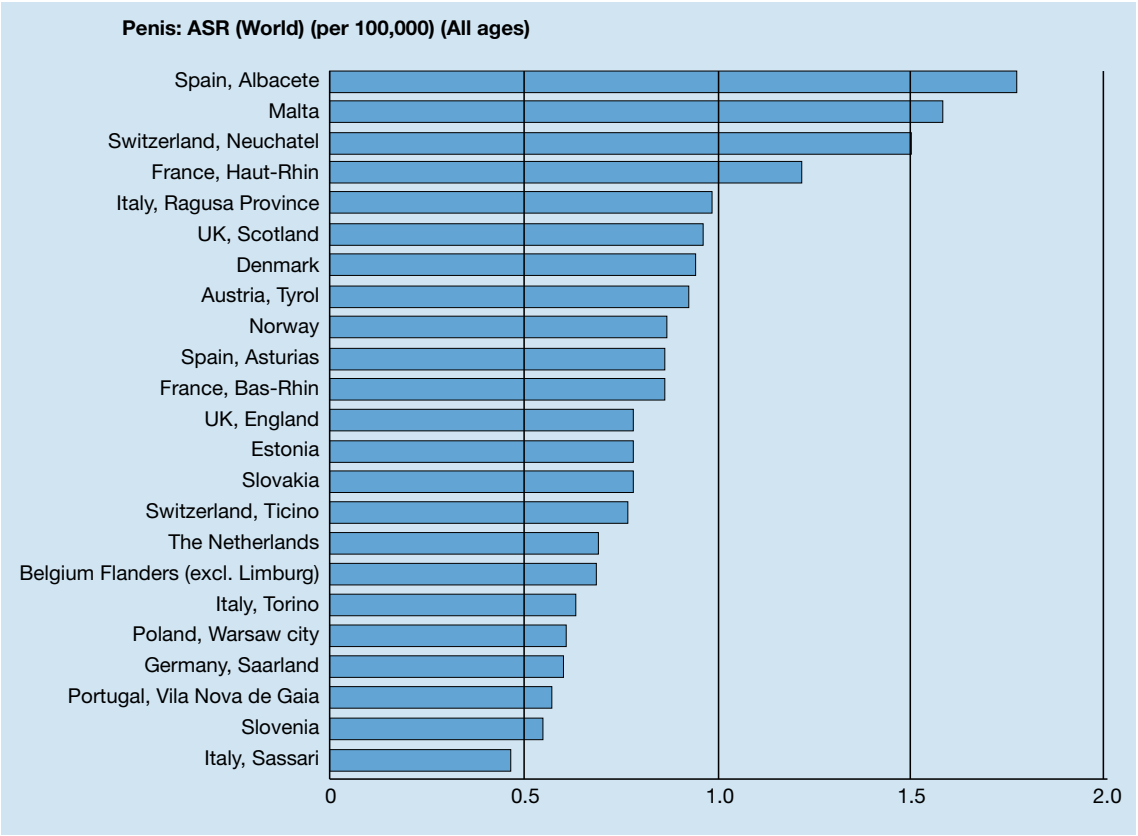
3.2 Epidemiology

In industrialised countries, penile cancer is uncommon, with an overall incidence of around 1/100,000 males in Europe and the USA [13, 14]. There are several areas in Europe with a higher incidence (Figure 1) [15]. Recent data from Scandinavia report an incidence of around 2/100,000 men. In the USA, the incidence of penile cancer is affected by race and ethnicity, with the highest incidence in white Hispanics (1.01), followed by Alaskans and Native American Indians (0.77), African Americans (0.62) and white non-Hispanics (0.51), per 100,000, respectively. In contrast, in some other parts of the world such as South America, South East Asia and parts of Africa the incidence is much higher and can account for 1-2% of malignant diseases in men [15]. The annual age-adjusted incidence is 0.7-3.0 in India, 8.3 in Brazil (per 100,000, respectively) and even higher in Uganda, where it is the most commonly diagnosed male cancer [15, 16].

In the USA, the overall age-adjusted incidence rate decreased from 1973 to 2002 from 0.84 in 1973-1982 to 0.69 in 1983-1992, and to 0.58 in 1993-2002, per 100,000, respectively [13]. In Europe, the overall incidence has been stable from the 1980s until 2013 [14]. An increased incidence was observed in Denmark [17] and the UK (21% between 1979 and 2009) [18].

The incidence of penile cancer increases with age [14], with a peak in the sixth decade but it does occur in younger men [19]. Penile cancer is common in regions with a high prevalence of HPV and this may account for the worldwide variation in incidence [13]. About one third of cases are attributed to HPV-related carcinogenesis [20]. Penile cancer is not linked to HIV or AIDS.

Figure 1: Annual incidence rate (world standardised) by European region/country*



Adapted from [15].

3.3 Risk factors and prevention

Several risk factors for penile cancer have been identified (Table 2) [21] (LE: 2a).

Table 1: Recognised aetiological and epidemiological risk factors for penile cancer

Risk factors	Relevance	Ref
Phimosis	Odds ratio 11-16 vs. no phimosis	[22-24]
Chronic penile inflammation (balanoposthitis related to phimosis), lichen sclerosus	Risk	[25]
Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments	[26]
Smoking	Five-fold increased risk (95% Confidence interval (CI): 2.0-10.1) vs. non-smokers	[22, 23, 27]
HPV infection, condylomata acuminate	22.4% in verrucous squamous cell carcinoma 36-66.3% in basaloid-warty	[13, 28]
Rural areas, low socio-economic status, unmarried		[29-32]
Multiple sexual partners, early age of first intercourse	Three to five-fold increased risk of penile cancer	[21, 23, 33]

Human papilloma virus infection is a risk factor for penile cancer [34]. Human papilloma virus DNA has been identified in 70-100% of intra-epithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). The HPV virus interacts with oncogenes and tumour suppressor genes (*p16, P53, Rb* genes) [28, 35]. The rate of HPV-positivity differs between different histological subtypes of penile SCC. Human papilloma virus is a cofactor in the carcinogenesis of some variants of penile SCC, while others are not related to HPV. The commonest HPV subtypes in penile cancer are types 16 and 18 [36]. The risk of penile cancer is increased in patients with condyloma acuminata [37] (LE: 2b).

A significantly better five-year disease-specific survival has been reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) in one study [38], while no difference in lymph node metastases and ten-year survival was reported in another study [39] (Table 3). There is no association between the incidence of penile and cervical cancer, although both are linked to HPV [40, 41]. Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer [42].

Table 3: Outcomes for HPV and non-HPV penile carcinomas

Non HPV related	Prognosis	HPV related	Prognosis
SCC usual type/NOS	30% DOD	Basaloid SCC	> 50% DOD
Pseudohyperplastic carcinoma	0%	Papillary basaloid carcinoma	
Pseudoglandular carcinoma	> 50%	Warty carcinoma	Mortality low
Verrucous carcinoma	Good	Warty-basaloid carcinoma	30% DOD
Carcinoma cuniculatum	Good	Clear-cell carcinoma	20%
Papillary carcinoma NOS	Good	Lymphoepithelioma-like carcinoma	Not known
Adenosquamous carcinoma	Good		
Sarcomatoid carcinoma	75% DOD		

DOD = died of disease; HPV = human papillomavirus; SCC = squamous cell carcinoma.

At present, except for a few countries, there is no general recommendation for HPV vaccination in males because of the different HPV-associated risk patterns in penile- and cervical cancer. Furthermore, the epidemiological effects of HPV vaccination in girls still have to be assessed [43, 44].

Phimosis is strongly associated with invasive penile cancer [23, 29, 45, 46], due to associated chronic infection. However, smegma is not a carcinogen [45]. The incidence of lichen sclerosus is relatively high in penile cancer but is not associated with adverse histopathological features, including penile intraepithelial neoplasia (PeIN). Other epidemiological risk factors are cigarette smoking, low socioeconomic status and a low level of education [29, 46].

Neonatal circumcision reduces the incidence of penile cancer; however, it does not seem to reduce the risk of PeIN [23]. The lowest incidence of penile cancer is reported for Israeli Jews (0.3/100,000/year). One matched-pair, case-control study reported that the protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) was much weaker when the analysis was restricted to men without a history of phimosis (OR 0.79, 95% CI: 0.29-2) [23]. Circumcision in adult life does not have any protective effect.

The controversial discussion about neonatal circumcision should take into account that circumcision removes approximately half the tissue that can develop into penile cancer.

3.4 Pathology

Squamous cell carcinoma accounts for over 95% of penile malignancies (see Table 1). It is not known how often SCC is preceded by premalignant lesions (see Table 4) [47-50].

Different histological types of penile SCC with different growth patterns, clinical aggressiveness and HPV associations have been identified (see Table 5). Numerous mixed forms exist such as the warty-basaloid form, with 50-60% the most common mixed form, the usual-verrucous (hybrid), usual-warty, usual-basaloid and the usual-papillary, as well as other rarer combinations.

Other malignant lesions of the penis, all much less common than penile SCC, are melanocytic lesions, mesenchymal tumours, lymphomas and metastases. Penile metastases are frequently of prostatic or colorectal origin. Different types of penile sarcoma have been reported.

Table 4: Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with squamous cell carcinoma (SCC) of the penis: • Bowenoid papulosis of the penis (HPV related) • Lichen sclerosis
Premalignant lesions (up to one-third transform to invasive SCC): • Penile intraepithelial lesions • Giant condylomata (Buschke-Löwenstein) • Bowen's disease • Paget's disease (intradermal ADK)

Table 5: Classification of intra-epithelial neoplasia (PeIN)

• **Non-HPV-related PeIN**
• o Differentiated PeIN
• **HPV-related PeIN**
• o Basaloid PeIN
• **Warty PeIN**
• **Warty-basaloid PeIN**
• **Other rare patterns of PeIN** (pleomorphic, spindle, clear cell, pagetoid)

3.4.1 Gross handling of pathology specimens

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be fully included, bigger lesions should have at least 3-4 blocks. Lymph nodes must be included in their entirety after having been inked, in order to detect metastases. After having been inked, surgical margins have to be completely included [51]. Second-opinion pathology review is highly desirable for this rare tumour entity [52].

3.4.2 Pathology report

The pathology report must include the anatomical site of the primary tumour, the histological type of SCC, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum, surgical margins and the *p16*/HPV status (Table 6) [53-56].

Table 6: Outcomes for HPV and non-HPV penile carcinomas

Information to include in the pathology report	Recommended	required
Clinical information • Prior treatments (topic, radiotherapy, chemotherapy)	x	
Surgical procedure		x
Tumour localisation	x	
Macroscopic tumour dimension • Depth of invasion • Millimetres from basement membrane to deepest point of invasion • Maximum thickness • Size of tumour		x
Block identification	x	
Histological tumour type		x
Histological grade		x
Microscopic maximum dimensions • Combination of gross and microscopic if large tumours		x
Extent of invasion		x
LVI [58, 59]		x
Perineural invasion		x
Margin status in mm		x
Lymph node (LN) status • Size of largest nodal tumour deposit (not LN size) • Number of LN+, extracapsular spread (ECS), inguinal or pelvic, to be reported in every site separately		x
TNM Stage		x
p16/HPV status	x	

** See also www.ICCR-cancer.org. database.*

*3.4.3 **Grading***

The TNM classification for penile cancer includes tumour grade, due to its prognostic relevance (Table 9). Tumour grading in penile cancer has been shown to be highly observer-dependent and can be problematic, especially in heterogeneous tumours. Grading should use the categories specified by the WHO for penile cancer (Table 7).

Table 7: Grading recommendations for penile SCC

Feature	Grade 1	Grade 2	Grade 3	Sarcomatoid
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/well	Infiltrative/ill defined	Infiltrative/ill defined	Infiltrative/ill defined

*3.4.4 **Pathological prognostic factors***

Pathological subtype, perineural invasion, lymphovascular invasion [58], depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality [60]. Tumour grade is a predictor of metastatic spread, and lymphatic invasion is a predictor of metastasis. Venous embolism is often seen in advanced stages. The extent of lymph node metastasis and extracapsular spread are also strong predictors of prognosis.

The variants of penile SCC can be divided into three prognostically different groups (Table 8).

Table 8: Prognosis of the variants of penile SCC

Penile SCC	Good prognosis	Intermediate prognosis	Poor prognosis
Local growth	Destructive	Destructive	Destructive
Metastasis	Rare	Intermediate	Common
Risk of cancer-related mortality	Very low	Intermediate	High
SCC variants	• Verrucous • Papillary • Warty Pseudohyperplastic carcinoma cuniculatum	• Usual SCC • Mixed forms • Pleomorphic form of warty carcinoma	• Basaloid, • Sarcomatoid adenosquamous

There is discussion as to whether cases that show invasion of the distal urethra have a worse prognosis; however, there is no evidence to support this [61]. Nevertheless, invasion of the more proximal urethra signifies a highly aggressive SCC with a poor prognosis (see Table 9). pT3 denotes a worse prognosis than pT2 [62, 63] (LE: 2b). Capsular extension in even one single lymph node carries a poor prognosis and is denoted as pN3 [64-66].

Chaux *et al.* suggested a prognostic index which incorporates grade, anatomical level of infiltration and perineural invasion to predict the likelihood of inguinal lymph node metastases and 5-year survival [67].

3.4.5 Penile cancer and HPV

The association between penile cancer and HPV is different for the different variants of penile SCC. A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile (39%) SCCs. Verrucous and papillary penile SCCs are HPV-negative. The commonest HPV-types in penile SCC are HPV-16 (72%), HPV-6 (9%) and HPV-18 (6%). Overall, only one-third of penile SCCs show HPV infection, but those that do are usually infected by several HPV strains.

3.4.6 Penile biopsy

Any doubtful penile lesion should be biopsied and, even in clinically obvious cases, histological verification must be obtained before local treatment. Before definitive surgical treatment, confirmatory frozen section excisional biopsy can be done. Histological confirmation is necessary to guide management when:

- there is doubt about the exact nature of the lesion (e.g. PeIN, metastasis or melanoma);
- treatment is planned with topical agents, radiotherapy or laser surgery.

The size of a biopsy is important. In one study, in biopsies with an average size of 0.1 cm it was difficult to evaluate the depth of invasion in 91% of cases. The grade at biopsy, and in the final specimen, may differ in up to 30% of cases, with failure to detect cancer in 3.5% of cases [47]. Furthermore, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy which is deep enough to properly assess the degree of invasion and stage is preferable.

3.4.7 Intra-operative frozen sections and surgical margins

Surgical treatment must completely remove the penile carcinoma with negative surgical margins, which may be confirmed by intra-operative frozen section [68]. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Only 3 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative [69].

3.4.8 Guidelines for the pathological assessment of tumour specimens

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 TNM classification

The 2016 UICC TNM classification for penile cancer [51] introduced some changes in comparison to previous editions. The T1 category is stratified into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and grading (Table 9). The classification T2 denotes invasion of the corpus spongiosum, while T3 is defined as invasion of the corpora cavernosa, due to the different prognosis of these two patterns [62, 63]. For penile cancer, unlike in other neoplasms, tumour grade is used for the TNM classification in the subdivision of the T1 stage (Table 9).

The current pN1 group consists of one or two ipsilateral inguinal lymph node metastases, pN2 is defined as more than two uni- or bilateral metastatic nodes and pN3 any pelvic nodes, uni- or bilateral, or any extranodal extension regardless of the number of lymph node metastases [51]. Retroperitoneal lymph node metastases are classified as extra-regional nodal and, therefore, distant metastases.

Table 9: 2016 TNM clinical and pathological classification of penile cancer [51]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the urethra
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph nodes
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in one or two inguinal lymph nodes
pN2	Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral *or* bilateral extranodal or extension of regional lymph node metastasis
pM - Distant Metastasis	
pM1	Distant metastasis microscopically confirmed
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

**Verrucous carcinoma not associated with destructive invasion.*

4.2 Guidelines on staging and classification

Recommendation	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade.	Strong

5. DIAGNOSTIC EVALUATION AND STAGING

Penile cancer can be cured in over 80% of cases if diagnosed early, but is a life-threatening disease when lymphatic metastasis occurs. Local treatment can be mutilating, and devastating for the patient's psychological well-being.

5.1 Primary lesion

Penile carcinoma is usually a clinically obvious lesion but it may be hidden under a phimosis [24]. Physical examination should include palpation of the penis to assess the extent of local invasion and palpation of both groins to assess the lymph node status.

Ultrasound (US) can provide information about infiltration of the corpora [70, 71]. Magnetic resonance imaging (MRI) with an artificially induced erection can be used to exclude corporal invasion but is very unpleasant for the patient [72, 73]. The sensitivity and specificity of MRI in predicting corporal or urethral invasion was reported as 82.1% and 73.6%, and 62.5% and 82.1%, respectively [74]. Penile Doppler US has been reported to have a higher staging accuracy than an MRI in detecting corporal infiltration [75].

5.2 Regional lymph nodes

Careful palpation of both groins for enlarged inguinal lymph nodes must be part of the initial physical examination of patients suspected of having penile cancer.

*5.2.1 **Non-palpable inguinal nodes***

If there are no palpable lymph nodes, the likelihood of micro-metastatic disease is about 25%. Imaging studies are not helpful in staging clinically normal inguinal regions, although may be used in obese patients in whom palpation is unreliable:

- Inguinal US (7.5 MHz) can detect abnormal, enlarged nodes. The longitudinal/transverse diameter ratio and absence of the lymph node hilum are findings with relatively high specificity [76].
- Conventional computed tomography (CT) or MRI cannot detect micro-metastases reliably [77].
- ^{18}FDG-positron emission tomography (PET/CT) does not detect lymph node metastases < 10 mm [78, 79].

Further management of patients with normal inguinal nodes should be guided by pathological risk factors of the primary tumour. Lymphovascular invasion, local stage and grade are predictive of lymphatic metastasis [80, 81]. Existing nomograms are not accurate. Invasive lymph node staging is required in patients at intermediate- or high risk of lymphatic spread (see Section 6.2).

*5.2.2 **Palpable inguinal nodes***

Palpably enlarged lymph nodes are highly indicative of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional imaging does not alter management and is not required (see Section 6).

A pelvic CT scan can be used to assess the pelvic lymph nodes. Imaging with ^{18}FDG-PET/CT has shown high sensitivity (88-100%) and specificity (98-100%) for confirming metastatic nodes in patients with palpable inguinal lymph nodes [79, 82].

5.3 Distant metastases

Staging for systemic metastases should be performed in patients with positive inguinal nodes [83-85] (LE: 2b). Abdominal and pelvic CT should be done plus a chest X-ray, although a thoracic CT is more sensitive. PET/CT is an option [81].

There is no tumour marker for penile cancer. The SCC antigen (SCC Ag) is increased in less than 25% of penile cancer patients. One study reported that SCC Ag did not predict occult metastatic disease, but was an indicator of disease-free survival (DFS) in lymph-node-positive patients [86].

5.4 Guidelines for the diagnosis and staging of penile cancer

Recommendations	Strength rating
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong
Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

The aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control. Local recurrence has little influence on long-term survival, so organ preservation strategies are justified [87].

There are no randomised controlled trials (RCTs) or observational comparative studies for any of the treatment options for localised penile cancer. Penile preservation appears to be superior in functional and cosmetic outcomes to partial or total penectomy, and is considered to be the primary treatment method for localised penile cancer. However, there are no RCTs comparing organ-preserving and ablative treatment strategies.

Histological diagnosis with local staging must be obtained before using non-surgical treatments. With surgical treatment, negative surgical margins must be obtained. Treatment of the primary tumour and of the regional nodes can be staged.

Local treatment modalities for small and localised penile cancer include excisional surgery, external beam radiotherapy (EBRT), brachytherapy and laser ablation. Patients should be counselled about all relevant treatment options.

6.1.1 Treatment of superficial non-invasive disease (PeIN)

Topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) is an effective first-line treatment. Circumcision is advisable prior to the use of topical agents. Due to high persistence/recurrence rates, treatment must be assessed by biopsy and long-term surveillance is warranted. An insufficient response may signify underlying invasive disease. Significant inflammatory responses may occur [88, 89]. Complete responses have been reported in up to 57% of PeIN cases [90] and in 74% of cases treated by circumcision and 5-FU without relapse. If topical treatment fails, it should not be repeated.

Laser treatment with a neodymium:yttrium-aluminium-garnet (Nd:YAG) or Carbon dioxide (CO_2) laser is an effective treatment option [91-96]. Visualisation may be improved by photodynamic diagnosis with the CO_2 laser [97]. Rebiopsy for treatment control is mandatory.

Glans resurfacing, total or partial, can be a primary treatment for PeIN or a secondary option in case of failure of topical chemotherapy or laser therapy. Glans resurfacing consists of complete removal of the glandular epithelium followed by reconstruction with a graft (split skin or buccal mucosa). However, in one study in cases of glans resurfacing for presumed PeIN, up to 20% of patients were found to have invasive disease on histopathological examination [88].

*6.1.2 **Treatment of invasive disease confined to the glans (category T1/T2)***

Small and localised invasive lesions should receive organ-sparing treatment. Additional circumcision is advisable for glandular tumours. Foreskin tumours are treated by 'radical circumcision'. Local excision, partial glansectomy or total glansectomy with reconstruction are surgical options. External beam radiotherapy or brachytherapy are radiotherapeutic options. Small lesions can also be treated by laser therapy but the risk of more invasive disease must be recognised.

Treatment choice depends on tumour size, histology, stage and grade, localisation (especially relative to the meatus) and patient preference.

*6.1.2.1 **Intra-operative frozen section***

Many authors recommend intraoperative frozen sections to assess surgical margins. Others have suggested that frozen sections are only needed if there are definite concerns [98]. For glans resurfacing, some advocate the use of acetic acid staining to delineate abnormal areas [99]. Data from one multi-centre study suggests that differentiated penile intraepithelial neoplasia, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for cancer-specific survival [65].

*6.1.2.2 **Width of negative surgical margins***

There is no clear evidence as to the required width of negative surgical margins. With organ-sparing these can be minimal. For a general recommendation, 3-5 mm can be considered a safe maximum [100, 101]. A grade-based differentiated approach can also be used, with 3 mm for grade one, 5 mm for grade two and 8 mm for grade three. This approach has its limitations due to the difficulties with penile cancer grading.

*6.1.3 **Results of different surgical organ-preserving treatments***

*6.1.3.1 **Laser therapy***

The results of CO_2 laser treatment have been reported by three retrospective studies from the same institution with a median follow-up of five years and a total of 195 patients [91-93]. Laser treatment was given in combination with radiotherapy or chemotherapy for PeIN or T1 penile cancers. No cancer-specific deaths were reported. Local recurrence ranged from 14% for PeIN [93] to 23% for T1 tumours [92], with an estimated cumulative risk of local recurrence at five years of 10% for PeIN (n = 106) and 16% for T1 (n = 78) tumours [91]. The reported rate of inguinal nodal recurrence was between 0% [93] and 4% [92]. The rate of secondary partial penectomy at ten years was 3% for PeIN and 10% for T1 tumours [91].

Four studies, three from the same institution, reported results of Nd:YAG laser treatment for a total of 150 patients with a follow-up of at least four years [94-96, 102]. Local recurrence rates ranged from 10% to 48% [94, 95]. One study [96] reported recurrence-free survival rates of 100%, 95% and 89% at one, two and five years, respectively. Inguinal nodal recurrence was reported in 21% of patients [94] and cancer-specific mortality was reported as 2% [102] and 9% [95]. The three studies from the same institution reported overall survival (OS) rates of 100% at four years [94] and 85-95% [96, 103] at seven years. The rate of secondary partial penectomy was highly divergent, with 4% in one study [96] and 45% in another [95]. One study reported that no complications and no adverse effects on urinary or sexual function were observed [94].

Other studies have presented data on a variety of laser treatments with either a CO_2 or a Nd:YAG laser, a combination of both, or a potassium titanyl phosphate (KTP) laser [104-107], with a mean follow-up of 32-60 months with stages PeIN to T3 included. These studies reported on a total of 138 patients, with local recurrence rates of 11% [92], 19% [105] and 26% [107]. In one study, recurrence-free survival at five years was 88% [105]. The cancer-specific survival (CSS) probability at five years was 95% in one study [105], and 2% at five years in another [105].

*6.1.3.2 **Moh's micrographic surgery***

Moh's micrographic surgery is a historical technique by which histological margins are taken in a geometrical fashion around a conus of excision. The original description [108] consisted of 33 consecutive patients treated between 1936 and 1986 with 79% cured at five years [108]. The second study reported 68% recurrence-free survival at three years, 32% local recurrences and 8% inguinal nodal recurrence [109]. In both studies, one partial amputation and one cancer-specific death occurred. In a contemporary series of 48 cases, there were no recurrences among 10 primary invasive SCCs with a cure rate of 100% (mean follow-up, 161 months, median follow-up, 177 months), but one recurrence in 19 cases of penile intraepithelial neoplasia (cure rate 94.7%) [110].

*6.1.3.3 **Glans resurfacing***

Three studies have reported results of glans resurfacing in a total of 71 patients with PeIN or T1 with a median follow-up of 21-30 months [88, 111, 112]. No cancer-specific deaths were reported, the rates of local recurrence were 0% [111] and 6% [112], without reports of nodal recurrence or complications.

6.1.3.4 ***Glansectomy***

Results of glansectomy were reported in three studies [100, 113, 114], while a fourth also reported on glans-preserving surgery [114]. One study reported 87 patients with six local (6.9%), eleven regional (12.6%) and two systemic recurrences (2.3%) with a mean follow-up of 42 months [100]. The other two studies reported on a total of 68 patients with a follow-up of 63 [114] and 114 months [113], respectively, in which there was one patient (8%) with local recurrence [113], six (9%) with inguinal nodal recurrence, and no cancer-specific deaths.

6.1.3.5 ***Partial penectomy***

Results of partial penectomy were reported in rather heterogeneous studies with a total of 184 patients with T1-T3 tumours and a follow-up of 40-194 months [93, 114-119]. The rate of local recurrence ranged from 4-50% and cancer-specific mortality from 0-27%. The reported five-year OS ranged from 59-89% [117, 119, 120].

6.1.3.6 ***Summary of results of surgical techniques***

Although conservative, organ-sparing surgery may improve quality of life (QoL), local recurrence is more likely than after amputation surgery for penile cancer. In one study the local recurrence rate after organ-sparing surgery was 18%, most of these occurred within 36 months [121], and amputation was necessary in 17% of the recurrences. Compared to this, the local recurrence rate after amputation surgery (partial or radical) was lower (4%). Glansectomy with circumcision for the treatment of small penile lesions has a very low rate of local recurrence (2%) [100].

In one large cohort of patients undergoing organ-sparing surgery, isolated local recurrence was 8.9% and five-year disease-specific survival (DSS) 91.7%. Tumour grade, stage and lymphovascular invasion were predictors of local recurrence. In the largest cohort of penile surgery, the 5-year cumulative incidence of local recurrence after organ-sparing (including laser treatment) was 27% while it was only 3.8% in the amputation group [98]. Of the 451 patients treated by organ-sparing surgery, 16% eventually underwent amputation. However, there was no significant difference in survival between the organ-sparing and the amputation groups. These results suggest that the local recurrence rates following penile preserving surgery are higher than with partial penectomy, although survival appears to be unaffected.

6.1.4 ***Summary of results of radiotherapy for T1 and T2 disease***

Radiotherapy is an organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter [122-127] (LE: 2b). It can be given as external radiotherapy with a minimum dose of 60 Gy combined with a brachytherapy boost or as brachytherapy alone [123, 125]. Reported results are best with brachytherapy with local control rates ranging from 70-90% [123, 125]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology consensus statement for penile brachytherapy also reported good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for stages T1 and T2 [128]. Penile preservation rates of 70-88% have been reported [129], with overall penile conservation rates of 87% and 70% at five and ten years. Pulsed-dose-rate brachytherapy has been introduced as a new modality and 15% local recurrences have been reported in one series [130].

In the few comparisons of surgical treatment and radiotherapy, results of surgery were slightly better. In a meta-analysis comparing surgery and brachytherapy, 5-year OS and local control rates with surgery were 76%/84% for surgery and 73%/79% for brachytherapy, respectively [131]. The organ preservation rate for brachytherapy was 74% and there was no difference in survival. Local recurrence after radiotherapy can be salvaged by surgery [132].

Specific complications of radiotherapy for penile cancer are urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa [133] (LE: 3). With brachytherapy, meatal stenosis has been reported to occur in 40% of cases, but was much lower in a contemporary series of 73 patients with only 6.6%. In that series, 2.6% reported pain with sexual intercourse and 5.3% dysuria over a follow-up of 5 years. Penile amputation for necrosis was necessary in 6.8 % of patients [134].

Functional outcome after radiotherapy has not often been reported. In one report, 17/18 patients with normal erections before treatment maintained these after treatment [129].

Table 10 provides an overview of the complications and outcomes of primary local treatments.

Table 10: Summary of reported complications and oncological outcomes of local treatments*

Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths	References
ND:YAG laser	n.r.	10-48%	21%	2-9%	[94-96, 102]
C02 laser	Bleeding, meatal stenosis, both < 1%	14-23%	2-4%	n.r.	[91-93]
Lasers (unspecified)	Bleeding 8%, local infection 2%	11-26%	2%	2-3%	[104-107]
Moh's micrographic surgery	Local infection 3%, Meatal stenosis 6%	32%	8%	3-4%	[108-110]
Glans resurfacing	n.r.	4-6%	n.r.	n.r.	[88, 111, 112, 135]
Glansectomy	n.r.	8%	9%	n.r.	[113, 114]
Partial penectomy	n.r.	4-13%	14-19%	11-27%	[93, 117, 119, 120]
Brachytherapy	Meatal stenosis > 40%	10-30%	n.r.	n.r.	[122, 123, 125]
External beam radiotherapy	Urethral stenosis 20-35%, Glans necrosis 10-20%	n.r.	n.r.	n.r.	[123, 127, 128, 132, 133]

**The ranges are the lowest and highest number of occurrences reported in different series.*

*6.1.5 **Treatment recommendations for invasive penile cancer (T2-T4)***

6.1.5.1 Treatment of invasive disease confined to the glans with or without urethral involvement (T2)

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [115] (LE: 3). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [132].

6.1.5.2 Treatment of disease invading the corpora cavernosa and/or urethra (T3)

Glansectomy with distal corporectomy and reconstruction or partial amputation with reconstruction are standard [100, 101, 126]. Radiation therapy is an option.

6.1.5.3 Treatment of locally advanced disease invading adjacent structures (T4)

Extensive partial amputation or total penectomy with perineal urethrostomy is the standard advisable treatment [101]. For locally advanced and ulcerated cases, neoadjuvant chemotherapy may be an option. Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (see Sections 6.2.4 and 6.1.6).

6.1.5.4 Local recurrence after organ-conserving surgery

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion [97, 101, 121, 126, 136]. For large or high-stage recurrence, partial or total amputation is required [133]. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [137, 138].

*6.1.6 **Guidelines for stage-dependent local treatment of penile carcinoma***

Primary tumour	Use organ-preserving treatment whenever possible	Strength rating
Tis	Topical treatment with 5-fluorouracil (5-FU) or imiquimod for superficial lesions with or without photodynamic control.	Strong
	Laser ablation with carbon dioxide (CO_2) or neodymium:yttrium-aluminium-garnet (Nd:YAG) laser.	
	Glans resurfacing.	
Ta, T1a (G1, G2)	Wide local excision with circumcision, CO_2 or Nd:YAG laser with circumcision.	Strong
	Laser ablation with CO_2 or Nd:YAG laser.	
	Glans resurfacing.	
	Glansectomy with reconstruction.	
	Radiotherapy for lesions < 4 cm.	

T1b (G3) and T2	Wide local excision plus reconstruction.	Strong
	Glansectomy with circumcision and reconstruction.	
	Radiotherapy for lesions < 4 cm in diameter.	
T3	Partial amputation with reconstruction or radiotherapy for lesions < 4 cm in diameter.	Strong
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	Strong
T4	Neoadjuvant chemotherapy followed by surgery in responders or palliative radiotherapy.	Weak
Local recurrence	Salvage surgery with penis-sparing in small recurrences or partial amputation.	Weak
	Large or high-stage recurrence: partial or total amputation.	

6.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. The inguinal lymph nodes, followed by the pelvic lymph nodes, provide the regional drainage system of penis. The superficial and deep inguinal lymph nodes are the first regional node group to be affected, which can be uni- or bilateral [87].

The 'sentinel' inguinal nodes, i.e. those first affected by lymphatic spread, appear to be located in the medial superior zone followed by the central inguinal zones [90]. No solitary lymphatic spread has been observed from the penis to the two inferior groin regions and no direct drainage to the pelvic nodes, either [88, 97]. These findings confirm earlier studies.

Pelvic nodal disease does not occur without ipsilateral inguinal lymph node metastasis. Also, crossover metastatic spread, from one groin to the contralateral pelvis, has never been reported. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, para-caval) is classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for patient survival. Cure can be achieved in limited lymph node disease confined to the regional lymph nodes. Radical lymphadenectomy is the treatment of choice. Multimodal treatment combining surgery and chemotherapy is often indicated.

The management of regional lymph nodes is dependent on the clinical inguinal lymph node status. There are three possible scenarios. First, the clinical lymph nodes appear normal on palpation and are not enlarged. Secondly, the inguinal lymph nodes are palpably enlarged, either uni- or bilaterally. Thirdly, there are grossly enlarged and sometimes ulcerated inguinal lymph nodes, uni- or bilaterally.

In clinically node-negative patients (cN0), micro-metastatic disease occurs in up to 25% of cases and invasive lymph node staging is required since no imaging technique can reliably detect or exclude micro-metastatic disease. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and lymph node surgery with histology is required. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by (neoadjuvant) chemotherapy and surgery. Even if present in only one node, capsular penetration/extra-nodal extension in lymph node metastasis carries a high risk of progression and is classified as pN3, which also requires multimodal treatment.

*6.2.1 **Management of patients with clinically normal inguinal lymph nodes (cN0)***

Risk stratification for the micro-metastatic inguinal lymph node disease depends on stage, grade and the presence/absence of lymphovascular invasion in the primary tumour [100]. pTa/pTis tumours and those with low grade have a comparatively low risk of lymphatic spread. Well-differentiated G1 pT1 tumours are considered low risk, pT1G2 intermediate risk and pT1G3 and all higher stage tumours are considered high risk for lymphatic spread [101].

For these patients, three management strategies are possible: surveillance, invasive nodal staging or radical lymphadenectomy. Early inguinal lymphadenectomy in clinically node-negative patients is superior for long-term patient survival compared to later lymphadenectomy with regional nodal recurrence [91, 92]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in such patients reported significantly better five-year OS lymphadenectomy vs. inguinal radiotherapy or surveillance (74% vs. 66% and 63%, respectively) [93].

6.2.1.1 Surveillance

Surveillance of regional lymph nodes carries the risk of regional recurrence arising later from existing micro-metastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for regional recurrence [94, 95]. Patients considering surveillance must be informed about this risk. Surveillance is only recommended in patients with pTis/pTa tumours and with the appropriate caveats in low risk G1 pT1 tumours [94-96]. Compliance is required for surveillance.

6.2.1.2 Invasive nodal staging

Since no imaging technique can detect micro-metastatic disease, invasive lymph node staging is recommended for pT1 tumours of intermediate and high risk, as well as for T2-T4 tumours [92, 105] (LE: 2b). Fine-needle aspiration cytology also does not reliably exclude micro-metastatic disease and is not recommended.

Invasive nodal staging can be done by either dynamic sentinel-node biopsy (DSNB) or by modified inguinal lymphadenectomy (mILND), both of which are standard techniques [139]. Dynamic sentinel-node biopsy aims to detect affected sentinel nodes in both groins. Technetium-99m (^{99m}Tc) nanocolloid is injected around the penile cancer site on the day before surgery often combined with patent blue. A gamma-ray probe is used intra-operatively to detect the sentinel nodes, which is possible in 97% of cases. The protocol has been standardised for routine use [107]. Dynamic sentinel-node biopsy has a reported high sensitivity in some centres (90-94%) [107, 108] (LE: 2b). In a meta-analysis of eighteen studies, the pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [109].

Modified ILND is an alternative option, whereby the medial superficial inguinal lymph nodes and those from the central zone are removed bilaterally [87, 106] (LE: 3), leaving the greater saphenous vein untouched.

Both methods of invasive lymph node staging may miss micro-metastatic disease leading to regional recurrence [91]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [95, 96]. The false-negative rate of mILND is unknown. If lymph node metastasis is found, ipsilateral radical inguinal lymphadenectomy is indicated.

*6.2.2 **Management of patients with palpable inguinal nodes (cN1/cN2)***

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is highly likely. The notion that these may be inflammatory and that antibiotic treatment should first be used is unfounded and dangerous as it delays curative treatment.

Palpably enlarged groin lymph nodes should be surgically removed, pathologically assessed (by frozen section) and, if positive, a radical inguinal lymphadenectomy should be performed. In clinically doubtful cases, US-guided fine needle aspiration cytology is an option [140].

In such cases, CT or MRI can provide staging information about the pelvic nodal status and ^{18}F-FDGPET/CT can identify additional metastases [141]. Dynamic sentinel-node biopsy is not indicated in patients with palpably enlarged lymph nodes [142] (LE: 3).

6.2.2.1 Radical inguinal lymphadenectomy

Radical inguinal lymphadenectomy carries a significant morbidity due to impaired lymph drainage from the legs and scrotum. Morbidity can be as high as 50% [143] in the presence of significant risk factors such as increased body mass index (BMI). Recent series have reported lower morbidity in about 25% of cases [144, 145] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [146].

Tissue handling must be meticulous in order to minimise post-operative morbidity. Lymphatic vessel walls do not contain smooth muscle and are therefore not reliably closed by electrocautery. Numerous metal clips may also cause post-operative problems so that ligation of all lymphatic vessels is advisable [147, 148]. Post-operative morbidity may be reduced by preserving the saphenous vein and post-operative measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction and prophylactic antibiotics [149]. Transposition of the Sartorius muscle is not recommended. There is no benefit from using fibrin glue intraoperatively [150]. Advanced cases may require reconstructive surgery for wound closure. The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%) [144, 145].

Minimally-invasive surgical techniques (laparoscopic, robot-assisted) for inguinal lymphadenectomy are technically feasible and, in small series, have been reported to significantly reduce post-operative morbidity except for the rate of lymphoceles [144, 150-153].

6.2.2.2 Pelvic lymphadenectomy

Patients with two or more inguinal lymph node metastases on one side and/or extracapsular lymph node extension need to undergo ipsilateral pelvic lymphadenectomy. This recommendation is based on a study in which the rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% in those with more than three positive inguinal nodes or extracapsular extension [101, 154] (LE: 2b).

Positive pelvic nodes carry a worse prognosis than only inguinal nodal metastasis (five-year CSS 71.0% vs. 33.2%) [155]. In a study of 142 groin node-positive patients, significant risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off three), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extra-nodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors present [155].

Pelvic lymphadenectomy may be performed simultaneously with inguinal lymphadenectomy or as a secondary procedure. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated [156].

6.2.2.3 Adjuvant treatment

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended after lymphadenectomy [157] (see Section 6.3.1). One retrospective study reported long-term DFS of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery vs. 39% in historical controls without adjuvant chemotherapy after lymphadenectomy [157]. More recent studies have confirmed the survival benefit of adjuvant chemotherapy after radical inguinal lymphadenectomy [158-160].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, there are no data showing definite patient benefit. Adjuvant radiotherapy after inguinal lymphadenectomy should not be administered outside of clinical studies.

*6.2.3 **Management of patients with fixed inguinal nodes (cN3)***

Patients with large and bulky, sometimes ulcerated, inguinal lymph nodes require staging by thoracic, abdominal and pelvic CT for pelvic nodes and systemic disease. In clinically unequivocal cases, histological verification by biopsy is not required.

These patients have a poor prognosis. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in responders is recommended [161-163]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [161]. Contemporary studies have confirmed this patient benefit [162, 164, 165].

*6.2.4 **Management of lymph node recurrence***

Patients with regional recurrence should be treated in the same way as patients with primary cN1/cN2 disease. However, patients with regional lymph node recurrence after DSNB or modified inguinal lymphadenectomy already have disordered inguinal lymphatic drainage and are at a high risk of irregular metastatic progression. Inguinal nodal recurrence after radical inguinal lymphadenectomy has a five-year CSS rate of 16% [166].

There is no evidence for the best management in such cases. Multimodal treatment with neoadjuvant and/or adjuvant chemotherapy after radical lymph node surgery is recommended.

*6.2.5 **The role of radiotherapy in lymph node disease***

Radiotherapy is used in some institutions for the treatment of inguinal lymph nodes. However, this is not evidence-based. One of the rare prospective trials in penile cancer found that inguinal radical lymphadenectomy is superior to inguinal radiotherapy for lymph-node positive penile cancer patients [167].

There is no evidence that adjuvant radiotherapy after radical inguinal lymphadenectomy improves oncological outcome [168]. One study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [169]. Other studies have likewise not demonstrated a patient benefit [168-174].

In one comparative retrospective study, adjuvant chemotherapy was far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients [157]. A large retrospective analysis of the SEER database (National Cancer Institute Surveillance, Epidemiology and End Results Program) of 2,458 penile cancer patients treated with either surgery alone or surgery plus EBRT concluded that the addition of adjuvant EBRT 'had neither a harmful nor a beneficial effect on CSS' [175].

Due to this lack of positive evidence, radiotherapy cannot be recommended outside of controlled trials for the treatment of lymph node disease in penile cancer. Prophylactic radiotherapy for cN0 disease is not indicated. Radiotherapy for advanced lymph node disease remains a palliative option.

*6.2.6 **Guidelines for treatment strategies for nodal metastases***

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.	Weak

Pelvic lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported.	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

6.3 Chemotherapy

6.3.1 Adjuvant chemotherapy in node-positive patients after radical inguinal lymphadenectomy

Multimodal treatment can improve patient outcome. Adjuvant chemotherapy after radical lymphadenectomy in node-positive patients has been reported in a few small and heterogeneous series [158-160]. Comparing different small-scale clinical studies is fraught with difficulty.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was first demonstrated by a study which reported long-term (DFS) of 84% in 25 consecutive patients treated with twelve adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during 1979-1990 and compared this to a historical control group of 38 consecutive node-positive patients with radical lymphadenectomy (with- or without adjuvant inguinal radiotherapy) who had achieved a DFS rate of only 39% [161].

The same group also published results of an adjuvant chemotherapy regimen with three courses of cisplatin and 5-FU with lower toxicity and even better results compared to VBM [176] (LE: 2b). The same group has published results of adjuvant chemotherapy with cisplatin, 5-FU plus paclitaxel or docetaxel (TPF), with three to four cycles after resection of pN2-3 disease [177]. Of 19 patients, 52.6% were disease-free after a median follow up of 42 months and tolerability was good. Results of adjuvant treatment with paclitaxel and cisplatin also improved outcome [178].

Therefore, the use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible and there is curative intent (LE: 2b). There are no data concerning adjuvant chemotherapy in stage pN1 patients. Adjuvant chemotherapy in pN1 disease is, therefore, recommended only in clinical trials.

6.3.2 Neoadjuvant chemotherapy in patients with fixed or relapsed inguinal nodes

Bulky inguinal lymph node enlargement (cN3) indicates extensive lymphatic metastatic disease. Primary lymph node surgery is not generally recommended since complete surgical resection is unlikely and only a few patients will benefit from surgery alone.

Limited data is available on neoadjuvant chemotherapy before inguinal lymph node surgery. However, it allows for early treatment of systemic disease and down-sizing of the inguinal lymph node metastases. In responders, complete surgical treatment is possible with a good clinical response.

Results of neoadjuvant chemotherapy for bulky inguinal lymph node metastases were modest in retrospective studies including five to twenty patients treated with bleomycin-vincristine-methotrexate (BVM) or bleomycin-methotrexate-cisplatin (BMP) regimens [162, 163, 179], as well as in the confirmatory BMP trial of the Southwest Oncology Group [180]. However, treatment-related toxicity was unacceptable due to bleomycin-related mortality.

Cisplatin/5-FU (PF) chemotherapy achieved a response rate of 25-50% with more acceptable toxicity [181, 182]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in twenty patients [87], with long-term survival in 37% of responders who underwent radical lymph node surgery after neoadjuvant chemotherapy. In the EORTC cancer study 30992, 26 patients with locally advanced or metastatic disease received irinotecan and cisplatin chemotherapy. Although the study did not meet its primary endpoint (response rate), there were three cases of pathologically complete remissions [183].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in 15/30 patients, including three pathologically complete remissions (pCRs). The estimated median time to progression (TTP) was 8.1 months and the median OS was 17.1 months [164] (LE: 2a).

Hypothetical similarities between penile SCC and head and neck SCC led to the evaluation, in penile cancer, of chemotherapy regimens with an efficacy in head and neck SCC, including taxanes. The combination of cisplatin and 5-FU plus a taxane has been used in neoadjuvant and adjuvant settings [177]. An overall objective response rate of 44% was reported in 28 patients treated neoadjuvantly, including 14% pCR (LE: 2b). Similarly, a phase II trial with TPF using docetaxel instead of paclitaxel reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although the study did not meet its primary endpoint. However, there was significant toxicity [184] (LE: 2a). Further evidence of the benefit of neoadjuvant chemotherapy was published recently [165].

Overall, these results support the recommendation that neoadjuvant chemotherapy using a cisplatin- and taxane-based triple combination should be used in patients with fixed, unresectable, nodal disease (LE: 2a).

There are hardly any data concerning the potential benefit of radiochemotherapy together with lymph node surgery in penile cancer. It should therefore only be used in controlled clinical trials [185].

*6.3.3 **Palliative chemotherapy in advanced and relapsed disease***

A recent retrospective study of 140 patients with advanced penile SCC reported that visceral metastases and an > 1 ECOG-performance status were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [186] (LE: 3).

Before taxanes were introduced, chemotherapy data in penile cancer were limited by small numbers, patient heterogeneity and retrospective design (except for the EORTC trial [183]). Initial response rates ranged from 25% to 100%, with very few sustained responses and very few long-term survivors. The introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used [87, 162-164, 178-184, 187].

There are virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported a response rate of < 30% and no patient survived [188] (LE: 2a). Anecdotally, a benefit of second-line cisplatin with gemcitabine has been observed [189] (LE: 4).

*6.3.4 **Intra-arterial chemotherapy***

Intra-arterial chemotherapy which refers to intra-aortic application has been trialled in locally advanced cases, especially of cisplatin and gemcitabine in small case series [190-193]. Apart from a limited clinical response, the outcome was not significantly improved.

*6.3.5 **Targeted therapy***

Targeted drugs have been used as second-line treatment and they could be considered as single-agent treatment in refractory cases. Anti-epidermal growth factor receptor (EGFR) targeted monotherapy has been trialled [194], as EGFR is expressed in penile SCC [190, 191] and there are assumed similarities with head and neck SCC [190, 191]. There have been other studies, particularly with the anti-EGFR monoclonal antibodies panitumumab and cetuximab, without long-term response, however [195]. Some activity of tyrosine kinase inhibitors has been reported as well [193]. Further clinical studies are needed (LE: 4).

*6.3.6 **Guidelines for chemotherapy***

Recommendations	Strength rating
Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide).	Strong
Offer patients with non-resectable or recurrent lymph node metastases neoadjuvant chemotherapy (four cycles of a cisplatin- and taxane-based regimen) followed by radical surgery.	Weak
Offer palliative chemotherapy to patients with systemic disease.	Weak

7. FOLLOW-UP

7.1 Rationale for follow-up

Early detection of recurrence increases the likelihood of curative treatment since local recurrence does not significantly reduce long-term survival if successfully treated [87, 196]. In contrast, disease that has spread to the inguinal lymph nodes greatly reduces the rate of long-term DSS. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within two years of primary treatment [87]. After five years, all recurrences were either local or new primary lesions [87]. This supports an intensive follow-up regimen during the first two years, with a less intensive follow up later for a total of at least five years. Follow-up after five years may be omitted in motivated patients who will undertake regular self-examination reliably [87].

7.1.1 When and how to follow-up

After local treatment with negative inguinal nodes, follow-up should include physical examination of the penis and groins for local and/or regional recurrence. Additional imaging has no proven benefit. Follow-up also depends on the primary treatment modality. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases, CT or MRI imaging for the detection of systemic disease should be performed at three-monthly intervals for the first two years.

Although rare, late local recurrence may occur, with life-threatening metastases becoming very unusual after five years. Therefore, regular follow up can be stopped after five years, provided the patient understands the need to report any local changes immediately [197]. In patients unlikely to self-examine, long-term follow up may be necessary.

7.1.2 Recurrence of the primary tumour

Local recurrence is more likely with all types of local organ-sparing treatment but does not influence the rate of cancer-specific survival in contrast to regional lymph node recurrence [87, 196]. Local recurrence occurred during the first two years in up to 27% of patients treated with penis-preserving modalities [98]. After partial penectomy, the risk of local recurrence is about 4-5% [87, 98, 196].

Local recurrence is easily detected by physical examination, by the patient himself or his physician. Patient education is an essential part of follow-up and the patient should be urged to visit a specialist if any changes are seen.

7.1.3 Regional recurrence

Most regional recurrences occur during the first two years after treatment, irrespective of whether surveillance or invasive nodal staging were used. Although unlikely, regional recurrence can occur later than two years after treatment. It is therefore advisable to continue follow up in these patients [197]. The highest rate of regional recurrence (9%) occurs in patients managed by surveillance, while the lowest is in patients who have undergone invasive nodal staging by modified inguinal lymphadenectomy or DSNB and whose lymph nodes were negative (2.3%).

The use of US and fine needle aspiration cytology (FNAC) in suspicious cases has improved the early detection rate of regional recurrence [76, 198, 199]. There are no data to support the routine use of CT or MRI for the follow-up of inguinal nodes.

Patients who have had surgery for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [87]. Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant chemotherapy (see Section 6).

7.1.4 Guidelines for follow-up in penile cancer

	Interval of follow-up		**Examinations and investigations**	**Minimum duration of follow-up**	**Strength rating**
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia.	Five years	Strong
Amputation	Three months	One year	Regular physician or self-examination.	Five years	Strong
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	Strong
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	Strong

pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography/ magnetic resonance imaging optional.	Five years	Strong

7.2 Quality of life

*7.2.1 **Consequences after penile cancer treatment***

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance may adversely affect the patient's QoL [200]. However, there is very little data on sexual function and QoL after treatment for penile cancer. In particular, there is heterogeneity of the psychometric tools used to assess QoL outcomes and further research is needed to develop disease-specific patient reported outcome measures for penile cancer.

Comparative studies

There are only two comparative studies in the literature reporting on the health-related quality of life (HRQoL) outcomes following surgery for localised penile cancer. One study compared wide local excision with glansectomy [201]. Among 41 patients there was reduction in post-operative International Index of Erectile Function (IIEF) and the authors concluded that local excision led to better sexual outcomes than glansectomy. In another study of 147 patients, the IIEF-15, the SF36 Health Survey and the Impact of Cancer questionnaire were used [202].

Compared to an age-matched population sample, men after partial penectomy reported significantly more problems with orgasm, cosmesis, life interference and urinary function than those who had undergone penile-sparing surgery (83% vs. 43%, $p < 0.0001$). Interestingly, there were no differences in erectile function, sexual desire, intercourse satisfaction or overall sexual satisfaction.

*7.2.2 **Sexual activity and quality of life after laser treatment***

A retrospective interview-based Swedish study after laser treatment for penile PeIN [104] in 58 out of 67 surviving patients with a mean age of 63 years, of whom 46 participated, reported a marked decrease in some sexual practices, such as manual stimulation, caressing and fellatio, but a general satisfaction rate with life overall and sexuality which was similar to that of the general Swedish population.

A large study on CO_2 laser treatment of penile cancer in 224 patients reported no problems with erectile or sexual function following treatment [91]. In another study [107], no sexual dysfunction occurred in nineteen patients treated.

*7.2.3 **Sexual activity after glans resurfacing***

In one study with ten patients [111], 7/10 completed questionnaires (IIEF-5 and a non-validated 9-item questionnaire) at six months. The median IIEF-5 score was 24 (no erectile dysfunction). All patients who were sexually active before treatment were active after three to five months, 7/7 stated that the sensation at the tip of their penis was either no different or better after surgery, and 5/7 patients felt that their sex life had improved. Overall patient satisfaction with glans resurfacing was high.

*7.2.4 **Sexual activity after glansectomy***

Two studies reported sexual function after glansectomy [112, 113]. In one (n = 68) with unclear methodology [113], 79% did not report any decline in spontaneous erection, rigidity or penetrative capacity after surgery, and 75% reported recovery of orgasm. In the other study [114], all twelve patients had returned to 'normal' sexual activity one month after surgery.

*7.2.5 **Sexual function after partial penectomy***

Sexual function after partial penectomy was reported by three studies [203-205]. In one with 18 patients with a mean age of 52 years, the IIEF scores were significantly worse for all domains of sexual function after surgery [203] and 55.6% of patients had erectile function that allowed sexual intercourse. In patients who did not resume sexual activity, 50% were ashamed of their small penis and missing glans, while another third blamed surgical complications. Of those who had resumed sexual intercourse, 66.7% reported the same frequency and level of sexual activity as before surgery, while 72.2% continued to have ejaculation and orgasm every time with sexual activity. Overall, only 33.3% maintained their pre-operative frequency of sexual intercourse and were satisfied with their sex life.

In another study, an 'Overall Sexual Functioning Questionnaire' was used in 14 patients with a median time of 11.5 months after surgery (range 6-72) [204]. Prior to surgery, all patients had had normal erectile function and intercourse at least once a month. In 9/14 patients, sexual function was 'normal' or 'slightly decreased', while 3/14 had had no sexual intercourse since surgery. Alei *et al.* reported an improvement in erectile function over time [205]. In a report of 25 patients after partial penectomy and neoglans formation, the IIEF-5, Quality of Erection Questionnaire (QEQ), Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Self-Esteem and Relationship (SEAR) were used. This study reported a high percentage of patient and partner satisfaction with surgical treatment and recovery of sexual function, self-esteem, and overall relationship satisfaction [206].

*7.2.6 **Quality of life and sexual function after total penectomy***

In ten patients with penile cancer evaluated after total amputation of the penis, there were significant effects on sexual life and overall QoL, although there were no negative implications in terms of partner relationships, self-assessment or the evaluation of masculinity [207].

*7.2.7 **Quality of life after partial penectomy***

Several qualitative and quantitative instruments have been used to assess 'psychological behaviour and adjustment' and 'social activity' as QoL indicators [204, 208]. Patient-reported fears were those of mutilation, loss of sexual pleasure and of cancer death and what this would mean for their families. The study reported no significant levels of anxiety and depression on the General Health Questionnaire-12 and the Hospital Anxiety and Depression Scale. 'Social activity' remained the same after surgery in terms of living conditions, family life and social interactions.

7.3 Total phallic reconstruction

There is very limited data about total phallic reconstruction following full or near-total penile amputation [137, 209, 210]. Although it is not possible to restore function without a penile prosthesis, cosmetically acceptable results can be obtained.

7.4 Specialised care

Since penile cancer is rare, patients should be referred to a centre with experience and expertise in local treatment, pathological diagnosis, chemotherapy and psychological support for penile cancer patients. Some countries have centralised the care of penile cancer patients (Sweden, Denmark, the Netherlands, the UK).

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9. CONFLICT OF INTEREST

All members of the Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline/penile-cancer/.

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10. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

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1. INTRODUCTION

1.1 Aim and objectives

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and have a substantial economic burden. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH). It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and clinical epidemiological backgrounds. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.4 Publication history

The Non-neurogenic Male LUTS Guidelines was first published in 2000. The standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2020 document presents a limited update of the 2019 publication; the next update of the Non-neurogenic Male LUTS Guidelines will be presented in 2021.

2. METHODS

2.1 Introduction

For the 2020 Management of Non-Neurogenic Male LUTS Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between April 30th 2018 and April 1st 2019. A total of 1,254 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://www.uroweb.org/guideline/ treatment-of-non-neurogenic-male-luts/supplementary-material.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The Non-Neurogenic Male LUTS Guidelines were peer reviewed prior to publication in 2016.

2.3 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various non-neurogenic and non-malignant conditions such as LUTS/Benign Prostatic Obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with other contexts of LUT disease (e.g. concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following sections. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [5], they are prevalent, cause bother and impair QoL [6-9]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [10]. Lower urinary tract symptoms are strongly associated with ageing [6, 7], associated costs and burden are therefore likely to increase with future demographic changes [7, 11]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [12]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [13].

Most elderly men have at least one LUTS [7]; however, symptoms are often mild or not very bothersome [9, 10, 14]. Lower urinary tract symptoms can progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [7]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of BPH [5, 8]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [7, 15]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [15]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [16, 17]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [7].

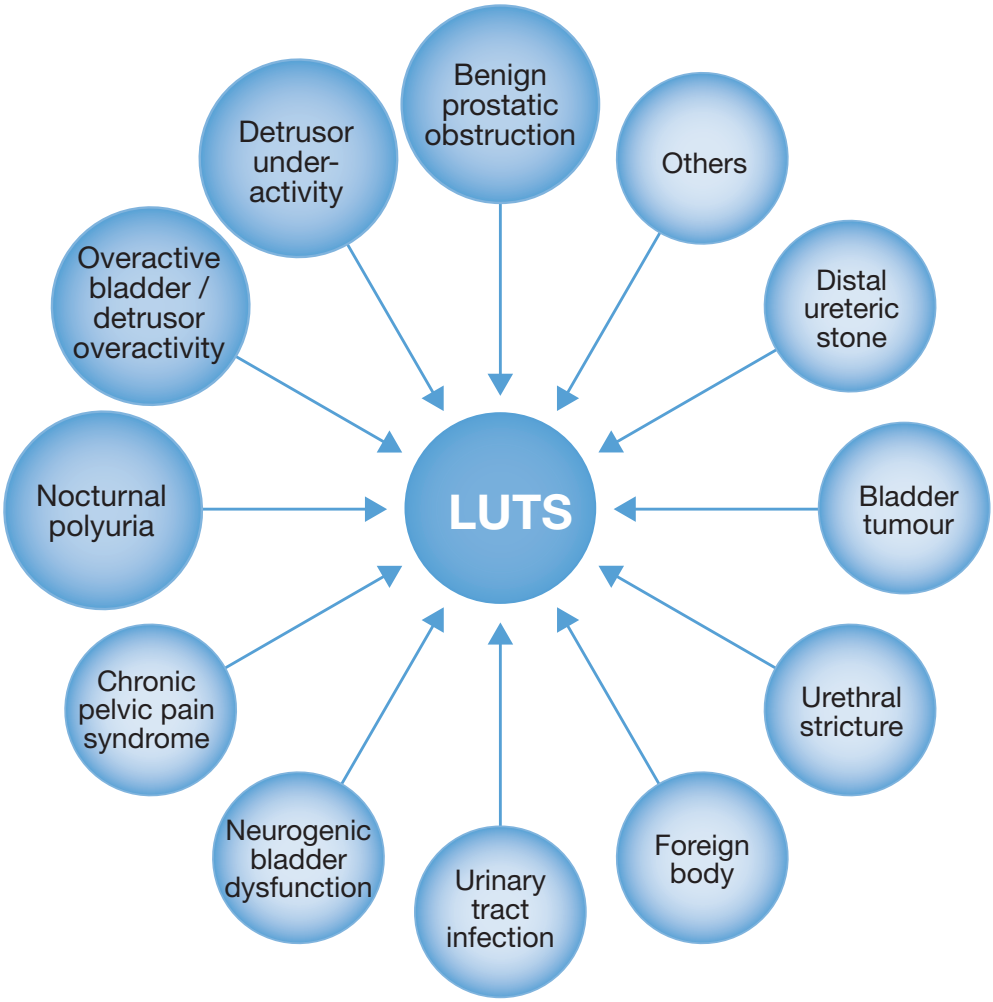
The definitions of the most common conditions related to male LUTS are presented below:

- Acute retention of urine is defined as a painful, palpable or percussible bladder, when the patient is unable to pass any urine [5].
- Chronic retention of urine is defined as a non-painful bladder, which remains palpable or percussible after the patient has passed urine. Such patients may be incontinent [5].
- Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increasing detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow-rate and detrusor pressure [5].
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [5]. In the Guidelines the term BPO or BOO is used as reported by the original studies.
- Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease.

- Detrusor overactivity (DO) is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [5].
- Overactive bladder syndrome is characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [18].

Figure 1 illustrates the potential causes of LUTS. In any man complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male LUTS



4. DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the risk of disease progression, treatment planning, and the prediction of treatment outcomes. The clinical assessment of patients with LUTS has two main objectives:

- to identify the differential diagnoses, since the origin of male LUTS is multifactorial, the relevant EAU Guidelines on the management of applicable conditions should be followed;
- to define the clinical profile (including the risk of disease progression) of men with LUTS in order to provide appropriate care.

4.1 Medical history

The importance of assessing the patient's history is well recognised [19-21]. A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, current medication, lifestyle habits, emotional and psychological factors must be reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite link between LUTS and prostate cancer (PCa) [22, 23].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 4.2) should be obtained to objectify and quantify LUTS. Voiding diaries are particularly beneficial when assessing patients with nocturia and/or storage symptoms (see section 4.3). Sexual function should also be assessed, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF) [24].

Summary of evidence	LE
A medical history is an integral part of a patient's medical evaluation.	4
A medical history aims to identify the potential causes of LUTS as well as any relevant comorbidities and to review the patient's current medication and lifestyle habits.	4

Recommendation	Strength rating
Take a complete medical history from men with LUTS.	Strong

4.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [19, 21]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [25-31]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant; however, they are not disease-, or age-specific. A systematic review (SR) evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard), for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [32].

4.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an eight-item questionnaire, consisting of seven symptom questions and one QoL question [26]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

4.2.2 The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

The ICIQ-MLUTS was created from the International Continence Society (ICS) Male questionnaire. It is a widely used and validated patient completed questionnaire [27]. It contains thirteen items, with subscales for nocturia and OAB, and is available in seventeen languages.

4.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [30] is a symptom score used mainly in Denmark and Finland. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Summary of evidence	LE
Symptom questionnaires are sensitive to symptom changes.	3
Symptom scores can quantify LUTS and identify which types of symptoms are predominant; however, they are not disease- or age-specific.	3

Recommendation	Strength rating
Use a validated symptom score questionnaire including bother and quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	Strong

4.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of additional information such as fluid intake, use of pads, activities during recording, or symptom scores is termed a bladder diary [5]. Parameters that can be derived from the FVC and bladder diary include: day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little

data [33, 34]. The FVC/bladder diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [35-37]. The use of FVCs may cause a 'bladder training effect' and influence the frequency of nocturnal voids [38].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [39]. A SR of the available literature recommended FVCs should continue for three or more days [40].

Summary of evidence	LE
Frequency volume charts and bladder diaries provide real-time documentation of urinary function and reduce recall bias.	3
Three and seven day FVCs provide reliable measurement of urinary symptoms in patients with LUTS.	2b

Recommendations	Strength rating
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	Strong
Tell the patient to complete a bladder diary for at least three days.	Strong

4.4 Physical examination and digital-rectal examination

Physical examination particularly focusing on the suprapubic area, the external genitalia, the perineum and lower limbs should be performed. Urethral discharge, meatal stenosis, phimosis and penile cancer must be excluded.

4.4.1 Digital-rectal examination and prostate size evaluation

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [41]. Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL [42]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [43]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50 mL [44].

Summary of evidence	LE
Physical examination is an integral part of a patient's medical evaluation.	4
Digital-rectal examination can be used to assess prostate volume; however, the correlation to actual prostate volume is poor.	3

Recommendation	Strength rating
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	Strong

4.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infections (UTI), microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, e.g. Guidelines on urinary tract cancers and urological infections [45-48].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [49, 50]. There is limited evidence, but general expert consensus suggests that the benefits outweigh the costs [51]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [52].

Summary of evidence	LE
Urinalysis (dipstick or sediment) may indicate a UTI, proteinuria, haematuria or glycosuria requiring further assessment.	3
The benefits of urinalysis outweigh the costs.	4

Recommendation	Strength rating
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	Strong

4.6 Prostate-specific antigen (PSA)

4.6.1 PSA and the prediction of prostatic volume

Pooled analysis of placebo-controlled LUTS/BPH trials showed that PSA has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76-0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [53].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [54]. A PSA threshold value of 1.5 ng/mL could best predict a prostate volume of > 30 mL, with a positive predictive value (PPV) of 78%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (± 20%) in > 90% of the cases [55, 56].

4.6.2 PSA and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [57]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.

4.6.3 PSA and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [58]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [59]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [60, 61]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [62, 63]. An equivalent link was also confirmed by the Olmsted County Study. The risk for treatment was higher in men with a baseline PSA of > 1.4 ng/mL [64]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The positive predictive value (PPV) of PSA for the detection of BPO was recently shown to be 68% [65]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [66].

Summary of evidence	LE
Prostate-specific antigen has a good predictive value for assessing prostate volume and is a strong predictor of prostate growth.	1b
Baseline PSA can predict the risk of AUR and BPE-related surgery.	1b

Recommendations	Strength rating
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	Strong
Measure PSA if it assists in the treatment and/or decision making process.	Strong

4.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [67]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [68].

One study reported that 11% of men with LUTS had renal insufficiency [67]. Neither symptom score nor QoL was associated with the serum creatinine level. Diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter *et al*. [69] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.* [70] concluded that only those with an elevated creatinine level require investigational ultrasound (US) of the kidney.

In the Olmsted County study community-dwelling men there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [71]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [72]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [73]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [74].

Summary of evidence	LE
Decreased Q_{max} and a history of hypertension and/or diabetes are associated with CKD in patients who present with LUTS.	3
Patients with renal insufficiency are at an increased risk of developing post-operative complications.	3

Recommendation	Strength rating
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	Strong

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity [DUA]) [75, 76]. Using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [77]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although it may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom progression [62, 63].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [63]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α1-blockers or WW [78]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established; this is a research priority.

Summary of evidence	LE
The diagnostic accuracy of PVR measurement, using a PVR threshold of 50 mL, has a PPV of 63% and a NPV of 52% for the prediction of BOO.	3
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendation	Strength rating
Measure post-void residual in the assessment of male LUTS.	Weak

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. As Q_{max} is prone to within-subject variation [79, 80], it is useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. A threshold Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [81]. If Q_{max} is > 15 mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [82], DUA or an under-filled bladder [83]. Therefore, it is limited as a diagnostic test as it is unable to discriminate between the underlying mechanisms. Specificity can be improved by repeated flow rate testing. Uroflowmetry can be used for monitoring treatment outcomes [84] and correlating symptoms with objective findings.

Summary of evidence	LE
The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. Specificity can be improved by repeated flow rate testing.	2b
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendations	Strength rating
Perform uroflowmetry in the initial assessment of male LUTS.	Weak
Perform uroflowmetry prior to medical or invasive treatment.	Strong

4.10 Imaging

*4.10.1 **Upper urinary tract***

Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [70, 85-87]. Several arguments support the use of renal US in preference to intravenous urography. Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, radiation dose and less side effects [85]. Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.

Summary of evidence	LE
Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population.	3
Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.	4

Recommendation	Strength rating
Perform ultrasound of the upper urinary tract in men with LUTS.	Weak

*4.10.2 **Prostate***

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography (CT), and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by transabdominal (suprapubic) US or TRUS [85].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy (OP), enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP), or minimally invasive therapies. It is also important prior to treatment with 5α-reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [87].

Transrectal US is superior to transabdominal volume measurement [88, 89]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach since medial lobe presence can be a contraindication for some minimally invasive treatments (see section 5.3).

Summary of evidence	LE
Assessment of prostate size by TRUS or transabdominal US is important for the selection of interventional treatment and prior to treatment with 5-ARIs.	3

Recommendations	Strength rating
Perform imaging of the prostate when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	Weak
Perform imaging of the prostate when considering surgical treatment.	Strong

*4.10.3 **Voiding cysto-urethrogram***

Voiding cysto-urethrogram (VCUG) is not recommended in the routine diagnostic work-up of men with LUTS, but it may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or urethral pathologies. Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures.

4.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.

A prospective study evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [90]. The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had a reduced Q_{max}.

Another study showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{max} value in 39 symptomatic men aged 53-83 years [91]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [92]. The authors noted a correlation between cystoscopic appearance

(grade of bladder trabeculation and urethral occlusion) and urodynamic indices, DO and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation [92].

Summary of evidence	LE
Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.	3
None of the studies identified a strong association between the urethrocystoscopic and urodynamic findings.	3

Recommendation	Strength rating
Perform urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies if the findings may change treatment.	Weak

4.12 Urodynamics

In male LUTS, the most widespread invasive urodynamic techniques employed are filling cystometry and pressure flow studies (PFS). The major goal of urodynamics is to explore the functional mechanisms of LUTS, to identify risk factors for adverse outcomes and to provide information for shared decision-making. Most terms and conditions (e.g. DO, low compliance, BOO/BPO, DUA) are defined by urodynamic investigation.

4.12.1 Diagnosing bladder outlet obstruction

Pressure flow studies are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outlet obstruction/BPO has to be differentiated from DUA, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [5].

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [93, 94]. In men with LUTS attributed to BPE, DO was present in 61% and independently associated with BOO grade and ageing [93].

The prevalence of DUA in men with LUTS is 11-40% [95, 96]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [97, 98]. There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS with respect to the outcome of treatment; however, a study has been completed in the UK, but the final results have not yet been published [99, 100].

A Cochrane meta-analysis was done to determine whether performing invasive urodynamic investigation reduces the number of men with continuing symptoms of voiding dysfunction. Two trials with 350 patients were included. Invasive urodynamic testing changed clinical decision making. Patients who underwent urodynamics were less likely to undergo surgery; however, no evidence was found to demonstrate whether this led to reduced symptoms of voiding dysfunction after treatment [101]. A more recent meta-analysis of retrospective studies showed that pre-operative urodynamic DOA has no diagnostic role in the prediction of surgical outcomes in patients with male BOO [102].

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative treatment has failed. The Guidelines Panel attempted to identify specific indications for PFS based on age, findings from other diagnostic tests and previous treatments. The Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which reflects the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s, although the Panel recognised that with a Q_{max} < 10 mL/s, BOO is likely and PFS is not necessarily needed.

Patients with neurological disease, including those with previous radical pelvic surgery, should be assessed according to the EAU Guidelines on Neuro-Urology [103].

4.12.2 Videourodynamics

Videourodynamics provides additional anatomical and functional information and may be recommended if the clinician considers this is needed to understand the pathophysiological mechanism of an individual patient's LUTS.

Summary of evidence	LE
There are no RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS with respect to the outcome of treatment.	3

Recommendations	Strength rating
Perform pressure-flow studies (PFS) only in individual patients for specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform PFS in men who have had previous unsuccessful (invasive) treatment for LUTS.	Weak
Perform PFS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform PFS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak
Perform PFS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post void residual > 300 mL.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak

4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS

4.13.1 Prostatic configuration/intravesical prostatic protrusion (IPP)

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [104]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [104].

Ultrasound measurement of IPP assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with a bladder volume of 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is > 10 mm.

Intravesical prostatic protrusion correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [105]. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [106]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter after AUR [107, 108]. However, no information with regard to intra- or inter-observer variability and learning curve is yet available. Therefore, whilst IPP may be a feasible option to infer BPO in men with LUTS, the role of IPP as a non-invasive alternative to PFS in the assessment of male LUTS remains under evaluation.

4.13.2 Bladder/detrusor wall thickness and ultrasound-estimated bladder weight

For bladder wall thickness (BWT) assessment, the distance between the mucosa and the adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the detrusor sandwiched between the mucosa and adventitia [109].

A correlation between BWT and PFS parameters has been reported. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL was best at differentiating between patients with or without BOO [110]. Detrusor wall thickness at the anterior bladder wall with a bladder filling > 250 mL (threshold value for BOO > 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89% agreement with PFS [73]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS are able to identify 81%, 89%, and 100% of patients with BOO, respectively [111].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal urodynamics, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [112]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [113]. Measurement of BWT/DWT is therefore not recommended for the diagnostic work-up of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35 g [114, 115]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [116].

4.13.3 Non-invasive pressure-flow testing

The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability [117] and inter-observer agreement [118]. A nomogram has also been derived [119] whilst a method in which flow is not interrupted is also under investigation [120].

The data generated with the external condom method [121] correlates with invasive PFS in a high proportion of patients [122]. Resistive index [123] and prostatic urethral angle [124] have also been proposed, but are still experimental.

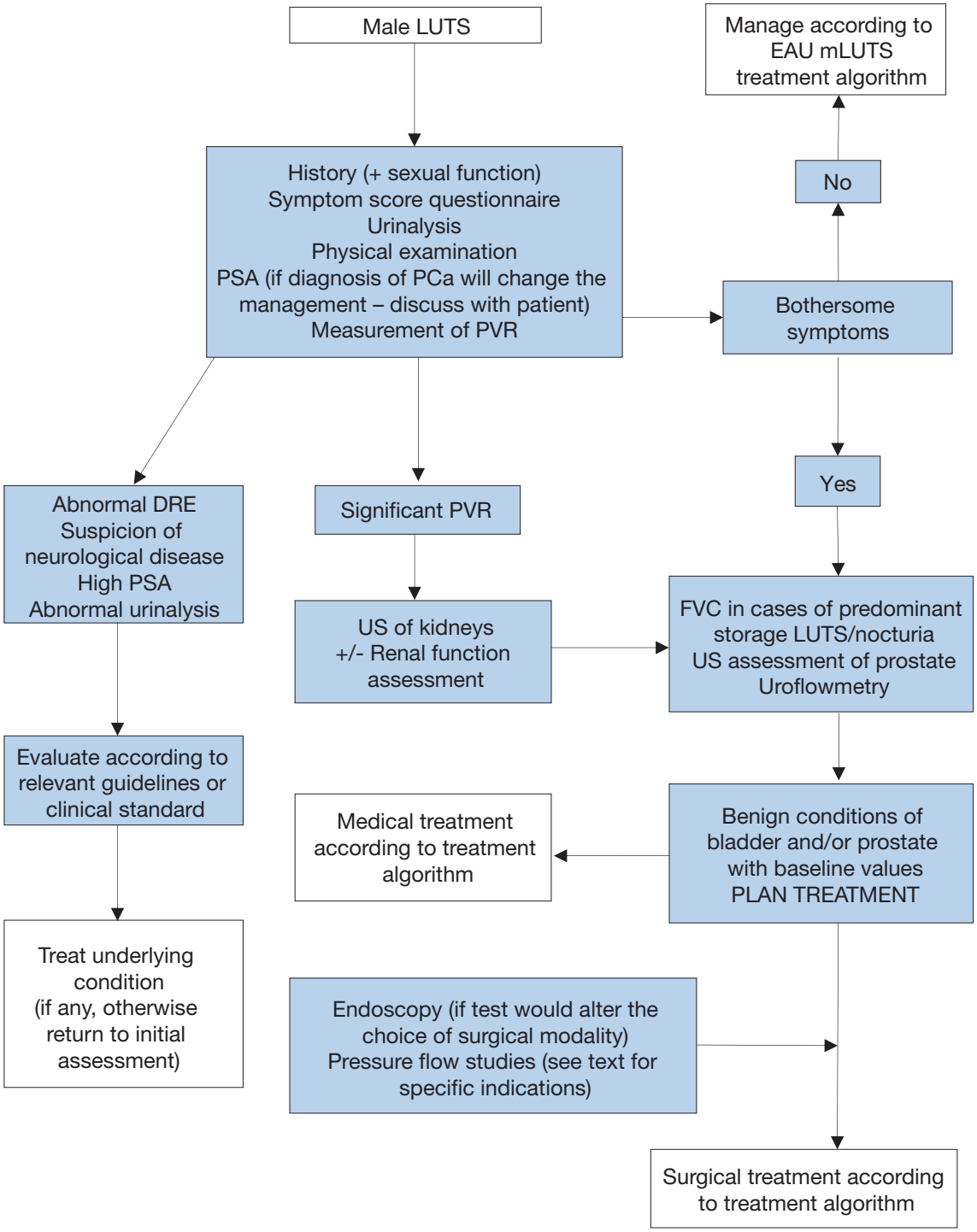
4.13.4 The diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies

The diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with PFS has been investigated in a SR [125]. A total of 42 studies were included is this review. The majority were prospective cohort studies, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; detrusor/bladder wall thickness; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

Summary of evidence	**LE**
Data regarding the diagnostic accuracy of non-invasive tests is limited by the heterogeneity of the studies as well as the small number of studies for each test.	1a
Specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.	1a

Recommendation	**Strength rating**
Do not offer non-invasive tests as an alternative to pressure-flow studies for diagnosing bladder outlet obstruction in men.	Strong

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older
Readers are strongly recommended to read the full text that highlights the current position of each test in detail.



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting (WW)

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and

complicated LUTS. Watchful waiting is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [126, 127], whilst others can remain stable for years [128]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [129].

A study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother; 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [130, 131]. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

*5.1.2 **Behavioural and dietary modifications***

It is customary for this type of management to include the following components:

- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [128, 129, 132, 133] such as:
    - reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public);
    - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
    - use of relaxed and double-voiding techniques;
    - urethral milking to prevent post-micturition dribble;
    - distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms;
    - bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids;
    - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
    - providing necessary assistance when there is impairment of dexterity, mobility or mental state;
    - treatment of constipation.

There now exists evidence that self-management as part of WW reduces both symptoms and progression [132, 133]. Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only, for up to a year [132].

*5.1.3 **Practical considerations***

The components of self-management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [134]. Further research in this area is required.

Summary of evidence	**LE**
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21%; 79% of patients were clinically stable.	1b
An additional study reported 81% of patients were clinically stable on WW after a mean follow-up of seventeen months.	2
Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care alone at up to a year. Self-management as part of WW reduces both symptoms and progression.	1b

Recommendations	**Strength rating**
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	Strong
Offer men with LUTS lifestyle advice prior to, or concurrent with, treatment.	Strong

5.2 Pharmacological treatment

5.2.1 α*1-Adrenoceptor antagonists (*α*1-blockers)*

Mechanism of action: α1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [135]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [136], and treatment-associated improvement of LUTS correlates poorly with obstruction [137]. Thus, other mechanisms of action may also be relevant.

Alpha-1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α1-adrenoceptor subtypes (α1B- or α1D-adrenoceptors) may play a role as mediators of effects. α1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

Currently available α1-blockers are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin); and naftopidil. Alpha-1-blockers exist in different formulations. Although different formulations result in different pharmacokinetic and tolerability profiles, the overall difference in clinical efficacy between the difference formulations seems modest.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [138]. Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [137].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, considerable improvements also occurred in the corresponding placebo arms [60, 139]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [60, 139]. A recent SR and meta-analysis suggested that Q_{max} variation underestimates the real effect of α1-blockers on BPO, as small improvements in Q_{max} correspond to relevant improvements in BOO index in PFS [140].

Alpha-1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [62, 141-144]. The efficacy of α1-blockers is similar across age groups [139]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [142-144]; however, recent evidence suggests that the use of a1-blockers (alfuzosin and tamsulosin) may improve resolution of AUR [145]. Nonetheless, IPSS reduction and Q_{max} improvement during α1-blocker treatment appears to be maintained over at least four years.

Tolerability and safety: Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common with alfuzosin and tamsulosin [146]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [147]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [148]. In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension [149].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [150]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [151]. However, the OR for IFIS was much higher for tamsulosin. It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use.

A SR concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but can cause abnormal ejaculation [152]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. In a recent meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR 0.80 and 1.78) were associated with a low risk of EjD [153]. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α1-blocker is the greater the incidence of EjD.

Practical considerations: α1-blockers are usually considered the first-line drug treatment for male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. However, α1-blockers do not prevent occurrence of urinary retention or need for surgery. Ophthalmologists should be informed about α1-blocker use prior to cataract surgery. Elderly patients treated with non-selective α1-blockers should be informed about the risk of orthostatic hypotension. Sexually active patients treated with selective α1-blockers should be counselled about the risk of EjD.

Summary of evidence	LE
α1-blockers are effective in reducing urinary symptoms (IPSS) and increasing the peak urinary flow rate (Q_{max}) compared with placebo.	1a
Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo.	1a
Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of IFIS.	1a
Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin.	1a

Recommendation	Strength rating
Offer α1-blockers to men with moderate-to-severe LUTS.	Strong

*5.2.2 **5α-reductase inhibitors***

Mechanism of action: Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α-reductase [154], which has two isoforms:

- 5α-reductase type 1: predominant expression and activity in the skin and liver.
- 5α-reductase type 2: predominant expression and activity in the prostate.

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits both 5α-reductase types (dual 5-ARI). 5α-reductase inhibitors induce apoptosis of prostate epithelial cells [155] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment [156]. Mean prostate volume and PSA reduction may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after treatment of at least six months. After two to four years of treatment 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement [62, 143, 144, 157-163]. An indirect comparison and one direct comparative trial (twelve months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [156, 164]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [165]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of AUR, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL [166, 167]. A long-term trial with dutasteride in symptomatic men with prostate volumes > 30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as the α1-blocker tamsulosin [143, 163, 168]. The greater the baseline prostate volume (or serum PSA level), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> 1 year) risk of AUR or need for surgery [62, 161, 169]. In the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years, compared with placebo [161]. In the MTOPS study, finasteride reduced the relative risk of AUR by 68% and need for surgery by 64% (absolute risk reduction 2% and 3%, respectively), also at four years [62]. A pooled analysis of three randomised trials with two-year follow-up data, reported that treatment with finasteride decreased the relative risk of AUR by 57%, and surgical intervention by 34% (absolute risk reduction 2% for both) in patients with moderately symptomatic LUTS [170]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [171, 172]. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [173, 174].

Tolerability and safety: The most common adverse events are reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [62, 144, 156, 175]. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients. Two studies have suggested that treatment with 5-ARIs is associated with a higher incidence of high-grade cancers although no causal relationship has been proven [176, 177]. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [178]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [178, 179].

Practical considerations: Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS and an enlarged prostate (> 40 mL) and/or elevated PSA concentration (> 1.4-1.6 ng/mL). They can prevent the risk of AUR and need for surgery. Due to the slow onset of action, they are not suitable for short-term use. Their effect on PSA needs to be considered in relation to PCa screening.

Summary of evidence	**LE**
After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement.	1b
5α-reductase inhibitors can prevent disease progression with regard to AUR and the need for surgery. Due to their slow onset of action, they are suitable only for long-term treatment (years).	1a
The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, ED and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume.	1b

Recommendations	**Strength rating**
Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong
Counsel patients about the onset of action (three to six months) of 5α-reductase inhibitors.	Strong

*5.2.3 **Muscarinic receptor antagonists***

Mechanism of action: The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells. Muscarinic receptors are also present on other cell types, such as bladder urothelial cells and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions [180, 181]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [182, 183].

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [184, 185].

Efficacy: Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for this assumption [186]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender had an impact on urgency, frequency, or urgency incontinence [187]. In a pooled analysis, which included a sub-analysis of male patients, fesoterodine 8 mg was superior to tolterodine extended release (ER) 4 mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week twelve, the urinary retention rate was around 2% [188].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [189-194]. Most trials lasted only twelve weeks. Four *post hoc* analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [186, 190, 195]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of

bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks [191, 194]. The TIMES RCT reported that tolterodine ER monotherapy significantly improved UUI episodes per 24 hours compared to placebo, at week twelve. Tolterodine ER did not significantly improve urgency, IPSS total or QoL score compared with placebo. A significantly greater proportion of patients in the tolterodine ER plus tamsulosin group reported treatment benefit compared with the other three treatment groups [193].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinics [196]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [194, 197]. In a small RCT propiverine improved frequency and urgency episodes [197].

Tolerability and safety: Antimuscarinic drug trials generally show approximately 3-10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [191]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%). These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Theoretically antimuscarinics might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A twelve week safety study on men with mild-to-moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not AUR (3% in both arms) [198]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index, Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [192].

Practical considerations: Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised. Men should be advised to discontinue medication if worsening voiding LUTS or urinary stream is noted after initiation of therapy.

Summary of evidence	**LE**
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	2
Antimuscarinic monotherapy can be associated with increased PVR after therapy, but acute retention is a rare event in men with a PVR volume of < 150 mL at baseline.	2

Recommendations	**Strength rating**
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Strong
Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL.	Weak

*5.2.4 **Phosphodiesterase 5 inhibitors***

Mechanism of action: Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [199]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [200]. Phosphodiesterase 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [201]. The exact mechanism of PDE5Is on LUTS remains unclear.

Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS.

Efficacy: Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL. However, Q_{max} did not significantly differ from placebo in most trials.

A recent Cochrane review included a total of sixteen randomised trials that examined the effects

of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [202]. Phosphodiesterase 5 inhibitors led to a small reduction (mean difference (MD) 1.89 lower, 95% CI 2.27 lower to 1.50 lower) in IPSS compared to placebo. There was no difference between PDE5Is and α1-blockers in IPSS. Most evidence was limited to short-term treatment up to twelve weeks and of moderate or low certainty. In earlier [203] and more recent [204] meta-analysis, PDE5Is were also found to improve IPSS and IIEF score, but not Q_{max}.

Tadalafil 5 mg reduces IPSS by 22-37% and improvement may be seen within a week of initiation of treatment [205]. A three point or greater total IPSS improvement was observed in 60% of tadalafil treated men within one week and in 80% within four weeks [206]. The maximum trial (open label) duration was 52 weeks [207]. A subgroup analysis of pooled data from four RCTs demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α-blockers or PDE5Is, total testosterone level or predicted prostate volume [208]. In a recent *post hoc* analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/comorbidities, except for patients receiving more than one antihypertensive medication. The use of diuretics may contribute to patients' perception of a negated efficacy [209]. Among sexually active men > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [208].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%, $p < 0.001$) vs. indirect (7.5%, $p = 0.32$) treatment effects via IIEF-EF improvement [210]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [211]. An integrated analysis of RCTs showed that tadalfil was not superior to placebo for IPSS improvement at twelve weeks in men ≥ 75 years (with varied effect size between studies), but was for men < 75 years [212]. An open label urodynamic study of 71 patients showed improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1; $p < 0.001$), and resolution of DO in 15 (38%) of 38 patients. Flow rate improved from 7.1 to 9.1 mL/s ($p < 0.001$) and mean IPSS from 18.2 to 13.4 [213].

A combination of PDE5Is and α-blockers has also been evaluated. A meta-analysis of five RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5 mL/s) compared with α-blockers alone [203]. A Cochrane review found similar findings [202]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms ($p < 0.022$ after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [214]. However, only tadalafil 5 mg has been licensed in the context of LUTS management while data on combinations of PDE5Is and other LUTS medications is emerging.

Tolerability and safety: Reported adverse effects in RCTs comparing the effect of all PDE5Is vs. placebo in men with LUTS include flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [203]. The discontinuation rate due to adverse effects for tadalafil was 2.0% [215] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [208].

Phosphodiesterase 5 inhibitors are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< three months) or stroke (< six months), myocardial insufficiency (New York Heart Association stage > 2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is.

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. The meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [203]. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one year follow-up [207], therefore conclusions about its efficacy or tolerability greater than one year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Summary of evidence	**LE**
Phosphodiesterase 5 inhibitors improve IPSS and IIEF score, but not Q_{max}.	1a
A three point or greater total IPSS improvement was observed in 59.8% of tadalafil treated men within one week and in 79.3% within four weeks.	1b

Recommendation	**Strength rating**
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	Strong

5.2.5 *Plant extracts - phytotherapy*

Potential mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations) [216].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [216]. *In vitro*, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [216-218]. The *in vivo* effects of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear.

Efficacy: The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects; therefore, the effects of one brand cannot be extrapolated to others [219]. In addition, batches from the same producer may contain different concentrations of active ingredients [220]. A review of recent extraction techniques and their impact on the composition/biological activity of available *Serenoa repens* based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [221], as the pharmacokinetic properties of the different preparations can vary significantly.

Heterogeneity and a limited regulatory framework characterise the current status of phytotherapeutic agents. The European Medicines Agency (EMA) has developed the Committee on Herbal Medicinal Products (HMPC). European Union (EU) herbal monographs contain the HMPC's scientific opinion on safety and efficacy data about a herbal substances and their preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, whilst also documenting long-standing use and experience in the EU. European Union monographs are divided into two sections: a) Well established use (marketing authorisation): when an active ingredient of a medicine has been used for more than ten years and its efficacy and safety have been well established (including a review of the relevant literature); and b) Traditional use (simplified registration): for herbal medicinal products which do not fulfil the requirements for a marketing authorisation, but there is sufficient safety data and plausible efficacy on the basis of long-standing use and experience. Table 1 lists the available EU monographs for herbal medicinal products.

Table 2: European Union monographs for herbal medicinal products

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [222]	Well established use	Symptomatic treatment of BPH	14/01/2016
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [222]	Traditional use	LUTS related to BPH*	14/01/2016
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [223]	Traditional use	LUTS related to BPH or related to OAB*	25/03/2013
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [224]	Traditional use	LUTS related to BPH*	01/09/2017
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [225]	Traditional use	LUTS related to BPH*	05/11/2012
Epilobium angustifolium L. and/or Epilobium parviflorum Schreb., herba (Willow herb) Preparation as defined in the monograph [226]	Traditional use	LUTS related to BPH*	13/01/2016

**after serious conditions have been excluded by a medical doctor*

Panel interpretation: Only hexane extracted *Serenoa reprens* has been recommended for well-established use by the HMPC. A detailed scoping search covering the timeframe between the search cut-off date of the EU monograph and April 2020 will be conducted for the update of the 2021 edition of the Guidelines. Following this a specific recommendation on phytotherapy will be given.

5.2.6 ***Beta-3 agonist***

Mechanism of action: Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. The mode of action of beta-3 agonists is not fully elucidated [227].

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America and Japan [228-232]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency and UUI and also patient perception of treatment benefit. These studies had a predominantly female study population. A meta-analysis of eight RCTS including 10,248 patients (27% male) found that mirabegron treatment resulted in reduced frequency, urgency and UUI rates, as well as an improved voided volume with a statistically significant improvement of nocturia as compared with both placebo and tolterodine [233].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated with or not associated with BPO confirmed by urodynamics [234]. Mirabegron 25 mg daily led to increased satisfaction and improved QoL, but symptoms assessed by validated questionnaires (IPSS and OAB-SS), only improved in non-obstructed patients. Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [235], again in a predominantly female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition, but did not report the results separately for the genders [236].

In a study of more than 1,000 patients of whom approximately 30% were male, combination therapy of mirabegron 25/50 mg and solifenacin 5/10 mg was associated with statistically significant improvements in patient outcomes and health related QoL vs. solifenacin 5 mg and placebo; however, they did not separate out the effects in men and women [237]. In another study, in which 28% patients were male, mirabegron significantly improved patient reported perception of their condition and QoL whether or not patients were incontinent [238]. A phase IV study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [239].

In an RCT evaluating add-on therapy with mirabegron for OAB symptoms remaining after treatment with tamsulosin 0.2 mg daily in men with BPO, combination therapy was associated with greater improvements in OAB symptom score, in the urinary urgency and daytime frequency part and storage subscore of the IPSS, and in the QoL index compared to monotherapy with tamsulosin [240]. A prospective analysis of 50 elderly men showed that mirabegron add-on therapy was effective for patients whose persistent LUTS and OAB symptoms were not controlled with α1-blocker monotherapy, without causing negative effects on voiding function [241].

An RCT compared the efficacy of mirabegron 50 mg or fesoterodine 4 mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms [242]. At three months, fesoterodine add-on therapy showed a significantly greater improvement then mirabegron add-on therapy in OAB symptom score-total (-2.8 vs.1.5, p = 0.004), IPSS-QoL (-1.5 vs. -1.1, p = 0.04), and OAB symptom score-urgency score (-1.5 vs. -0.9, p = 0.008). Fesoterodine was also superior in alleviating detrusor overactivity (52.6% vs. 28.9%, p = 0.03).

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [228-231]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure $\geq$ 180 mmHg or diastolic blood pressure $\geq$ 110 mmHg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment. A combination of thirteen clinical studies including 13,396 patients, 25% of whom were male, showed that OAB treatments (anticholinergics or mirabegron) were not associated with an increased risk of hypertension or cardiovascular events compared to placebo [243]. The proportion of patients with dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [228]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{max}, detrusor pressure at maximum flow and bladder contractility index [244]. The overall change in PVR with mirabegron is small [244].

A small prospective study (mainly focused on males) has shown that mirabegron 25 mg is safe in patients aged 80 years or more with multiple comorbidities [245]. A pooled analysis of three trials each of twelve weeks and a one year trial showed, in patients aged > 65 years, a more favourable tolerability profile for

mirabegron than antimuscarinics [246]. In an eighteen week study of 3,527 patients (23% male), the incidence of adverse events were higher in the combination (solifenacin 5 mg plus mirabegron 25 mg) group (40%) than the mirabegron 25 mg alone group (32%). Events recorded as urinary retention were low (< 1%), but were reported slightly more frequently in the combined group when compared with the monotherapy and placebo groups. The PVR volume was slightly increased in the combined group compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups. Combined therapy with solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg provided improvements in efficacy generally consistent with an additive effect [247].

In a retrospective analysis of persistence and adherence in 21,996 patients, of whom 30% were male, the median time to discontinuation was significantly longer for mirabegron (169 days) compared to tolterodine (56 days) and other antimuscarinics (30-78 days) ($p < 0.0001$). There was no statistical difference between men and women [248]. Data on the safety of combination therapy at twelve months are awaited from the SYNERGY II trial.

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are pending. However, pharmacokinetic interaction upon add-on of mirabegron or tamsulosin to existing tamsulosin or mirabegron therapy does not cause clinically relevant changes in safety profiles [249]. Available studies on mirabegron in combination with antimuscarinics in OAB patients had a predominantly female study population, while further trials are still pending.

Summary of evidence	**LE**
Mirabegron improves the symptoms of OAB, including micturition frequency, urgency and UUI.	2
Patients prescribed mirabegron remained on treatment longer than those prescribed antimuscarinics.	3

Recommendation	**Strength rating**
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Weak

*5.2.7 **Combination therapies***

5.2.7.1 α1-blockers + 5α-reductase inhibitors

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a 5-ARI (Section 5.2.2). The α1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop full clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, terazosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α1-blocker, 5-ARI or placebo alone. Initial studies with follow-up periods of six to twelve months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α1-blocker monotherapy [158, 159, 250]. In studies with a placebo arm, the α1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study showed similar results [62].

Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [62, 143, 144].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for AUR and the need for surgery after eight months [144]. Thus, the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [251, 252]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [251], with almost three quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recent trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [252]. Lower urinary tract symptom improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of the studies include the short duration of the studies and the short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence, or an increase in creatinine > 50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [62]. In addition, finasteride (alone or in combination), but not doxazosin alone, significantly reduced both the risks of AUR and the need for BPH related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [253]. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two year RCT with a total of 742 patients. In both arms detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression, the difference in IPSS at 24 months was 5.4 in the active arm and 3.6 in the placebo arm ($p < 0.001$) [254]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [255].

More recently, a combination of the 5-ARI, finasteride, and tadalafil 5 mg was tested in a large scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in the chapter on PDE5Is [214].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [62, 143, 144]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy. The MTOPS study demonstrated that the incidence of treatment related adverse events is higher during the first year of combined treatment between doxazosin and finasteride [256]. A meta-analysis measuring the impact of medical treatments for LUTS/BPH on ejaculatory function, reported that combination therapy with α1-blockers and 5-ARIs resulted in a three-fold increased risk of EjD as compared with each of the monotherapies [153].

Practical considerations: Compared with α1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max} and is superior in prevention of disease progression. However, combination therapy is also associated with a higher rate of adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended and patients should be informed about this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Summary of evidence	**LE**
Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery.	1b
The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy.	1b
The CombAT study found that combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and 5-ARIs.	1b

Recommendation	Strength rating
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong

5.2.7.2 α1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α1-blocker together with an antimuscarinic aiming to antagonise both α1-adrenoceptors and muscarinic receptors. The possible combinations have not all been tested in clinical trials yet.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α1-blocker [193, 253, 257-263]. One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [264]. A high proportion of men with voiding and storage LUTS need to add anticholinergics after α1-blocker monotherapy, particularly those with longer duration of symptoms at presentation, and men with storage symptoms and a small prostate volume [265].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [193, 266]. Symptom improvement is higher regardless of PSA concentration with combination therapy, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [196].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, [253, 257, 263, 267, 268]. Two SRs of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [269, 270]. In a meta-analysis of sixteen studies with 3,548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication improvement storage symptoms and QoL compared to α1-blocker monotherapy without causing significant deterioration of voiding function [271]. There was no difference in total IPSS and Q_{max} between the two groups.

Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [272]. Long term use of combination therapy has been reported in patients receiving treatment for up to one year, showing symptomatic response is maintained, with a low incidence of AUR [273]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150 mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health related quality of life compared with placebo and α1-blocker monotherapy [274].

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics. The most common side-effect is dry mouth. Some side-effects (e.g.dry mouth or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low up to one year of treatment [269, 275]. Antimuscarinics do not cause evident deterioration in maximum flow rate used in conjunction with an α1-blocker in men with OAB symptoms [266, 276].

A recent RCT investigated safety in terms of maximum detrusor pressure and Q_{max} for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [277]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased vs. placebo [277].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α1-blocker and antimuscarinic. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR is recommended during combination treatment.

Summary of evidence	LE
Combination treatment with α1-blockers and antimuscarinics is effective for improving LUTS-related QoL impairment.	2
Combination treatment with α1-blockers and antimuscarinics is more effective for reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone.	2
Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics.	1
There is a low risk of AUR using α1-blockers and antimuscarinics in men known to have a PVR urine volume of < 150 mL.	2

Recommendations	Strength rating
Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	Strong
Do not prescribe combination treatment in men with a post-void residual volume > 150 mL.	Weak

Note: All patients should be counselled about pharmacological treatment related adverse events in order to select the most appropriate treatment for each individual patient.

5.3 Surgical treatment

Despite the advent of new technologies, monopolar TURP has remained the cornerstone of LUTS/BPO surgical treatment for more than nine decades. Extensive clinical research for a more effective and safer alternative is often hindered by methodological limitations, including inadequate follow up. Based on Panel consensus, timeframes defining short-, mid- and long-term follow up of patients submitted to surgical treatments are 12, 36 and over 36 months, respectively. Clinicians should inform patients that long-term surgical RCTs are lacking.

5.3.1 Monopolar Transurethral resection of the prostate and transurethral incision of the prostate

Mechanism of action: Monopolar transurethral resection of the prostate (M-TURP) removes tissue from the transition zone of the gland. Transurethral incision of the prostate involves incising the bladder outlet without tissue removal. This technique may replace M-TURP in selected cases, especially in prostate sizes < 30 mL without a middle lobe.

Efficacy: In a meta-analysis of 20 RCTs with a maximum follow-up of five years, M-TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [278]. Monopolar-TURP delivers durable outcomes as shown by studies with a follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO [279]. One study with a mean follow-up of thirteen years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than re-development of BPO [98]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed that the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) remained unchanged during the last decade (0.9%, 3.7%, 9.5% and 12.7% at three months, one year, five years, and eight years, respectively), and that the respective incidence of re-TURP was 0.8%, 2.4%, 6.1% and 8.3% [280, 281].

A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [282]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 mL and three < 60 mL.

A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A review analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [283]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after M-TURP (7.2%) [282].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [284]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed a 20% reduction in mortality rate over time, to 0.1% at 30 days and 0.5% at 90 days [280, 281].

The risk of TUR-syndrome decreased to < 1.1% [283, 285]. No case has been recorded after TUIP. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% [284]. The risk after TUIP is negligible. Similar results for M-TURP complications were reported by an analysis of contemporary RCTs using M-TURP as a comparator: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and UTI 4.1% (0-22%) [278]. Long-term complications comprise urinary incontinence, urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [283].

Practical considerations: Monopolar-TURP and TUIP are effective treatments for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and M-TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [284]. The upper limit for M-TURP is suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, choice of resectoscope size and resection speed), as surgical duration increases, there is a significant increase in the rate of complications and the procedure is safest when performed in under 90 minutes [286].

5.3.1.1 Modifications of M-TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of M-TURP by allowing performance in normal saline. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). Prostatic tissue removal is identical to M-TURP. The various bipolar devices available differ in the way in which current flow is delivered [287, 288]. Prostatic tissue removal is identical to M-TURP.

Efficacy: Bipolar TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from 56 RCTs have been reported [289], of which around half have been pooled in RCT-based meta-analyses [278, 290-294]. Early pooled results concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL score and Q_{max}) [291]. Subsequent meta-analyses supported these conclusions though trial quality was generally poor [278, 290, 292-294]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [295-303].

A meta-analysis was conducted to evaluate the quasi-bipolar transurethral resection in saline (TURis, Olympus Medical) system vs. M-TURP, ten unique RCTs (1,870 patients) were included. It was concluded that TURis was of equivalent efficacy to M-TURP [304].

Tolerability and safety: Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable due to a more favourable peri-operative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [291]. Subsequent meta-analyses supported these conclusions [278, 290, 292-294]. However, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [291]. An RCT based meta-analysis has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP [294]. It was concluded that TURis is associated with improved peri-operative safety, eliminating the risk of TUR syndrome (RR: 0.18; 95% CI, 0.05-0.61; p = 0.006), reducing the risk of blood transfusion/clot retention (RR: 0.34; 95% CI, 0.18-0.61; p = 0.0003 and 0.43; 95% CI, 0.22-0.86; p = 0.0161, respectively), and hospital stay (MD: 0.56 d; 95% CI, 0.77 - 0.35; p < 0.0001). No significant difference was detected in urethral stricture rates.

Data from the vast majority of individual RCTs with mid- to long-term follow-up (up to 60 months), showed no differences in urethral stricture/BNC rates [295-303], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [302, 305]. A significantly higher stricture (urethral stricture + BNC) rate was detected in the B-TURP arm performed with a "quasi" bipolar system (TURis, Olympus Medical) in patients with a prostate volume > 70 mL at 36 months follow up (9/23 [39.1%] vs. 1/22 [4.6%]; p = 0.01) [302]. In addition, a significantly higher BNC, but not urethral stricture, rate was detected in the B-TURP arm performed with a "true" bipolar system (Gyrus PK SuperPulse, Olympus Medical) in 137 patients followed up to twelve months (0.0% vs. 8.5%; p = 0.02) [305].

Randomised controlled trials using the erectile function domain of the IIEF (IIEF-ED) and the ejaculatory domain of the male sexual-health questionnaire (Ej-MSHQ) showed that M-TURP and B-TURP have a similar effect on erectile and ejaculatory function [306, 307]. Comparative evaluations of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at twelve months follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [307, 308].

Practical considerations: Bipolar TURP in patients with moderate-to-severe LUTS secondary to BPO, has similar efficacy with M-TURP, but lower peri-operative morbidity. The duration of improvements with B-TURP were documented in a number of RCTs with mid-term follow-up. Long-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

5.3.1.1.1 Modifications of B-TURP: bipolar transurethral vaporisation of the prostate

Mechanism of action: Bipolar transurethral vaporisation of the prostate (B-TUVP) was introduced in the late 1990's ("plasmakinetic" B-TUVP). The technique was derived from plasmakinetic B-TURP and utilised a bipolar electrode and a high-frequency generator to create a plasma effect able to vaporise prostatic tissue [309]. With minimal direct tissue contact (near-contact; hovering technique) and heat production the bipolar electrode produces a constant plasma field (thin layer of highly ionized particles; plasma corona), allowing it to glide over the tissue and vaporise a limited layer of prostate cells without affecting the underlying tissue whilst achieving haemostasis, leaving behind a TURP-like cavity [310]. A distinct difference between B-TUVP and its ancestor (monopolar TUVP), is that B-TUVP displays thinner (< 2 mm) coagulation zones [311], compared to the disproportionate extent of those created by the former (up to 10 mm) [312] that potentially lead to mostly irritative side-effects and stress urinary incontinence [311, 313, 314].

Efficacy: B-TUVP has been evaluated as a TURP alternative for treating moderate-to-severe LUTS in thirteen RCTs to date, including a total of 1,244 men with a prostate size of < 80 mL [298, 315-326]. Early RCTs evaluated the plasmakinetic B-TUVP system [315-319]; however, during the last decade, only the "plasma" B-TUVP system with the "mushroom- or button-like" electrode (Olympus, Medical) has been evaluated [298, 320-326]. Results have been pooled in three RCT-based meta-analyses [278, 327, 328], and a narrative synthesis has been produced in two SRs [278, 329]. The follow up in most RCTs is twelve months [315-318, 320-322, 324, 326]. The longest follow up is 36 months in a small RCT (n = 40) and eighteen months in a subsequent RCT (n = 340); evaluating plasmakinetic [319] and plasma B-TUVP [298], respectively.

Early pooled results concluded that no significant differences exist in short-term efficacy (IPSS, QoL score, Q_{max} and PVR) between plasmakinetic B-TUVP and TURP [278]. However, the promising initial efficacy profile of the former may be compromised by inferior clinical outcomes (IPSS, Q_{max}, re-intervention rate) at mid-term. Larger RCTs with longer follow-up are necessary to draw definite conclusions [278, 319]. A SR of seven RCTs [329] comparing plasmakinetic [315, 317, 318] and plasma B-TUVP [298, 320-322] with TURP concluded that functional outcomes of B-TUVP and TURP do not differ. The poor quality of the included RCTs and the fact that most data was derived from a single institution was highlighted [329]. A similar SR of eight RCTs [278] comparing both B-TUVP techniques with TURP [298, 315, 316, 318-322] concluded that not enough consistent data suitable for a meta-analysis exists; that main functional results are contradictory; and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions. A meta-analysis [328] of six RCTs [298, 320-322, 324, 325] specifically evaluating plasma B-TUVP vs. TURP, concluded that both techniques result in a similar improvement of LUTS.

Tolerability and safety: Early pooled results concluded that no statistically significant differences exist collectively for intra-operative and short-term complications between plasmakinetic B-TUVP and TURP but peri-operative complications are significantly fewer after B-TUVP [278]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [278]. Mid-term safety results (urethral stricture, ED, and retrograde ejaculation) have also been reported to be similar [319], but larger RCTs with longer follow-up are necessary to draw definite conclusions [278, 319]. A SR of seven RCTs [329] comparing plasmakinetic [315, 317, 318] and plasma B-TUVP [298, 320-322] with TURP concluded that most RCTs suggest a better haemostatic efficiency for B-TUVP, resulting in shorter catheterisation (42.5 vs. 77.5 hours) and hospitalisation times (3.1 vs. 4.4 days); however, the poor quality of the included RCTs and the fact that the majority of the data was derived from a single institution was highlighted [329]. A similar SR of eight RCTs [278] comparing both B-TUVP techniques with TURP [298, 315, 316, 318-322] concluded that not enough consistent data suitable for a meta-analysis exists and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions. A meta-analysis [328] of six RCTs [298, 320-322, 324, 325] specifically evaluating plasma B-TUVP vs. TURP, concluded that no significant differences exist between the techniques in overall complication and transfusion rates. However, a statistically significant difference was detected collectively in major complication rates (Clavien 3, 4; including urethral stricture, severe bleeding necessitating re-operation and urinary incontinence) and in the duration of catheterisation favouring plasma B-TUVP.

Practical considerations: B-TUVP and TURP have similar short-term efficacy. Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP. Plasma B-TUVP has a lower short-term major morbidity compared to TURP. Randomised controlled trials of higher quality, multicentre RCTs, and longer follow up periods are needed to evaluate B-TUVP in comparison to TURP.

Summary of evidence	**LE**
Monopolar TURP is the current standard surgical procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO.	1
Transurethral incision of the prostate shows similar efficacy and safety to M-TURP for treating moderate-to-severe LUTS secondary to BPO in men with prostates < 30 mL.	1
No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the re-operation rate is higher compared to M-TURP.	1
Bipolar TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable peri-operative safety profile.	1b
Bipolar TUVP and TURP have similar short-term efficacy.	1
Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1

The choice between TUIP and TURP should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively).	4

Recommendations	Strength rating
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	Strong
Offer bipolar- or monopolar-transurethral resection of the prostate (TURP) to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong
Offer bipolar transurethral vaporisation of the prostate as an alternative to monopolar TURP to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Weak

5.3.2 ***Open prostatectomy***

Mechanism of action: Open prostatectomy is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands (> 80-100 mL).

Efficacy: Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98% [330-334]. Efficacy is maintained for up to six years [335].

Two RCT-based meta-analyses evaluated the overall efficacy of OP vs. endoscopic enucleation of the prostate (EEP) for treating patients with large glands [336, 337]. The larger study included RCTs involving 758 patients [337]. Five RCTs compared OP with HoLEP [330, 331, 338] and four RCTs compared OP with EEP using bipolar circuitry [335, 339-341]. Open prostatectomy was performed via a transvesical approach in all RCTs. At 3-, 6-, 12- and 24-month follow-up, there were no significant differences in Q_{max} between EEP and OP. Post-void residual, PSA, IPSS and QoL score also showed no significant difference at 1-, 3-, 6- and 12-months. Furthermore, IIEF also showed no significant difference at 3-, 6- and 12- months. It was concluded that EEP appears to be an effective minimally invasive option for treating large prostates.

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [334]. Data from an Austrian nationwide study of two cohorts totalling 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days. The endourological re-intervention rates after primary OP were 0.9%, 3.0%, 6.0%, and 8.8%, at three months, one year, five years, and eight years, respectively. The respective incidence of re-TURP was 0.5%, 1.8%, 3.7% and 4.3%, respectively [281]. The estimated transfusion rate is about 7-14% [330, 333, 334, 336]. Long-term complications include transient urinary incontinence (up to 10%), BNC and urethral stricture (about 6%) [330-332, 336, 342].

Two recent RCT-based meta-analyses evaluated the overall safety of OP vs. EEP for treating patients with large glands [336, 337]. Operation time was significantly longer for EEP, due to the significantly longer operation time needed for HoLEP (no difference was detected between OP and EEP using bipolar circuitry). Catheterisation and hospitalisation time was significantly shorter with EEP whilst IIEF-5 showed no significant difference between OP and EEP at twelve months. Endoscopic enucleation of the prostate was also associated with fewer blood transfusions but there were no significant differences regarding other complications. It was concluded that EEP appears to be a minimally invasive option for treating large prostates.

Practical considerations: Open prostatectomy is the most invasive surgical method, but it is an effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium including a holmium laser or a bipolar system, OP is the surgical treatment of choice for men with prostates > 80 mL.

Summary of evidence	LE
Open prostatectomy is an effective and durable procedure for the treatment of LUTS/BPO but it is the most invasive surgical method.	1b
Endoscopic enucleation of the prostate is an effective minimally invasive alternative for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1
Endoscopic enucleation of the prostate achieves similar short- and mid-term efficacy to OP.	1
Endoscopic enucleation of the prostate has a more favourable peri-operative safety profile compared with OP.	1
Open prostatectomy or EEP such as holmium laser or bipolar enucleation of the prostate are the first choice of surgical treatment in men with a substantially enlarged prostate and moderate-to-severe LUTS.	1

Recommendation	Strength rating
Offer open prostatectomy in the absence of endoscopic enucleation to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong

*5.3.3 **Laser treatments of the prostate***

5.3.3.1 Holmium laser enucleation and holmium laser resection of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis [343].

Efficacy: Meta-analyses of trials on HoLEP vs. TURP found that symptom improvement was comparable [344] and even superior with HoLEP [278, 344, 345]. One RCT comparing HoLEP with TURP in a small number of patients with a seven year follow-up found that the functional long term results of HoLEP were comparable with TURP [346]. Another meta-analysis demonstrated the superiority of HoLEP when compared to TURP with regards to post-operative Q_{max} [278]. A retrospective study of HoLEP with the longest follow-up of up to ten years (mean 62 months) reported durable functional results with low re-operation rates [347]. Randomised controlled trials indicate that HoLEP is as effective as OP for improving micturition in large prostates [330, 331], with similar improvement regarding Q_{max}, IPSS score and re-operation rates after five years [278, 330]. These findings are supported by two meta-analyses [336, 337].

Tolerability and safety: Compared to TURP, HoLEP has shorter catheterisation and hospitalisation times [348, 349]. Three meta-analyses found that HoLEP has shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [344, 345, 350]. In a meta-analysis, no significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress urinary incontinence (1.5% vs. 1.5%), and re-intervention (4.3% vs. 8.8%) [351]. Holmium laser enucleation of the prostate is superior to OP for blood loss, catheterisation and hospitalisation time [330, 331].

Holmium laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications [352]. However, current limitations include: a lack of RCTs; limited data on short- and mid-term complications and bridging therapy; data presentation does not allow for separate interpretation of either of the two substantially different topics of antiplatelet (AP) and anticoagulant (AC) therapy. No significant differences in pre-operative characteristics were found between 116 patients who did and 1,558 patients who did not receive AC/AP therapy [352]. Intra-operative characteristics showed shorter enucleation time (51 minutes vs. 65 minutes) for patients under AC/AP vs. no AC/AP, respectively. Post-operative outcomes were comparable except for length of hospital stay (27.8 hrs vs. 24 hrs) and duration of continuous bladder irrigation (15 hrs vs. 13.5 hrs) with both in favor of no AC/AP. No difference was seen between the cohorts for post-operative haemoglobin drop or transfusion rate. With regard to surgical revision two patients (1.9%) in the AC/AP cohort vs. ten patients (0.7%) in the no AC/AP cohort required clot evacuation [352]. Another study of 160 patients on single or dual anti-platelet therapy, who were part of a larger study of > 1000 patients, showed that HoLEP was as effective in patients on anti-platelet therapy with no significant difference in complication rates [353].

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP/OP [331, 354, 355]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP. Data have shown that ejaculation and orgasm perception are the two most impacted domains after HoLEP [356]. Attempts to maintain ejaculatory function with HoLEP have been reported to be successful in up to 46.2% of patients [357].

Practical considerations: HoLEP requires experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [358, 359]. Mentorship programmes are advised to improve surgical performance from both an institutional and personal learning curve perspective [360, 361]. With the advent of HoLEP and the fact that no relevant publications on HoLRP have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.3.1.1 Summary of evidence and recommendations for HoLEP

Summary of evidence	LE
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates higher haemostasis and intra-operative safety when compared to TURP and OP. Peri-operative parameters like catheterisation time and hospital stay are in favour of HoLEP.	1a

Laser enucleation of the prostate using Ho:YAG laser (HoLEP) did not negatively affect erectile function.	1a
The long-term functional results of HoLEP are comparable to OP.	1a

Recommendation	Strength rating
Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate or open prostatectomy.	Strong

5.3.3.2 532 nm ('Greenlight') laser vaporisation of the prostate

Mechanism of action: The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue. Three "Greenlight" lasers exist, which differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each. The standard Greenlight device is the 180-W XPS laser, but the majority of evidence is published with the former 80-W KTP or 120-W HPS (LBO) laser systems.

Efficacy and safety: A meta-analysis of the nine available RCTs comparing photoselective vaporisation of the prostate (PVP) using the 80-W and 120-W lasers with TURP was performed in 2012 [362]. No differences were found in Q_{max} and IPSS between 80-W PVP and TURP, but only three RCTs provided sufficient twelve month data to be included in the meta-analysis [363-365]. Another meta-analysis from 2016, of four RCTs including 559 patients, on the 120-W laser, demonstrated no significant difference in functional and symptomatic parameters at 6-, 12-, and 24-month follow-up when compared to TURP [366].

The 180-W XPS laser is non-inferior to TURP in terms of IPSS, Q_{max}, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. The 180-W XPS laser prostatectomy is superior to TURP in terms of catheterisation time, length of hospital stay and time to stable health status [367].

The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 months and showed a comparable improvement in IPSS, Q_{max}, and PVR [368]. The re-operation rate was significantly higher after PVP (11% vs. 1.8%; p = 0.04) [368]. Similar improvements in IPSS, QoL, Q_{max}, or urodynamic parameters were reported from two RCTs with a maximum follow-up of 24 months [364, 369].

The only available RCT for the 180-W laser reported efficacy and safety outcomes similar to TURP with stable results at 24 months follow-up; however, there was a higher retreatment rate after 24 months in the PVP arm [367].

One RCT comparing HoLEP to PVP, in patients with prostates > 60 mL, showed comparable symptom improvement, but significantly higher flow rates and lower PVR volume after HoLEP at short-term follow-up; in addition, PVP showed a 22% conversion rate to TURP [370].

Tolerability and safety: A meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time, but shorter catheterisation time and length of hospital stay after PVP [278]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis [278]. In a meta-analysis including trials with the 120-W laser, patients in the PVP group demonstrated significantly lower transfusion rates, shorter catheterisation time and shorter duration of hospital stay compared to TURP. Re-operation rates and operation time were in favour of TURP. No significant differences were demonstrated for treatment for urethral stricture, BNC, incidence of incontinence and infection [366].

According to the Goliath Study, 180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications. Re-operation free survival during 24 months follow up was comparable between the TURP-arm and the 180-W XPS laser-arm [367].

Based mostly on case series the 80-,120- and 180-W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [371-374]; however, patients under anticoagulation therapy were either excluded from or represented a very small sample in currently available RCTs. In one study, anticoagulant patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [374]. In contrast, another retrospective study focusing on the 180-W LBO laser did not find any significant differences between patients receiving or not receiving anticoagulants [375]. A retrospective study of a mixed cohort of patients, treated with 80-W KTP PVP and 120-W LBO HPS, revealed that delayed gross haematuria was common in patients (33.8%) during an average follow-up of 33 months [376]. Of these 8.5% presented in the emergency department, 4.8% needed hospitalisation, and surgical revision was required in 4.5%. Multivariate analysis revealed that the odds of bleeding increased with prostate size longer follow-up and anticoagulant use and decreased with increasing age and use of a 5-ARIs

[376]. Available data are further hampered by the absence of details about anticoagulation management in the peri-operative setting (i.e. interruption, bridge or continuation). A retrospective review of a database of patients undergoing 180-W PVP, without interruption of anticoagulation therapy, had a 30.5% rate of peri-operative adverse events with a significant occurrence of high grade Clavien Dindo events [377]. Having significantly more comorbidities, this group of patients also had significantly longer lengths of hospital stay and catheterisation time.

Safety in patients with urinary retention, impaired detrusor contractility, elderly patients or prostates > 80 mL was shown in various prospective short-term non-randomised trials. No RCT including prostates > 100 mL has been reported; therefore, comparison of retreatment rates between prostate volumes of different sizes is not possible [378-380].

An RCT with twelve months follow-up reported a retrograde ejaculation rate of 49.9% following PVP with an 80-W laser vs. 56.7% for TURP, there was no impact on erectile function in either arm of the trial [381]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [382, 383]. However, IIEF-5 scores were significantly decreased at 6-, 12-, and 24- months in patients with pre-operative IIEF-5 greater than 19 [384].

Practical considerations: The 180-W XPS represents the current standard of generators for PVP; however, the number and quality of supporting publications are low, especially for large glands (> 100 mL), with no long-term follow-up.

5.3.3.2.1 Summary of evidence and recommendations for 532 nm ('Greenlight') laser vaporisation of prostate

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 80-W KTP and the 120-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay are in favour of PVP, whereas operation time and risk of re-operation are in favour of TURP. Short-term results for the 80-W KTP laser and mid-term results for the 120-W LBO laser were comparable to TURP.	1a
Laser vaporisation of the prostate using the 180-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay were in favour of PVP, whereas operation time was in favour of TURP. Short- to mid-term results are comparable to TURP.	1b
Laser vaporisation of the prostate using the 80-W KTP and 120-W LBO lasers seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy.	2
Laser vaporisation of the prostate using the 180-W LBO laser seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy; however, the level of available evidence is low.	3

Recommendations	**Strength rating**
Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate (TURP).	Strong
Offer 120-W 532-nm Lithium Borat (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 180-W 532-nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer laser vaporisation of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL.	Weak

5.3.3.3 Diode laser treatment of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318, and 1,470 nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [385].

Efficacy: Two RCTs for 120-W 980 nm diode laser vaporisation vs. M-TURP are available [386, 387]. The first RCT with 24 month follow-up reported equal symptomatic and clinical parameters at one and six months. However, at 12- and 24-months the results were significantly in favour of TURP, repeat TURP was more frequent in the diode laser group [386]. The second RCT reported equivocal results for both interventions at 3-month follow-up [387].

Three RCTs with a twelve month follow-up compared 980 nm diode laser enucleation with bipolar enucleation and found no significant difference with regard to clinical outcome [388-390]. One small RCT with a six month follow-up comparing laser enucleation using a 1,318 nm diode laser with B-TURP reported similar efficacy [391]. An RCT of 154 patients undergoing 1,470 nm diode laser enucleation of the prostate (DiLEP) or plasmakinetic resection of the prostate (PKRP) revealed no difference in post-operative IPSS, QoL, Q_{max}, and PVR, however DiLEP had decreased risk of hemorrhage, operative time, bladder irrigation time, catheterisation duration, and hospital stay [392].

A one year RCT comparing transurethral endoscopic enucleation of the prostate using a 980 nm diode laser vs. bipolar plasmakinetic enucleation (BEEP) for the treatment of LUTS/BPO in 111 patients showed equivalence for both procedures. Post-operative results for DiLEP were comparable to BEEP regarding Q_{max} (28.0 ± 7.0 vs. 28.1 ± 7.2 mL/s) and IPSS (3.0 ± 2.2 vs. 2.9 ± 2.6) at twelve months. There was also no significant difference in tissue removal (71.8% vs. 73.8%) and complications at twelve months [390].

Tolerability and safety: Published studies on 980 nm laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [393, 394]. In a number of studies, a high rate of post-operative dysuria was reported [386, 393-395]. In an RCT reflecting on peri-operative and post-operative complications no significant differences were demonstrated for clot retention, re-catheterisation, UUI and UTI [386]. Moreover, for late complications no significant differences could be demonstrated for re-operation rate, urethral stricture, bladder neck sclerosis, *de novo* sexual dysfunction and mean time of dysuria [386].

Fibre modifications can potentially reduce surgical time [396]. Early publications on diode vaporisation reported high re-operation rates (8-33%) and persisting stress urinary incontinence (9.1%) [386, 393-395]. In contrast, the four RCTs on diode laser enucleation showed that blood loss, hospitalisation and catheterisation time were in favour of diode laser enucleation, with equivalent clinical outcome for either bipolar enucleation [388-390] or TURP [391] during short-term follow-up.

Practical considerations: Diode laser vaporisation leads to similar improvements in clinical and symptomatic parameters during short-term follow-up and provides good haemostatic properties. Diode laser enucleation seems to offer similar efficacy and safety when compared to either TURP or bipolar enucleation. Based on the limited number, mainly low quality RCTs, and controversial data on the retreatment rate, results for diode laser vaporisation and enucleation should be evaluated in further higher quality RCTs.

5.3.3.3.1 Summary of evidence and recommendations for diode laser treatment of the prostate

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 120-W 980 nm laser demonstrated high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay were in favour of diode lasers. Short-term results are comparable to TURP.	1b
In a number of studies severe post-operative complications such as severe storage symptoms or persisting incontinence occurred with laser vaporisation of the prostate using the 120-W 980 nm diode laser.	3
Laser enucleation of the prostate using the 980 nm laser showed comparable efficacy to bipolar endoscopic enucleation in the short term. Peri-operative parameters like blood loss, catheterisation time and hospital stay were in favour of diode enucleation.	1b
Laser vaporisation using the 120-W 980 nm diode laser seems to be safe with regard to haemostasis in patients receiving anticoagulant therapy.	3

Recommendations	**Strength rating**
Offer 120-W 980 nm diode laser vaporisation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to transurethral resection of the prostate (TURP).	Weak
Offer 120-W 980 nm diode laser or 1,318 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to TURP or bipolar enucleation.	Weak

5.3.3.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG)

Mechanism of action: In the Tm:YAG laser, a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [385, 397]. Different applications, ranging from vaporisation (ThuVAP), vaporesection (ThuVARP), and enucleation (ThuVEP vapoenucleation i.e. excising technique/ThuLEP blunt thereby primarily anatomical enucleation with Tm:YAG support) are published [398-400].

Efficacy: Two meta-analyses compared ThuVARP with TURP. The first meta-analysed data from three RCTs, one quasi-RCT and two case control studies. Studies with mono- or bipolar-TURP were included. Both treatments were efficacious with a difference in IPSS improvement in favour of ThuVARP at twelve months [401]. The second meta-analysis included data from six RCTs and three retrospective studies with different follow-ups and with only B-TURP as the comparator. There was no significant difference in terms of IPSS, Q_{max}, and PVR between the two therapies [402]. An RCT with a four year follow-up comparing ThuVARP to M-TURP, showed comparable efficacy and favourable re-operation rates in the ThuVaRP group [403]. Yang *et al*. demonstrated no significant difference with regard to symptoms and voiding parameters at one, three and five years follow-up [404]. A prospective multicentre study on ThuVARP, including 2,216 patients, showed durable post-operative improvement in IPSS, QoL, Q_{max}, and PVR for the entire eight years of follow-up [405].

There are mainly prospective case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [406-409]. One RCT with eighteen months follow up showed comparable outcomes in both arms for ThuLEP and HoLEP [410]. Furthermore, ThuLEP and bipolar enucleation were compared in one RCT with twelve months follow-up. The outcome showed no difference with regard to efficacy whilst the decrease in haemoglobin level and catheter time were significantly lower for ThuLEP [411]. An RCT with five years follow-up compared ThuLEP with bipolar TURP. No difference was found between the two procedures in terms of Q_{max}, IPSS, PVR, and QoL; however, the attrition rate was 50% at five years [404].

Tolerability and safety: ThuVARP, ThuLEP and ThuVEP show high intra-operative safety in RCTs [403, 412-414], as well as in case series in patients with large prostates [406] and anticoagulation or bleeding disorders [407, 415, 416]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [412, 414, 417, 418]. These results were confirmed in the two meta-analyses comparing ThuVARP with TURP [401, 402]. The rate of post-operative urethral strictures after ThuVARP was 1.9%, the rate of BNC was 1.8%, and the re-operation rate was 0-7.1% during follow-up [412, 417, 419]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall retreatment rate was 3.4% (mean follow-up 16.5 months) [399]. No urethral and bladder neck strictures after ThuLEP were reported during the eighteen months follow-up [413]. Recently, a study focusing on post-operative complications after ThuVEP reported adverse events in 31% of cases, with 6.6% complications greater then Clavien grade 2 [420]. One case control study on ThuVEP with 48-month follow-up reported long-term durability of voiding improvements and overall re-operation rates of 2.4% [415]. Two studies (one case control, one RCT vs. TURP) addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [421, 422]. Another case control study evaluated the impact of thulium laser prostatectomy (resection and vapoenucleation) on erectile function. The IIEF-5 scores dropped significantly during the first three post-operative months and then gradually increased returning to pre-operative levels at the twelve month follow-up assessment [423].

Urethral stricture and BNC was 2.6% and 1.6%, respectively in a prospective multicentered study of ThuVARP. Persistent stress incontinence was found in 0.1% whilst, re-operation due to BPH recurrence was required in 1.2% patients [405].

In two RCTs on ThuLEP vs. TURP [424], one RCT on ThuLEP vs. bipolar enucleation [411] and one RCT on ThuLEP vs. HoLEP [410], ThuLEP appeared to be superior with regard to intra-operative haemostasis. The same was demonstrated for ThuVEP vs. TURP in one RCT [414]; however, in two further RCTs on ThuLEP vs. HoLEP no significant difference could be demonstrated at 6, 12 and 18 months follow up [413, 425].

Practical considerations: As a limited number of RCTs and only a few studies with long-term follow-up support the efficacy of thulium laser prostatectomy, there is a need for ongoing investigation of the technique.

5.3.3.4.1 Summary of evidence and recommendations for the use of the Thulium: yttrium-aluminium-garnet laser (Tm:YAG)

Summary of evidence	**LE**
Laser enucleation of the prostate using either vapoenucleating (ThuVEP) or laser assisted blunt technique (ThuLEP) demonstrates high intra-operative safety with regard to haemostatic properties when compared to TURP. Short-term results are comparable to TURP.	1b
Laser vapoenucleation of the prostate using a Tm:YAG laser (ThuVEP) seems to be safe in patients receiving anticoagulant or antiplatelet therapy.	2b
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) demonstrates high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay are in favour of thulium lasers. Long-term results are similar to TURP.	1a

Recommendations	Strength rating
Offer laser enucleation of the prostate using Tm:YAG vapoenucleation (ThuVEP) and Tm:YAG laser assisted anatomical enucleation (ThuLEP) to men with moderate-to-severe LUTS as alternatives to TURP and holmium laser enucleation (HoLEP).	Weak
Offer ThuVEP to patients receiving anticoagulant or antiplatelet therapy.	Weak
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Strong
Offer ThuVARP to patients receiving anticoagulant or antiplatelet therapy.	Weak

5.3.4 ***Prostatic urethral lift***

Mechanism of action: The prostatic urethral lift (PUL) represents a novel minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance (Urolift®) resulting in an opening of the prostatic urethra that leaves a continuous anterior channel through the prostatic fossa extending from the bladder neck to the verumontanum.

Efficacy: In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%) [426-431]. Prostatic urethral lift was initially evaluated vs. sham in a multicentre study with one [428] three [432] and five [433] years follow-up. The primary endpoint was met at three months with a 50% reduction in IPSS. In addition, Q_{max} increased significantly from 8.1 to 12.4 mL/s compared to baseline at three months and this result was confirmed at twelve months. The difference in clinical response for Q_{max} between both groups was of statistical significance. A relevant benefit with regard to PVR was not demonstrated compared to baseline or sham. At three years, average improvements from baseline were significant for total IPSS, QoL, Q_{max} and individual IPSS symptoms. There were no *de novo*, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL. Improvements in IPSS, QoL, BPH impact index (BPHII), and Q_{max} were durable throughout the five years with improvement rates of 36%, 50%, 52%, and 44%, respectively. The re-treatment rate was 13.6% over five years. Adverse events were mild to moderate and transient. Sexual function was stable over five years with no *de novo*, sustained erectile, or ejaculatory dysfunction.

Another RCT of 80 patients was conducted in three European countries, comparing PUL to TURP. At twelve months, IPSS improvement was -11.4 for PUL and -15.4 for TURP. There was no retrograde ejaculation among PUL patients, while 40% of TURP patients lost the ability to ejaculate. Surgical recovery was measured using a validated instrument and confirmed that recovery from PUL is more rapid and more extensive in the first three to six months [434]. However, TURP resulted in much greater improvements in Q_{max} after twelve months compared to PUL. At 24 months, significant improvements in IPSS, IPSS QoL, BPHII, and Q_{max} were observed in both arms. Change in IPSS and Q_{max} in the TURP arm were superior to the PUL arm [435]. Improvements in QoL and BPHII score were not statistically different between the study arms. Prostatic urethral lift resulted in superior quality of recovery and ejaculatory function preservation. Ejaculatory function and bother scores did not change significantly in either treatment arm.

In a meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS, Q_{max}, and QoL [431]. Sexual function was preserved with a small improvement estimated at twelve months.

Tolerability and safety: The most common complications reported post-operatively included haematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence (3.6-16%), and UTI (2.9-11%) [428, 431-433]. Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure.

Prostatic urethral lift seems to have no significant impact on sexual function. Evaluation of sexual function as measured by IIEF-5, Male Sexual Health Questionnaire-Ejaculatory Dysfunction, and Male Sexual Health Questionnaire-Bother in patients undergoing PUL showed that erectile and ejaculatory function were preserved [426-430].

Practical considerations: An obstructed/protruding middle lobe cannot be effectively treated, and the effectiveness in large prostate glands has not been shown yet. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques.

Summary of evidence	LE
Prostatic urethral lift improves IPSS, Q_{max} and QoL; however, these improvements are inferior to TURP at 24 months.	1b

Prostatic urethral lift has a low incidence of sexual side effects.	1b
Patients should be informed that long-term effects including the risk of retreatment have not been evaluated.	4

Recommendation	Strength rating
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strong

*5.3.5 **Intra-prostatic injections***

Mechanism of action: Various substances have been injected directly into the prostate in order to improve LUTS, these include Botulinum toxin-A (BoNT-A), fexapotide triflutate (NX-1207) and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [436]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data associates apoptosis-induced atrophy of the prostate with both drugs [436].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [437, 438]. A recent SR and meta-analysis showed no differences in efficacy compared with placebo and concluded that there is no evidence of clinical benefits in medical practice [439]. The positive results from Phase II-studies have not be confirmed in Phase III-trials for PRX302 [440, 441]. NX-1207 was evaluated in two multicentre placebo controlled double-blind randomised parallel group trials including a total of 995 patients with a mean follow-up of 3.6 years, IPSS change from baseline was significantly higher and AUR rate was significantly reduced in the treatment arm. The authors concluded that NX-1207 is an effective transrectal injectable for long-term treatment for LUTS and that treated patients have reduced need for further intervention [442].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [436]. A recent SR and meta-analysis showed low incident rates of procedure-related adverse events [439]. Two multicentre placebo controlled double-blind randomised parallel group trials with long-term follow up evaluating NX-1207 detected no significant safety differences between the study arms [442].

Practical considerations: Although experimental evidence for compounds such as BoNT-A and PRX302 were promising for their transition to clinical use positive results from Phase II-studies have not be confirmed in Phase III-trials. Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results of NX-1207

Summary of evidence	LE
Results from clinical trials have shown no clinical benefits for BoNT-A compared to placebo for the management of LUTS due to BPO.	1a
Results from clinical trials have shown clinical benefits for NX-1207 compared to placebo for the management of LUTS due to BPO.	1b

Recommendation	Strength rating
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strong

*5.3.6 **Techniques under investigation***

Recommendations on new interventions will only be included in the Guidelines once supported by RCTs looking at both efficacy and safety, with adequate follow-up (> 3 yrs), and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [443]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include (1) proof of concept, (2) RCTs on efficacy and safety, as well as (3) cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [443]. The panel will assess the quality of all RCTs and if they do not meet the standard required the intervention will continue to have no recommendation i.e. a RCT does not guarantee inclusion in the Guidelines. In the current Guideline, a recommendation is given for Aquablation and Prostatic Artery Embolisation (PAE); however, these two techniques should still be considered as under investigation in order to better define their position in the armamentarium of invasive therapies for BPO and to better define the subgroups of patients who will benefit most from them.

5.3.6.1 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [444], while the first RASP was reported in 2008 [445]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP. An extraperitoneal approach is mostly used for LSP, while a transperitoneal approach is mostly used for RASP.

Efficacy: A SR and meta-analysis showed that in 27 observational studies including 764 patients, the mean increase in Q_{max} was 14.3 mL/s (95% CI 13.1-15.6), and the mean improvement in IPSS was 17.2 (95% CI 15.2-19.2) [446]. Mean duration of operation was 141 minutes (95% CI 124-159), and the mean intra-operative blood loss was 284 mL (95% CI 243-325). One hundred and four patients (13.6%) developed a surgical complication. In comparative studies to OP, length of hospital stay, length of catheter use and estimated blood loss were significantly lower in the MISP group, while the duration of operation was longer than in OP. There were no differences in improvements in Q_{max}, IPSS and peri-operative complications between both procedures.

Two recent retrospective series on RASP were not included in the meta-analysis which confirm these findings [447, 448]. The largest retrospective series reports 1,330 consecutive cases including 487 robotic (36.6%) and 843 laparoscopic (63.4%) simple prostatectomy cases. The authors confirm that both techniques can be safely and effectively done in selected centres [447].

Tolerability and safety: In the largest series, the post-operative complication rate was 10.6% (7.1% for LSP and 16.6% for RASP), most of the complications being of low grade. The most common complications in the RASP series were haematuria requiring irrigation, UTI and AUR; in the LSP series, the most common complications were UTI, ileus and AUR. In the most recent, largest comparative analysis of robotic vs. open simple prostatectomy (OSP) for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OSP demonstrated a significant shorter average length of stay (1.5 vs. 2.6 days), but longer mean operative time (161 vs. 93 minutes). The robotic approach was also associated with a lower estimated blood loss (339 vs. 587 mL). Improvements in maximal flow rate, IPSS, QoL, PVR and post-operative PSA levels were similar before and after surgery for both groups. There was no difference in complications between the groups [449].

Practical considerations: Minimal invasive simple prostatectomy seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [446]. However, most studies are of a retrospective nature. High quality studies are needed to compare the efficacy, safety, and hospitalisation times of MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated.

Summary of evidence	**LE**
Minimal invasive simple prostatectomy is feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

5.3.6.2 (i)TIND

Basic principle: The iTIND is a device designed to remodel the bladder neck and the prostatic urethra and is composed of three elongated struts and an anchoring leaflet, all made of nitinol. Under direct visualisation the iTIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis in defined areas of interest. The iTIND is left in position for five days. The resulting incisions may be similar to a Turner Warwick incision. In an outpatient setting the device is removed by standard urethroscopy.

Efficacy: A single-arm, prospective study of 32 patients with a follow up of three years was conducted to evaluate feasibility and safety of the procedure [450]. The change from baseline in IPSS, QoL score and Q_{max} was significant at every follow-up time point [451].

Tolerability and safety: The device has been reported to be well tolerated by all patients. Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%), and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up period.

Practical considerations: Randomised controlled trials comparing iTIND to a reference technique are ongoing.

5.3.6.3 Aquablation – image guided robotic waterjet ablation: AquaBeam

Basic principle: AquaBeam uses the principle of hydro-dissection to ablate prostatic parenchyma while sparing collagenous structures like blood vessels and the surgical capsule. A targeted high velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal ultrasound guidance. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [452].

Efficacy: In a double-blind, multicentre, prospective RCT 181 patients were randomised to TURP or Aquablation [453]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes, p = 0.2752), but resection time was lower for Aquablation (4 vs. 27 minutes, p < 0.0001). At six months patients treated with Aquablation and TURP experienced large IPSS improvements (-16.9 and -15.1, respectively). The study non-inferiority hypothesis was satisfied (p < 0.0001). Larger prostates (50-80 mL) demonstrated a more pronounced benefit. At one year follow-up, mean IPSS reduction was 15.1 in the Aquablation group and 15.1 in the TURP group with a mean percent reduction in IPSS score of 67% in both groups. Ninety three percent and 86.7% of patients had improvements of at least 5 points from baseline, respectively. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was reported between both groups. One TURP subject (1.5%) and three Aquablation subjects (2.6%) underwent re-TURP within one year of the study procedure [454]. In a cohort study of 101 men with a prostate volume between 80-150 mL mean IPSS improved from 23.2 at baseline to 5.9 at six months. Improvement in IPSS, QoL, Q_{max} and reduction of PVR were also significant at six months. No secondary procedures for tissue removal occurred as of the six months [455].

Tolerability and safety: Aquablation was shown to be non-inferior to TURP (26% vs. 42%, p = 0.0149). Among sexually active men the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). There were no procedure-related adverse events after six months [454]. In patients with a prostate volume between 80-150 mL, bleeding related events were observed in fourteen patients (13.9%) of which eight (7.9%) occurred prior to discharge and six (5.9%) occurred within one month of discharge. Blood transfusions were required in eight (7.9%) patients, return to the theatre for fulguration in three (3.0%) patients, and both transfusion and fulguration in two patients (2.0%). Ejaculatory dysfunction occurred in 19% of sexually active men [455].

Practical considerations: During short-term follow-up, Aquablation provides non-inferior functional outcomes compared to TURP in patients with LUTS and a prostate volume between 30-80 mL. Longer term follow up is necessary to assess the clinical value of Aquablation.

Summary of evidence	**LE**
Aquablation appears to be as effective as TURP both subjectively and objectively; however, there are still some concerns about the best methods of achieving post-treatment haemostasis.	1b

Recommendations	**Strength rating**
Offer Aquablation* to patients with moderate-to-severe LUTS and prostates between 30-80 mL as an alternative to TURP.	Weak
Inform patients about the risk of bleeding and the lack of long-term follow up data.	Strong

** Aquablation remains under investigation*

5.3.6.4 Convective water vapour energy (WAVE) ablation: The Rezum system

Basic principle: The Rezum system uses radiofrequency power to create thermal energy in the form of water vapour, which in turn deposits the stored thermal energy when the steam phase shifts to liquid upon cell contact. The steam disperses through the tissue interstices and releases stored thermal energy onto prostatic tissue effecting cell necrosis. The procedure can be performed in an office based setting. Usually, one to three injections are needed for each lateral lobe and one to two injections may be delivered into the median lobe.

Efficacy: In a multicentre, randomised, controlled study 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment (rigid cystoscopy with imitated treatment sounds) [456]. At three months relief of symptoms, measured by a change in IPSS and Q_{max} were significantly improved and maintained compared to the sham arm, although only the active treatment arm was followed up to twelve months. No relevant impact was observed on PVR. Quality of life outcome was significantly improved with a meaningful treatment response of 52% at twelve months (p < 0.0001). Further validated objective outcome measures such as BPHII, Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and International Continence Society Male Item Short Form Survey for male incontinence

demonstrated significant amelioration of symptoms at three months follow-up with sustained efficacy throughout the study period of twelve months. The reported two year results in the Rezum cohort arm of the same study and the recently reported four year results confirmed durability of the positive clinical outcome after convective water vapour energy ablation [457, 458]. Surgical retreatment rate was 4.4% over four years [458].

Tolerability and safety: Safety profile was favourable with adverse events documented to be mild to moderate and resolving rapidly. Preservation of erectile and ejaculatory function after convective water vapour thermal therapy was demonstrated utilising validated outcome instruments such as IIEF and Male Sexual Health Questionnaire-Ejaculation Disorder Questionnaire [456].

Practical considerations: Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapour energy treatment.

5.3.6.5 Prostatic artery embolisation

Basic principle: Prostatic artery embolisation can be performed as a day procedure under local anaesthesia with access through the femoral or radial arteries. Digital subtraction angiography displays arterial anatomy and the appropriate prostatic arterial supply is selectively embolised to effect stasis in treated prostatic vessels. Different techniques have been used for PAE. Atherosclerosis, excessive tortuosity of the arterial supply and the presence of adverse collaterals are anatomical obstacles for the technical approach. Cone beam computed tomography can help identify prostatic arteries and prevent off-target embolisation particularly in patients with challenging anatomical configurations [459].

Efficacy: In a prospective multi-centre matched cohort study of 216 PAE patients and 89 TURP patients, PAE achieved a 10-point improvement in primary outcome of IPSS at twelve months compared with a 15-point improvement with TURP and -3.0 in QoL compared with -4.0 with TURP. There was a 28% reduction in prostate volume with PAE [460].

Another retrospective review of 93 patients undergoing PAE for prostates > 80 mL recorded significant changes in prostate volume 141 mL to 98 mL (-31%), IPSS 22 to 7 (-68%) and QoL 4.4 to 1.3 (-71%), Q_{max} 7.7 to 12.8 mL/s (+66%) and PVR 196 mL to 61 mL (-69%) at twelve months. The authors concluded that PAE may be an alternate treatment for patients for whom conventional surgical options are limited or associated with significant morbidity [461].

Two prospective RCTs were conducted for direct comparison of PAE with TURP [462, 463]. Both studies observed significant treatment outcomes for both procedures as compared to baseline values, but TURP was superior when considering urodynamic parameters such as Q_{max} and PVR. Improvement of LUTS as determined by IPSS and QoL was slightly more pronounced after TURP and reduction of prostate volume was significantly more efficient after TURP than PAE.

Another RCT comparing PAE with TURP in 99 patients (48 vs. 51) showed a mean reduction in IPSS from baseline to twelve weeks of –9.23 points after PAE and –10.77 points after TURP. At twelve weeks, PAE was less effective than TURP regarding improvements in Q_{max} (5.19 mL/s vs. 15.34 mL/s), PVR (–86.36 mL vs. –199.98 mL), prostate volume (–12.17 mL vs. –30.27 mL), and desobstructive effectiveness according to pressure flow studies (56% vs. 93%) shift towards less obstructive category; p = 0.003). For secondary outcomes, compared with PAE, procedural time was shorter for TURP, but in PAE patients bladder catheter indwelling time, and duration of hospital stay were significantly shorter [459].

A SR and meta-analysis of thirteen studies of 1,254 PAE patients between 2014 and 2017 showed IPSS improvement of 67%, QoL (64%) and prostate volume reduction of 26%. Quality of life, IPSS, prostate volume, PVR, & IIEF improvements were maintained at three years [464].

Tolerability and safety: In an earlier SR of comparative studies PAE resulted in more adverse events than TURP/OP (41.6% vs. 30.4%, p = 0.044). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%, p = 0.006) [465]. Non-comparative studies reported an improvement in IIEF after PAE (weighted mean difference 1.31, 95% CI: 0.82, 1.81).

Another RCT however, reported fewer adverse events occurred after PAE than after TURP (36 vs. 70 events; p = 0.003). For secondary outcomes, PAE showed favourable results in terms of blood loss [459]. A SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the post-operative complications rate between TURP and PAE [466]. Concerns still exist about non-target embolisation, reported in earlier studies [467]; however, more recent studies report less incidents [460, 468].

Practical considerations: A multidisciplinary team approach of urologists and radiologists is mandatory and patient selection should be done by urologists and interventional radiologists. The investigation of patients with LUTS to indicate suitability for invasive techniques should be performed by urologists only. This technically demanding procedure should only be done by an interventional radiologist with specific mentored training and expertise in PAE [469]. Patients with larger prostates (> 80 mL) may have the most to gain from PAE. The selection of LUTS patients who will benefit from PAE still needs to be better defined. Further data with medium- and long-term follow up are still required and comparison with other minimally invasive techniques would be valuable. However, current evidence of safety and efficacy of PAE appears adequate to support the use of this procedure for men with moderate-to-severe LUTS provided proper arrangements for consent and audit are in place; therefore, a recommendation has been given, but PAE remains under investigation.

Summary of evidence	**LE**
Prostatic artery embolisation is less effective than TURP at improving symptoms and urodynamic parameters such as flow rate.	1a
Procedural time is longer for PAE compared to TURP, but blood loss, catheterisation and hospitalisation time are in favour of PAE.	1b

Recommendations	**Strength rating**
Offer prostatic artery embolisation (PAE)* to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal objective outcomes compared with transurethral resection of the prostate.	Weak
Perform PAE only in units where the work up and follow up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strong

**PAE remains under investigation*

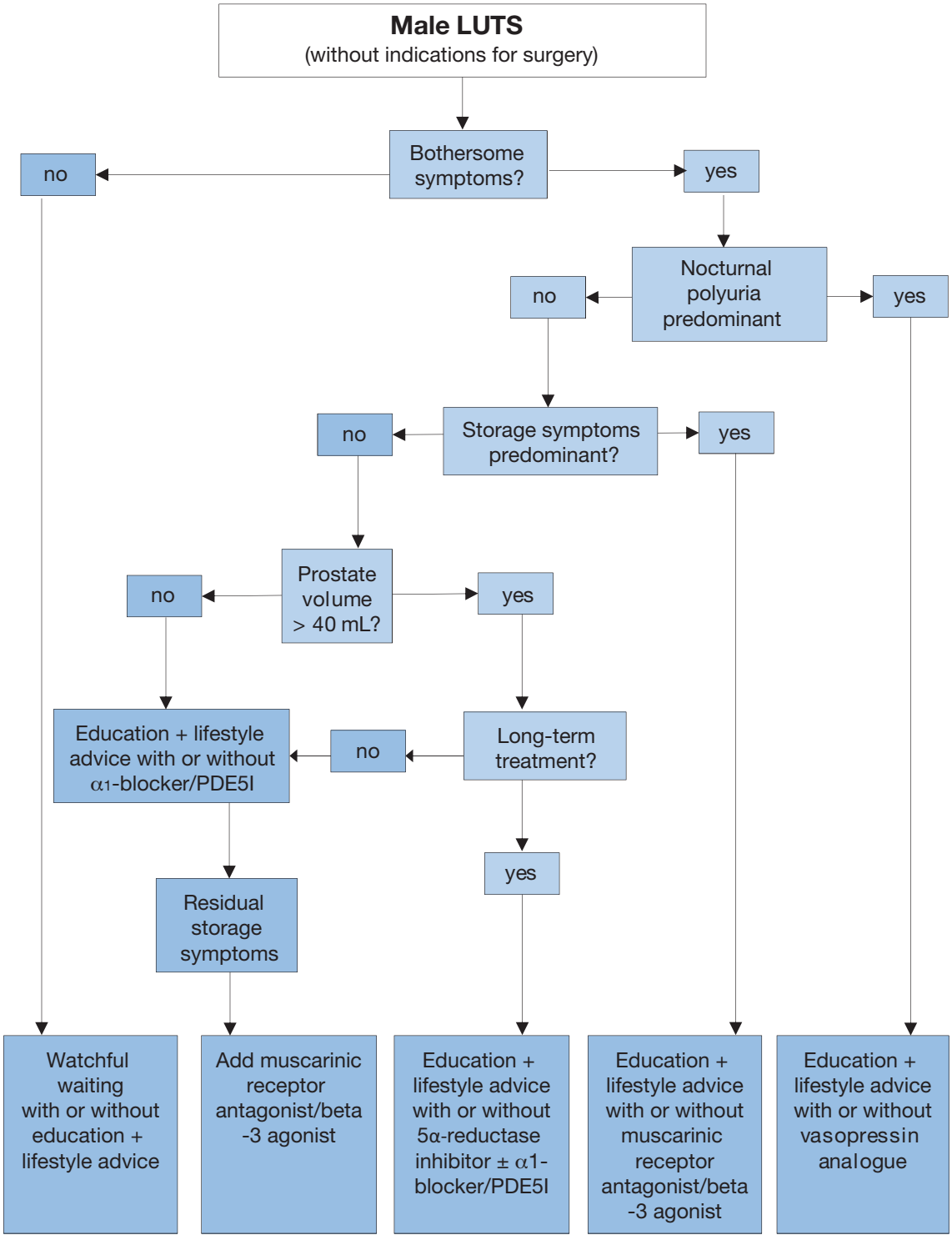
5.4 Patient selection

The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles. Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

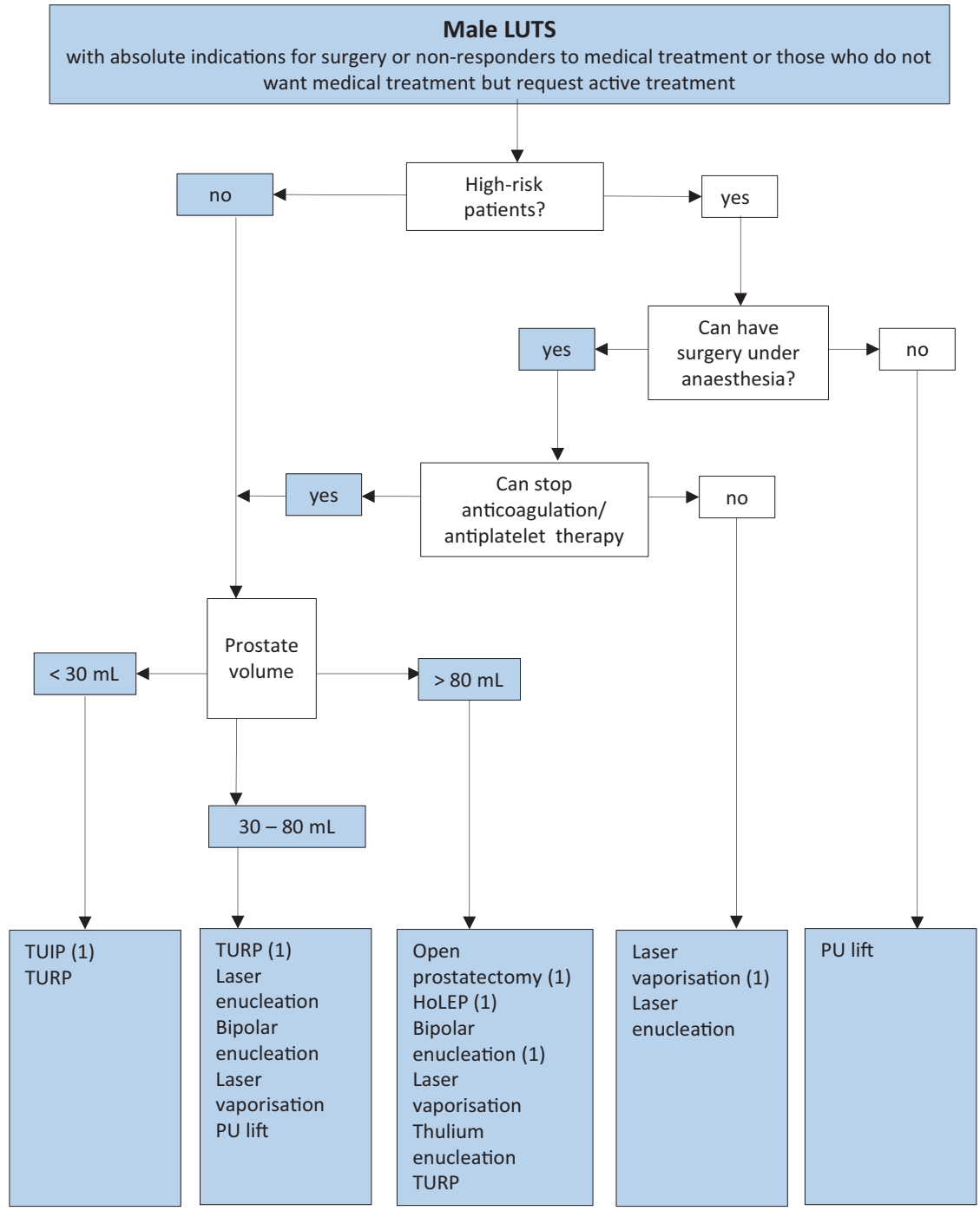
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches according to evidence-based medicine and the patient's profile is provided in Figure 4.

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation. Note that patients' preferences may result in different treatment decisions.



PDE5I = phosphodiesterase type 5 inhibitors.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart is stratified by the patient's ability to have anaesthesia, their cardiovascular risk and prostate size.



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation. Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate and PU = prostatic urethral.

5.5 Management of Nocturia in men with lower urinary tract symptoms

The following section reports a SR of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia [470].

Nocturia is defined as the complaint of waking at night to void [5]. It reflects the relationship between the amount of urine produced while asleep, and the ability of the bladder to store the urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), such as OAB and chronic pelvic pain syndrome. Nocturia can also occur in association with other forms of LUTD, such as BOO, but here it is debated whether the link is one of causation or simply the co-existence of two common conditions. Crucially, nocturia may have behavioural, sleep disturbance (primary or secondary) or systemic causes unrelated to LUTD (Table 2). Differing causes often co-exist and each has to be considered in all cases. Only where LUTD is contributory should nocturia be termed a LUTS.

Table 2: Categories of nocturia

CATEGORY	Disproportionate urine production (at all times, or during sleep)	Low volume of each void (at all times, or overnight)
Behavioural	Inappropriate fluid intake	"Bladder awareness" due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt output	"Bladder awareness" due to primary sleep disturbance
LUTD		Impaired storage function and increased filling sensation

*5.5.1 **Diagnostic assessment***

Evaluation is outlined in Figure 5;

1. Evaluate for LUTD according to the relevant guidelines. The severity and bother of individual LUTS should be identified with a symptom score, supplemented by directed questioning if needed. A validated bladder diary is mandatory.
2. Review whether behavioural factors affecting fluid balance and sleep are contributing.
3. Review of medical history and medications, including directed evaluation for key conditions, such as renal failure, diabetes mellitus, cardiac failure, and obstructive sleep apnoea. If systemic factors or sleep disorders are potentially important, consider involving appropriate medical expertise (see Figure 6). This is appropriate where a known condition is suboptimally managed, or symptoms and signs suggest an undiagnosed condition.

*5.5.2 **Medical conditions and sleep disorders Shared Care Pathway***

Causative categories for nocturia comprise [471]:

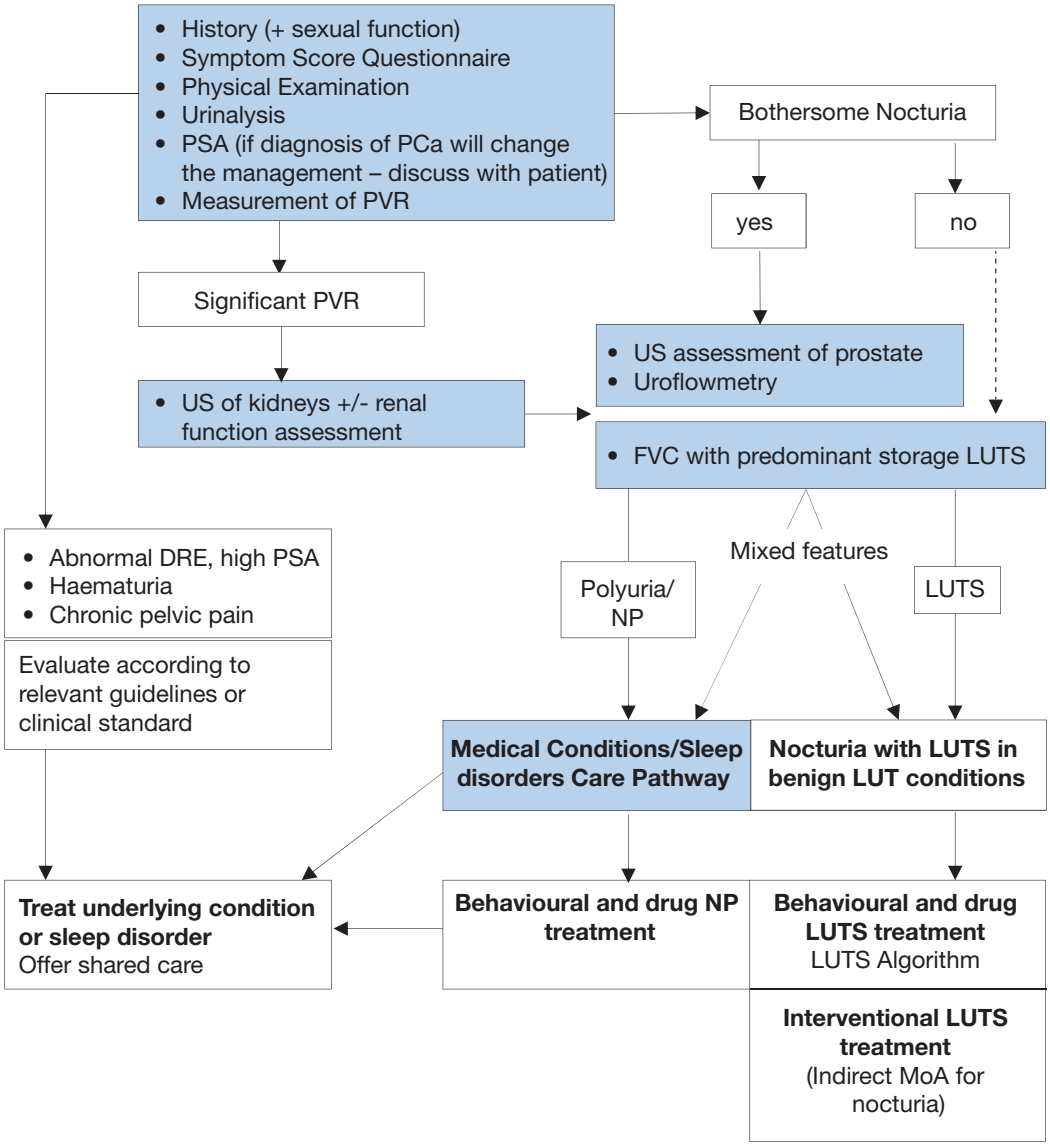
1. bladder storage problems;
2. 24-hour (global) polyuria (> 40 mL/kg urine output over a 24-hour period);
3. nocturnal polyuria (NP; nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [5]);
4. sleep disorders;
5. mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on: levels of free water, salt, other solutes and plasma oncotic pressure; endocrine regulation e.g. by antidiuretic hormone; natriuretic peptides; cardiovascular and autonomic control; renal function; neurological regulation, e.g. circadian regulation of the pineal gland, and renal innervation. As nocturia is commonly referred to the specialty without full insight into cause, the urologist must review the likely mechanisms underlying a presentation with nocturia and instigate review by relevant specialties accordingly. Thus, the managing urologist needs to evaluate nocturia patients in a context where additional medical expertise is available (Table 3). They should not proceed along any LUTD management pathway unless a causative link with LUTD is justifiably suspected, and systemic or sleep abnormalities have been considered.

In patients with non-bothersome nocturia, the medical evaluation (history and physical examination) should consider the possibility of early stages of systemic disease, and whether there is possibility of earlier diagnosis or therapy adjustment.

Some important potentially treatable non-urological causes of nocturia include; obstructive sleep apnoea (OSA), congestive cardiac failure, poorly controlled diabetes mellitus and medications (e.g. diuretics, or lithium).

Figure 5. Evaluation of Nocturia in non-neurogenic Male LUTS.



Assessment must establish whether the patient has polyuria, LUTS, a sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment with a frequency volume chart (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
FVC = frequency volume chart; DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound.

Table 3: Shared care pathway for nocturia, highlighting the need to manage potentially complex patients using relevant expertise for the causative factors.

UROLOGICAL CONTRIBUTION	SHARED CARE	MEDICAL CONTRIBUTION
Diagnosis of LUTD • Urological/LUTS evaluation • Nocturia symptom scores • Bladder diary		**Diagnosis of conditions causing NP** • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*
Conservative management Behavioural therapy • Fluid/sleep habits advice • Drugs for storage LUTS • (Drugs for voiding LUTS) • ISC/catherisation Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS	**Conservative management** • Antidiuretic • Diuretics • Drugs to aid sleep	**Management** • Initiation of therapy for new diagnosis • Optimised therapy of known conditions * Potential causes of polyuria NEPHROLOGICAL DISEASE • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE • Cardiac disease • Vascular disease ENDOCRINE DISEASE • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE • Obstructive sleep apnoea BIOCHEMICAL • Altered blood oncotic pressure

5.5.3 ***Treatment for Nocturia***

5.5.3.1 Antidiuretic therapy

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and control of urine production by binding to V2 receptors in the renal collecting ducts. Arginine vasopressin increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. Arginine vasopressin also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for treating nocturia/nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. It has been investigated for treating nocturia [472], with specific doses, titrated dosing, differing formulations, and options for route of administration. Most studies have short follow-up. Global interpretation of existing studies is difficult due to the limitations, imprecision, heterogeneity and inconsistencies of the studies.

A SR of randomised or quasi-randomised trials in men with nocturia found that desmopressin may decrease the number of nocturnal voids by -0.46 compared to placebo over short-term follow-up (up to three months); over intermediate-term follow-up (three to twelve months) there was a change of -0.85 in nocturnal voids in a substantial number of participants without increase in major adverse events [473].

Another SR of comparative trials of men with nocturia as the primary presentation and LUTS including nocturia or nocturnal polyuria found that antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep [470]. Adverse events include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients (1.3%), with one death. There were seventeen cases of hyponatraemia (3.2%) and seven of hypertension (1.3%). Headache was reported in 53 (10%) and nausea in fifteen (2.8%) [470]. Hyponatremia is the most important concern, especially in patients > 65 years of age, with potential life threatening consequences. Baseline values of sodium over 130 mmol/L have been used as inclusion criteria in some research protocols. Assessment of sodium levels must be undertaken at baseline, after initiation of treatment or dose titration and during treatment. Desmopressin is not recommended in high-risk groups [470].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [474, 475]. Almost 87% of included patients had nocturnal polyuria and approximately 48% of the patients were > 65 years. The co-primary endpoints in both trials were change in number of nocturia episodes per night from baseline and at least a 33% decrease in the mean number of nocturnal voids from baseline during three months of treatment. The mean change in nocturia episodes from baseline was greater with desmopressin ODT compared to placebo (difference: women = -0.3 [95% CI: -0.5, -0.1]; men = -0.4 [95% CI: -0.6, -0.2]). The 33% responder rate was also greater with desmopressin ODT compared to placebo (women: 78% vs. 62%; men: 67% vs. 50%).

Analysis of three published placebo-controlled trials of desmopressin ODT for nocturia showed that clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dosage groups, including those receiving the minimum effective dose for desmopressin (11% of men aged ≥ 65 years vs. 0% of men aged < 65 years receiving 50 mcg; 4% of women ≥ 65 aged years vs. 2% of women aged < 65 years receiving 25 mcg). Severe hyponatraemia, defined as ≤ 125 mmol/L serum sodium, was rare, affecting 22/1,431 (2%) patients overall [476].

Low dose desmopressin (ODT) has been approved in Europe, Canada and Australia for the treatment of nocturia with ≥ 2 episodes in gender-specific low doses 50 mcg for men and 25 mcg for women; however, it initially failed to receive FDA approval, with the FDA citing uncertain benefit relative to risks as the reason. Following resubmission to the FDA in June 2018 desmopressin acetate sublingual tablet, 50 mcg for men and 25 mcg for women, was approved for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void with a boxed warning for hyponatremia.

Desmopressin acetate nasal spray is a new low-dose formulation of desmopressin and differs from other types of desmopressin formulation due to its bioavailability and route of administration. Desmopressin acetate nasal spray has been investigated in two RCTs including men and women with nocturia (over two episodes per night) and a mean age of 66 years. The average benefit of treatment relative to placebo was statistically significant, but low, -0.3 and -0.2 for the 1.5 mcg and 0.75 mcg doses of desmopressin acetate, respectively. The number of patients with a reduction of more than 50% of nocturia episodes was 48.5% and 37.9%, respectively compared with 30% in the placebo group [477]. The reported adverse event rate of the studies was rather low and the risk of hyponatremia was 1.2% and 0.9% for desmopressin acetate 1.5 mcg and 0.75 mcg, respectively. Desmopressin acetate nasal spray was approved by the FDA in 2017 for the treatment of nocturia due to nocturnal polyuria, but it is not available in Europe.

Practical considerations

A complete medical assessment should be made, to exclude potentially non-urological underlying causes, e.g. sleep apnea, before prescribing desmopressin in men with nocturia due to nocturnal polyuria. The optimal dose differs between patients, in men < 65 years desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased up to a dosage of 0.4 mg/day every week until maximum efficacy is reached. Desmopressin is taken once daily before sleeping. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. Low dose desmopressin may be prescribed in patients > 65 years. In men ≥ 65 years or older, low dose desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatremia. Urologists should be cautious when prescribing low-dose desmopressin in patients under-represented in trials (e.g. patients > 75 years) who may have an increased risk of hyponatremia.

5.5.3.2 Medications to treat LUTD

Where LUTD is diagnosed and considered causative of nocturia, relevant medications for storage (and voiding) LUTS may be considered. Applicable medications include; selective α1-adrenergic antagonists [478], antimuscarinics [479-481], 5-ARIs [482] and PDE5Is [483]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [470]. Data on OAB medications (antimuscarinics, beta-3 agonist) generally had a female-predominant population. No studies specifically addressing the impact of OAB medications on nocturia in men were identified [470]. Benefits with combination therapies were not consistently observed.

5.5.3.3 Other medications

Agents to promote sleep [484], diuretics [485], non-steroidal anti-inflammatory agents (NSAIDs) [486] and phytotherapy [487] were reported as being associated with response or QoL improvement [470]. Effect size of these medications in nocturia is generally small, or not significantly different from placebo. Larger responses have been reported for some medications, but larger scale confirmatory RCTs are lacking. Agents to promote sleep do not appear to reduce nocturnal voiding frequency, but may help patients return to sleep.

Summary of evidence	LE
No clinical trial of pathophysiology-directed primary therapy has been undertaken.	4
No robust clinical trial of behavioural therapy as primary intervention has been undertaken.	4
Antidiuretic therapy reduces nocturnal voiding frequency in men with baseline severity of ≥ two or more voids per night.	1b
There is an increased risk of hyponatremia in patients 65 years of age or older under antidiuretic therapy.	1b
Antidiuretic therapy increases duration of undisturbed sleep.	1b
α1-blocker use is associated with improvements in undisturbed sleep duration and nocturnal voiding frequency, which are generally of only marginal clinical significance.	2
Antimuscarinic medications can reduce night-time urinary urgency severity, but the reduction in overall nocturia frequency is small or non-significant.	2
Antimuscarinic medications are associated with higher incidence of dry mouth compared with placebo.	2
5α-reductase inhibitors reduce nocturia severity in men with baseline nocturia severity of ≥ two or more voids per night.	2
A trial of timed diuretic therapy may be offered to men with nocturia due to nocturnal polyuria. Screening for hyponatremia should be undertaken at baseline and during treatment.	1b

Recommendations	Strength rating
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	Weak
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia, and improve sleep quality.	Weak
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria.	Weak
Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong
Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS.	Weak
Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak
Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume. Frequency volume charts or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after twelve weeks and six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS, uroflowmetry and PVR volume. Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day three and seven, one month after initiating therapy and periodically during treatment. If serum sodium concentration has remained normal during periodic screening follow-up screening can be carried out every three months subsequently. However, serum sodium concentration should be monitored more frequently in patients $\geq$ 65 years of age and in patients at increased risk of hyponatremia. The following tests are recommended at follow-up visits: serum-sodium concentration and FVC. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

Patients after prostate surgery should be reviewed four to six weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary. The following tests are recommended at follow-up visit after four to six weeks: IPSS, uroflowmetry and PVR volume.

Summary of evidence	LE
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	4

Recommendations	Strength rating
Follow up all patients who receive conservative, medical or surgical management.	Weak
Define follow-up intervals and examinations according to the specific treatment.	Weak

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8. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Urinary Incontinence in Adults

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1. INTRODUCTION

Urinary incontinence (UI) is an extremely common complaint in every part of the world. It causes a great deal of distress and embarrassment, as well as significant costs, to both individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Urinary Incontinence are written by a multidisciplinary group, primarily for urologists, and are likely to be referred to by other professional groups. They aim to provide sensible and practical evidence-based guidance on the clinical problem of UI rather than an exhaustive narrative review. Such a review is already available from the International Consultation on Incontinence [1], and so the EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of UI. The focus of these Guidelines is entirely on assessment and treatment reflecting clinical practice. The Guidelines also do not consider patients with UI caused by neurological disease, or in children, as this is covered by complementary EAU Guidelines [2, 3].

The current Guidelines provide:

- A clear pathway (algorithm) for common clinical problems. This can provide the basis for thinking through a patient's management and also for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little or no high-quality evidence.

In this edition the Panel has continued to focus, largely, on the management of a 'standard' patient. The Panel has referred in places to patients with 'complicated incontinence', by which we mean patients with associated morbidity, a history of previous pelvic surgery, surgery for UI, radiotherapy and women with associated genitourinary prolapse. An appendix is included on non-obstetric genitourinary fistulae. The subject of prevention of UI has not been addressed. A systematic review (SR) on nocturnal incontinence found no studies on the topic. The Panel are of the opinion that nocturnal incontinence should be considered in future research studies.

1.1.1 The elderly

The Panel decided to include a separate but complimentary set of recommendations referring to the elderly population within each section. Older people with UI deserve special consideration for a number of reasons. Physiological changes with natural ageing mean that all types of UI become more common with increasing age. Urinary incontinence commonly co-exists with other comorbid conditions, reduced mobility, and impaired cognition and may require specific interventions, such as assisted toileting.

For the elderly person expectations of assessment and treatment may need to be modified to fit in with specific circumstances, needs, and preferences, while also taking into account any loss of capacity for consent. When the urologist is dealing with a frail elderly patient with urinary incontinence, collaboration with other healthcare professionals such as elderly care physicians is recommended.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urinary Incontinence Panel consists of a multidisciplinary group of experts, including urologists, a gynaecologist and a physiotherapist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/urinary-incontinence.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text versions. Two scientific publications in the journal European Urology are also available [4, 5]. All documents are accessible through the EAU website: http://www.uroweb.org/guideline/urinary-incontinence.

1.4 Publication history

The EAU published the first Urinary Incontinence Guidelines in 2001. Section 4.3 Surgical Management has been completely updated in this 2018 publication.

1.4.1 Summary of changes.

Changed evidence summaries and recommendations can be found in sections:

4.2.6.3 Additional recommendations for antimuscarinic drugs in the elderly

Recommendations	Strength rating
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction	Strong

SUI = stress urinary incontinence.

4.3.1.6 Recommendations for women with uncomplicated stress urinary incontinence

Recommendations	Strength rating
Inform women about the higher risk of groin pain following a transobturator approach when compared to a retropubic approach.	Strong
Inform women that any vaginal surgery may have an impact on sexual function, which is generally positive.	Weak
Offer bulking agents to women with SUI who request a low-risk procedure with the understanding that repeat injections are likely and long-term durability is not established.	Strong

SUI = stress urinary incontinence.

4.3.1.3.3 Summary of evidence for mid-urethral slings

Summary of evidence	LE
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route provides equivalent patient-reported outcome at five years.	1a
Mid-urethral synthetic sling inserted by the retropublic routes has higher objective patient-reported cure rates at 8 years.	1b
Long-term analysis of TVT cohorts showed a sustained response up to 17 years.	2b
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a
Long-term analysis showed no difference in terms of efficacy for the skin-to-vagina compared to vagina-to-skin directions up to nine years.	2a
The top-to-bottom direction in the retropubic approach is associated with a higher risk of post-operative voiding dysfunction.	1b
Incontinence surgery has similar outcomes in older patients (≥ 65 years).	2a
Incontinence surgery may be safely performed in obese women, however, outcomes may be inferior.	2b
Improvement in sexual life is higher with single incision slings than with standard MUS.	1a

SUI = stress urinary incontinence; TVT = tension-free vaginal tape.

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVT-S) device and although this device is no longer available, many women still have the device in place.

4.3.1.4.3 Summary of evidence for open and laparoscopic surgery for stress urinary incontinence

Summary of evidence	LE
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a

4.3.1.5.3 Summary of evidence for bulking agents

Summary of evidence	LE
Peri-urethral injection of a bulking agent may provide short-term improvement and cure (twelve months), in women with SUI.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Peri-urethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

SUI = stress urinary incontinence.

4.3.2.1.3 Summary of evidence for colposuspension or sling following failed surgery

Summary of evidence	LE
TVT and TOT have similar outcomes in patients with recurrent SUI.	1a
Burch colposuspension has similar patient reported or objective cure rates when compared to TVT.	1b

TOT = trans-obturator tape; TVT = tension-free vaginal tape.

4.3.3.4 Recommendations for women with both stress urinary incontinence and pelvic organ prolapse

Recommendations for women requiring surgery for bothersome pelvic organ prolapse who have symptomatic or unmasked stress urinary incontinence	Strength rating
Inform women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone, as well as the risk of UI progression if UI is untreated at the time of POP repair.	Strong

POP = pelvic organ prolapse; UI = urinary incontinence.

4.3.5.1.1 Summary of evidence for drug therapy in men with stress urinary incontinence

Summary of evidence	LE
Duloxetine, either alone or combined with conservative treatment, can hasten recovery but does not improve continence rate following prostate surgery. However, it can be associated with significant, albeit often transient, side effects.	1b

4.3.5.3.3 Summary of evidence for fixed male sling

Summary of evidence	LE
There is no evidence that intraoperative placement of an autologous sling during RARP improves return of continence at 6 months.	1b

RARP = robotic assisted radical prostatectomy.

4.3.5.6 Recommendations for men with stress urinary incontinence

Recommendation	Strength rating
Offer duloxetine only to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events and that its use is off label for this indication in most European countries.	Weak

4.3.6.2.3 Summary of evidence for sacral nerve stimulation

Recommendations	LE
Sacral nerve neuromodulation is not more effective than OnabotulinumA toxin 200 U injection at 6 months.	1b

4.3.6.3.4 Recommendations for cystoplasty/urinary diversion

Recommendations	Strength rating
Offer augmentation cystoplasty to patients with UI who have failed all other treatment options.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they need lifelong surveillance.	Weak

UI = urinary incontinence.

2. METHODS

2.1 Introduction

For the 2018 Urinary Incontinence Guidelines, the literature has been assessed for Section 4.3 – Surgical Management. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 2012 and March 15th, 2017, Four different PICOS were developed (Slings and tapes, Botox and SNS, Other procedures including Colposuspension and Major surgery), resulting in a total of 2,142 records identified which were retrieved and screened for relevance. Detailed search strategies are available online for each of these PICOS: https://uroweb. org/guideline/urinary-incontinence/?type=appendices-publications.

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [6, 7]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The Surgical Management section has been peer reviewed prior to publication in 2018. The remainder of the document was peer reviewed prior to publication in 2015. The decision for re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

2.3 Future goals

- A systematic review on the topic of female nocturia is ongoing [10].

3. DIAGNOSTIC EVALUATION

3.1 History and physical examination

Taking a careful clinical history is fundamental to the clinical process. Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI. The history should include details of the type, timing and severity of UI, associated voiding and other urinary symptoms. The history should allow UI to be categorised into stress urinary incontinence (SUI), urgency urinary incontinence (UUI) or mixed urinary incontinence (MUI). It should also identify patients who need rapid referral to an appropriate specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease. In women, an obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. The patient should also be asked about other ill health and for the details of current medications, as these may impact on symptoms of UI.

Similarly, there is little evidence from clinical trials that carrying out a clinical examination improves care, but wide consensus suggests that it remains an essential part of assessment of people with UI. It should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum (prostate) and/or vagina. Examination of the perineum in women includes an assessment of oestrogen status and a careful assessment of any associated pelvic organ prolapse (POP). A cough test may reveal SUI if the bladder is sufficiently full while pelvic floor contraction together with urethral mobility can be assessed digitally.

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires, scales, indexes, patient-reported outcome measures (PROMs) and health-related quality of life (HRQoL) measures. The latter include generic or condition specific measures. Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, must have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on patient-reported outcome instruments (questionnaires) in 2009 [11].

*3.2.1 **Questions***

- In patients with UI, can the use of Questionnaires/PROMS differentiate between stress, urgency and mixed incontinence, and does this differentiation impact on quality of life (QoL) after treatment?
- In adults with UI, does assessment using either urinary symptom or QoL questionnaires improve treatment outcome for UI?
- In adults with UI, does assessment of the patient perspective (concerns or expectations) improve patient outcomes, regarding either urinary symptoms or QoL, compared to no patient-reported assessment?

*3.2.2 **Evidence***

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs most of these studies did not include adult patients diagnosed with UI. This limits the extent to which results and conclusions from these studies can be applied in adults with UI. Some questionnaires (QUID, 3IQ) have potential to discriminate UI types in women [12, 13]. In men ICIQ-UI-SF score does not differentiate UI types [14]. Some questionnaires are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [15-17]. No evidence was found to indicate whether use of QoL or condition specific questionnaires have an impact on outcome of treatment.

Table 1 shows a summary of the ICUD review (2012) with recent additions. Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.

Table 1: Summary of the ICUD review 2012*.

	Category A (all 3 criteria fulfilled)**	**Category B (2 criteria fulfilled)****	**Category C (only 1 criterion fulfilled)****
Symptom measures and health-related QOL measures	ICIQ-UI Short Form, ICIQFLUTS,ICIQ-MLUTS IIQ and IIQ-7, I-QOL (ICIQ-Uqol), ISS, KHQ, LIS (?-interview), N-QoL, OAB-q SF, OAB-q (ICIQOABqol), PFDI and PFDI-20, PFIQ and PFIQ-7, PRAFAB, UISS	Contilife, EPIQ, LUTS tool IOQ,YIPS	ABSST ISI, ISQ, UIHI, UIQ
Measure of patient satisfaction (patient's measure of treatment satisfaction)	BSW, OAB-S, OABSAT-q, TBS	PPQ	EPI, GPI, PSQ
Goal attainment scales		SAGA	
Screening tools (used to identify patients with UI)	B-SAQ, OAB-SS, OABV8, OAB-V3, QUID	ISQ, USP	3IQ, CLSS, MESA, PUF
Patient symptom scale			
Assessment of symptom bother and overall bother	PPBC, UDI or UDI-6, LUSQ, PGI-I and PGI-S	PFBQ, SSI and SII	PMSES, POSQ, UI-4
Assessment of the impact of urgency	IUSS, U-IIQ, UU Scale, U-UDI	PPIUS, SUIQ, UPScore, UPScale, UQ, USIQ-QOL, USIQ-S, USS	
Questionnaires to assess sexual function and urinary symptoms		FSFI, ICIQ-VS, PISQ, SQoL-F	SFQ
Treatment adherence Measures		MASRI	

** For all abbreviations please see the Abbreviations list in the Appendix at the end of the full Guidelines.*
*** Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.*

To date, there is no one questionnaire that fulfils all requirements for assessment of people with UI. Clinicians must evaluate the tools which exist, for use alone or in combination, for assessment and monitoring of treatment outcome [18].

The questionnaires can be found on the following websites: www.iciq.net, www.proqolid.org, www.mapi-institute.com, www.pfizerpatientreportedoutcomes.com, www.ncbi.nlm.nih.gov.

3.2.3 Summary of evidence and recommendations for patient questionnaires

Summary of evidence	**LE**
Validated condition specific symptom scores assist in the screening for, and categorisation of, UI.	3
Validated symptom scores measure the severity of UI.	3
Both condition specific and general health status questionnaires measure current health status, and change following treatment.	3

Recommendation	**Strength rating**
Use a validated and appropriate questionnaire when standardised assessment is required (See Table 1, above).	Strong

UI = urinary incontinence.

3.3 Voiding diaries

Measurement of the frequency and severity of lower urinary tract symptoms (LUTS) is an important step in the evaluation and management of lower urinary tract (LUT) dysfunction, including UI. Voiding diaries are a semi-objective method of quantifying symptoms, such as frequency of UI episodes. They also quantify urodynamic variables, such as voided volume and 24-hour or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient counselling. In addition, voided volume measurement can be used to support diagnoses, such as overactive bladder (OAB) or polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a voiding diary is unlikely to accurately report 24-hour urine output and so voided volume may be lower than total bladder capacity.

*3.3.1 **Question***

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of a voiding diary compared to patient history or symptom score?

*3.3.2 **Evidence***

Two articles have suggested a consensus has been reached in the terminology used in voiding [19, 20]. However, the terms micturition diary, frequency voiding chart and voiding diary, have been used interchangeably for many years and include information on fluid intake, times of voiding, voided volumes, incontinence episodes, pad usage, degree of urgency and degree of UI recorded for at least 24 hours. When reviewing the evidence all possible terminology has been included.

Two studies have demonstrated the reproducibility of voiding diaries in both men and women [21, 22]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded by uroflowmetry [23, 24]. Another study found that keeping a voiding diary had a therapeutic benefit [25].

A number of observational studies have demonstrated a close correlation between data obtained from voiding diaries and standard symptom evaluation [26-29].

*3.3.3 **Summary of evidence and recommendations for voiding diaries***

Summary of evidence	**LE**
Voiding diaries of three to seven days duration are a reliable tool for the objective measurement of mean voided volume, day time and night time frequency, and incontinence episode frequency.	2b
Voiding diaries are sensitive to change and are a reliable measure of outcome.	2b

Recommendations	**Strength rating**
Ask patients with UI to complete a voiding diary when standardised assessment is needed.	Strong
Use a diary duration of at least three days.	Strong

UI = urinary incontinence.

3.4 Urinalysis and urinary tract infection

Reagent strip ('dipstick') urinalysis may indicate UTI, proteinuria, haematuria or glycosuria requiring further assessment. Refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [30].

*3.4.1 **Question***

- In adults with UI, what is the diagnostic accuracy of urinalysis to detect UTI?
- In adults with UI does treatment of UTI or asymptomatic bacteriuria cure or improve UI compared to no treatment?

*3.4.2 **Evidence***

Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI in people with UI [31] and should be included, with urine culture when necessary, in the evaluation of all patients with UI. Urinary incontinence may occur during symptomatic UTI [32] and existing UI may worsen during UTI [33]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [34].

*3.4.3 **Summary of evidence and recommendations for urinalysis***

Summary of evidence	LE
Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI.	1
Urinary incontinence may be a symptom during UTI.	3
The presence of a symptomatic UTI worsens symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of a patient with UI.	Strong
If a symptomatic UTI is present with UI, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve UI.	Strong

UI = urinary incontinence; UTI = urinary tract infection.

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both bladder outlet obstruction and detrusor underactivity contribute to the development of PVR. Post-void residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR in patients with UI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume.

*3.5.1 **Question***

In adults with UI, what are the benefits of measuring PVR?

*3.5.2 **Evidence***

Most studies investigating PVR have not included patients with UI. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to adults with non-neurogenic UI. The results of studies investigating the best method of measuring PVR [35-40] have led to the consensus that US measurement of PVR is preferable to catheterisation.

In peri- and post-menopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [41]. In women with UUI, a PVR > 100 mL was found in 10% of cases [42]. Other research has found that a high PVR is associated with pelvic organ prolapse (POP), voiding symptoms and an absence of SUI [41, 43-45].

In women with SUI, the mean PVR was 39 mL measured by catheterisatiovn and 63 mL measured by US, with 16% of women having a PVR > 100 mL [42].

*3.5.3 **Summary of evidence and recommendations for post-void residual***

Summary of evidence	LE
Lower urinary tract symptoms coexisting with UI are associated with a higher rate of PVR compared to asymptomatic subjects.	2

Recommendations	Strength rating
When measuring PVR, use US.	Strong
Measure PVR in patients with UI who have voiding symptoms.	Strong
Measure PVR when assessing patients with complicated UI.	Strong
Post-void residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction, including surgery for SUI.	Strong

PVR = post void residual urine; SUI = stress urinary incontinence; UI = urinary incontinence; US = ultrasound.

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome, or facilitate discussion during counselling. For all these reasons,

urodynamics is often performed prior to invasive treatment for UI. These Guidelines will focus on invasive tests, including multichannel cystometry, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry, Valsalva leak point pressure estimation, and retrograde urethral resistance measurement.

3.6.1 ***Question***

In adults with UI, what is the reproducibility, diagnostic accuracy and predictive value of urodynamic testing?

3.6.2 ***Evidence***

3.6.2.1 Variability

In common with most physiological tests there is variability in urodynamics results. A number of small studies, assessing same-session repeatability of urodynamic testing, present contradictory findings [46, 47]. Measurement of urethral closure pressure (MUCP) correlates poorly with incontinence severity [48] and there is conflicting evidence about its reproducibility [49, 50]. One method of recording MUCP cannot be compared meaningfully to another [51].

Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressure did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [52]. The predictive value of the tests, regarding the outcome of treatment, remains unclear. No studies on the reproducibility of ambulatory monitoring were found.

3.6.2.2 Diagnostic accuracy

The diagnostic accuracy of urodynamics is assessed in terms of its correlation with clinical diagnosis of UI and incontinence severity. The problem is that clinical diagnosis and urodynamic findings often do not correlate [53, 54], and normal healthy people may have urodynamic abnormalities.

The diagnostic accuracy of urethral pressure profilometry [48] and 'urethral retro-resistance' is generally poor [55]. Urethral reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [56].

Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is uncertain [57, 58].

3.6.2.3 Question

Does urodynamics influence the outcome of conservative therapy?

3.6.2.4 Evidence

A Cochrane review of seven randomised control trials (RCTs) showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision making altered the clinical outcome of treatment [59]. Subanalysis of an RCT comparing fesoterodine to placebo [60, 61] showed no predictive value for treatment response, by the urodynamic diagnosis of detrusor overactivity (DO).

3.6.2.5 Question

Does urodynamics influence the outcome of surgery for urinary incontinence?

3.6.2.6 Evidence

A high-quality RCT (n = 630) compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. Whilst urodynamics changed the clinical diagnosis in 56% of women [62], there was no difference in levels of UI or any secondary outcome at twelve months follow-up after surgery [63]. Another similar study closed with only 59 women included due to recruitment problems, found that the omission of urodynamics was not inferior in the pre-operative work up of SUI [64]. This study was then redesigned so that patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on urodynamics. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [65].

In observational studies there is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery [27-30]. The same is true for a secondary analysis of an RCT [66].

Augmentation cystoplasty is only performed in patients with a urodynamic diagnosis of DO, so no statement can be made about predictive value for this group [61].

The Panel recognise that it may be valuable to use urodynamic test results to select the optimum surgical procedure but, at the time of this review, there is inconsistent evidence regarding any predictive value that would support this approach.

3.6.2.7 Question

Does urodynamics help to predict complications of surgery for UI?

3.6.2.8 Evidence

There have been no RCTs designed to answer this question.

The presence of pre-operative DO has been associated with post-operative UUI, but did not predict overall treatment failure following mid-urethral sling [66] or following sling surgery or colposuspension.

Whilst low pre-operative flow rate has been shown to correlate with post-operative voiding dysfunction [67, 68], *post-hoc* analysis of two high-quality surgical trials showed that no pre-operative urodynamic parameter had the ability to predict post-operative voiding dysfunction in a selected population of women with low pre-operative PVR [69, 70].

3.6.2.9 Question

Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men?

3.6.2.10 Evidence

There are no RCTs examining the clinical usefulness of urodynamics in post-prostatectomy UI. Whilst urodynamics will distinguish causes of incontinence, its ability to predict outcome of surgery for incontinence for these men is uncertain [71, 72].

*3.6.3 **Summary of evidence and recommendations for urodynamics***

Summary of evidence	**LE**
Most urodynamic parameters show variability within the same session and over time, and this limits their clinical usefulness.	3
Different techniques of measuring urethral function may have good test-retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing SUI or DO.	2
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics can influence the choice of treatment for UI, but does not affect the outcome of conservative therapy or drug therapy for SUI.	1a
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable, SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that pre-operative DO is associated with surgical failure of MUS in women.	3
The presence of pre-operative DO may be associated with persistence of urgency post-operatively.	3
There is no evidence that urodynamics predicts the outcomes of treatment for post-prostatectomy incontinence in men.	4

Recommendations *(NB: Concerning only neurologically intact adults with UI)*	**Strength rating**
When performing urodynamics in patients with UI adhere to 'Good Urodynamic Practice' standards as described by the International Continence Society [73]: • attempt to replicate the patient's symptoms; • check recordings for quality control; • interpret results in the context of the clinical problem; • remember there may be physiological variability within the same individual.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated SUI.	Strong

Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence.	Strong

DO = detrusor overactivity; MUS = mid-urethral sling; SUI = stress urinary incontinence; UI = urinary incontinence.

*3.6.4 **Research priority***

Does any individual urodynamic test, or combination of tests, influence the choice of treatments or prediction of treatment outcome for UI?

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.

*3.7.1 **Questions***

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of pad testing?
- In adults with UI, is one type of pad test better than another?

*3.7.2 **Evidence***

The clinical usefulness of pad tests for people with UI has been assessed in two SRs [74, 75]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [76]. Pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [77]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [74, 78] although early post-operative testing may predict future continence in men after prostatectomy [79]. Pad test is responsive to change following successful treatment [80]. There is no evidence that one type of pad test is superior to another.

*3.7.3 **Summary of evidence and recommendations for pad testing***

Summary of evidence	**LE**
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2

Recommendations	**Strength rating**
Use a pad test of standardised duration and activity protocol.	Strong
Use a pad test when quantification of UI is required.	Weak

UI = urinary incontinence.

*3.7.4 **Research priority***

- Do the results of pad testing influence the choice of treatments or the prediction of the outcome of treatment for UI?
- Does the amount of physical activity influence the outcome of 24-hour pad testing leading to overestimation of the severity of UI?

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause UI. In clinical research, imaging is used to understand the relationship between anatomy and function, between conditions of the central nervous system (CNS) or of the LUT and UI, and to investigate the relationship between LUT and pelvic floor imaging and treatment outcome.

Ultrasound and magnetic resonance imaging (MRI) have largely replaced X-ray imaging. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability. Studies on LUT imaging in patients with UI often include an evaluation of surgical outcomes, making design and conduct of these trials challenging.

*3.8.1 **Questions***

In adults with UI:

- What is the reliability and accuracy of imaging in the diagnosis of UI?
- Do the results of imaging influence the choice of treatment for UI?
- Do the results of imaging help predict outcome of treatment for UI?
- Do the results of imaging help evaluate outcome of treatments for UI?

*3.8.2 **Evidence***

Many studies have evaluated the imaging of bladder neck mobility by US and MRI, and concluded that UI cannot be identified by a particular pattern of urethrovesical movements [81]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with *de novo* SUI [82].

There is a general consensus that MRI provides good global pelvic floor assessment, including pelvic organ prolapse (POP), defecatory function and integrity of the pelvic floor support [83]. However, there is a large variation in MRI interpretation between observers [84] and little evidence to support its clinical usefulness in the management of UI. Studies have assessed the use of imaging to assess the mechanism of mid-urethral sling (MUS) insertion for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not mobility of the bladder neck [85]. Following MUS, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [86].

Several imaging studies have investigated the relationship between sphincter volume and function in women [87] and between sphincter volume and surgery outcome, in men and women [88, 89]. In patients undergoing radical prostatectomy, longer membranous urethra before and after surgery was associated with a higher rate of continence [90]. However, no imaging test has been shown to predict the outcome of treatment for UI. Imaging of the pelvic floor can identify *levator ani* detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of UI.

Detrusor wall thickness

As OAB has been linked to DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). However, there is no evidence that BWT/DWT imaging improves management of OAB in practice. No consensus exists as to the relationship between OAB and increased BWT/DWT [91].

*3.8.3 **Summary of evidence and recommendations for imaging***

Summary of evidence	**LE**
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of UI.	3

Recommendation	**Strength rating**
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of UI.	Strong

UI = urinary incontinence.

*3.8.4 **Research priority***

More research is needed into the relationship between sling position, as determined by imaging, and surgical outcome.

4. DISEASE MANAGEMENT

4.1 Conservative management

In clinical practice, it is the convention that non-surgical therapies are tried first because they usually carry the least risk of harm. They are often used in combination which makes it difficult to determine which components are effective. Containment devices play an important role, especially for individuals who prefer to avoid the risks of interventional treatments, or in whom active treatment is impossible for any reason.

*4.1.1 **Simple clinical interventions***

4.1.1.1 Underlying disease/cognitive impairment

Urinary incontinence, especially in the elderly, has been associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease including stroke and multiple sclerosis;
- general cognitive impairment;
- sleep disturbances, e.g. sleep apnoea;
- depression;
- metabolic syndrome.

It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

4.1.1.1.1 Question

In adults with UI, does improving an associated condition improve UI compared to no correction of that condition?

4.1.1.1.2 Evidence

There is compelling evidence that there is a higher prevalence of UI in women with type 2 diabetes. One study showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life vs. conventional treatment [92].

4.1.1.1.3 Summary of evidence and recommendations regarding associated conditions

Summary of evidence	**LE**
There is a lack of evidence that improving any associated condition improves UI, with the exception of weight loss (see section 4.1.2.4 Obesity and weight loss).	3

Recommendation	**Strength rating**
Patients with UI who have associated conditions, should have appropriate treatment for those conditions in line with good medical practice.	Strong

UI = urinary incontinence.

4.1.1.2 Adjustment of other (non-incontinence) medication

Although UI is listed as an adverse effect of many drugs in drug compendia, this mainly results from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of UI as a primary outcome, or were powered to assess the occurrence of statistically significant UI, or worsening rates against placebo. In most cases, it is therefore not possible to be sure that a drug causes UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidity or ageing on UI. Although changing drug regimens for underlying disease may be considered as a possible early intervention for UI, there is very little evidence of benefit [53]. There is also a risk that stopping or altering medication may result in more harm than benefit.

4.1.1.2.1 Question

In adults with UI, does adjustment of other (non-incontinence) medication improve UI compared to no change in treatment?

4.1.1.2.2 Evidence

Structured literature review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of UI. Also, there is little evidence relating to the occurrence or worsening of UI in relation to prescription of any specific drugs.

4.1.1.2.3 Summary of evidence and recommendations for adjustment of other (non-incontinence) medication

Summary of evidence	**LE**
There is very little evidence that alteration of non-incontinence medication can cure or improve symptoms of UI.	3

Recommendations	**Strength rating**
Take a history of current medication use from all patients with UI.	Strong
Review any new medication associated with the development or worsening of UI.	Weak

UI = urinary incontinence.

4.1.1.3 Constipation

Several studies have shown strong associations between constipation and UI. Constipation can be improved by behavioural, physical and medical treatments.

4.1.1.3.1 Question

Does treatment for constipation improve UI?

4.1.1.3.2 Evidence

Two, large, cross-sectional population-based studies [93, 94] and two longitudinal studies [95, 96] showed that constipation was a risk factor for LUTS. An observational study comparing women with UI and women with POP to controls found that a history of constipation was associated with both prolapse and UI [97]. One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc., reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [98].

In conclusion, constipation appears to be associated with UI. However, there is no evidence to show whether or not treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

4.1.1.3.3 Summary of evidence and recommendations for constipation

Summary of evidence	**LE**
There is a consistent association between a history of constipation and the development of UI and POP.	3
There is no consistent evidence in adults that treatment of constipation alone improves UI.	4

Recommendation	**Strength rating**
Adults with UI who also suffer from constipation should be given advice about bowel management in line with good medical practice.	Strong

POP = pelvic organ prolapse; UI = urinary incontinence.

4.1.1.3.4 Research priority

Does the normalisation of bowel habit improve UI in patients who are constipated?

4.1.1.4 Containment

Containment is important for people with UI when active treatment does not cure the problem, or when it is not available or not possible. Some individuals may prefer containment rather than undergo active treatment with

its associated risks. This includes the use of absorbent pads, urinary catheters, external collection devices, penile clamps for men and intravaginal devices for women. Studies of catheter use are not specific to patients with non-neurogenic UI. Detailed literature summaries can be found in the current ICUD monograph [1] and in European Association of Urological Nurses guidance documents [99-101]. A useful resource for health care professionals and patients can be found at: www.continenceproductadvisor.org.

4.1.1.4.1 Question
For adults with UI, is one type of containment device better than another?

4.1.1.4.2 Evidence
One RCT involving elderly women in care comparing management with pads to indwelling urethral catheter found no difference in dependency level or skin integrity score at six months [102]. Use of an external sheath was compared with indwelling catheterisation over 30 days in an RCT involving elderly men resident in hospital [103]; there were no differences in bacteriuria or symptomatic UTI but the sheath was more comfortable. A short-term (two weeks) crossover RCT in men with UI found that disease specific QoL was better when using an external sheath and more men preferred it, compared to pads [104].

4.1.1.4.3 Question
For men or women with UI, is one type of pad better than another?

4.1.1.4.4 Evidence
A SR of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, whilst evidence that disposable pads were better than washable pads was inconsistent [105]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [106]. A series of three crossover RCTs examined performance of different pad designs for differing populations [107]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe incontinence, disposable pull-up pants were more effective for women, whilst for men disposable diapers were more effective during the day and washable diapers at night.

4.1.1.4.5 Question
For men or women with UI, is one type of catheter or external collection device better than another?

4.1.1.4.6 Evidence
A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [108]. A SR of non-randomised studies found no differences in UTI outcome or UUT changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [109]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [110]. However, there is recent evidence from a narrative review suggesting that in certain populations using single-use catheters may reduce urethral trauma and UTI [111]. A Cochrane review summarising five trials comparing washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [112].

A further Cochrane review summarising eight trials testing whether antibiotic prophylaxis was beneficial for adults using intermittent or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [113].

4.1.1.4.7 Question
For men and women with UI, are external pressure devices more effective than standard treatment and is one device better than another?

4.1.1.4.8 Evidence
A crossover RCT in twelve men with post-prostatectomy incontinence found a hinge-type penile clamp to be more effective than circular clamps for control of UI and that the hinge-type penile clamp was preferred by participants, although it reduced penile blood flow [114].

A Cochrane review summarised seven trials comparing mechanical devices in women with UI finding limited evidence that SUI was reduced by intravaginal devices, no evidence on the effectiveness of intra-urethral devices, and that there was no difference in control of UI between intravaginal and intra-urethral devices [115].

There was no difference in outcome at twelve months in women with SUI between vaginal pessary alone; pelvic floor muscle training (PFMT) alone; and vaginal pessary + PFMT, although vaginal pessary was inferior to PFMT at three months for bother from UI.

4.1.1.4.9 Summary of evidence and recommendations for containment

Summary of evidence	**LE**
Pads are effective in containing urine.	1b
Hinge-type penile clamps are more effective than circular clamps to control SUI in men.	2a
Vaginal devices may improve SUI in women in selective groups.	2a

Recommendations	**Strength rating**
Ensure that adults with UI and/or their carers are informed regarding available treatment options before deciding on containment alone.	Strong
Offer incontinence pads and/or containment devices for management of UI.	Strong

SUI = stress urinary incontinence; UI = urinary incontinence.

4.1.1.4.10 Research priority

To develop methods for assessing the best method of containment for individual adults with UI.

*4.1.2 **Lifestyle interventions***

Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI.

4.1.2.1 Caffeine reduction

Many drinks contain caffeine, particularly tea, coffee and cola. Anecdotal evidence of urinary symptoms being aggravated by excessive caffeine intake has focused attention on whether caffeine reduction may improve UI. However, a cross-sectional population survey found no statistical association between caffeine intake and UI [116]. Lack of knowledge about the caffeine content of different drinks has made the role of caffeine reduction in alleviating UI difficult to assess.

4.1.2.1.1 Question

In adults with UI, does caffeine reduction improve UI or QoL compared to no caffeine reduction?

4.1.2.1.2 Evidence

Four studies were found on the effect of caffeine reduction on UI [117-120]. They were of moderate quality and the results were inconsistent. The studies were mainly in women, so results can only be cautiously generalised to men [118, 119]. One RCT showed that reducing caffeine intake as an adjunct to behavioural therapy resulted in reduced urgency but not reduced UI compared to behavioural therapy alone [118]. Another RCT found that reducing caffeine had no benefit for UI [119]. A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI [120]. In a large prospective cohort study there was no evidence that caffeine reduction reduced the risk of progression of UI over two years [121].

4.1.2.1.3 Sumary of evidence for caffeine reduction

Summary of evidence	**LE**
Reduction of caffeine intake does not improve UI.	2
Reduction in caffeine intake may improve symptoms of urgency and frequency.	2

UI = urinary incontinence.

4.1.2.2 Physical exercise

Regular physical activity may strengthen the pelvic floor musculature and possibly decrease the risk of developing UI, especially SUI. However, it is also possible that heavy physical exercise may aggravate UI.

4.1.2.2.1 Question

Does physical exercise cause, improve or exacerbate UI in adults?

4.1.2.2.2 Evidence

The association between exercise and UI is unclear. Four studies [116, 122-124] in differing populations concluded that strenuous physical exercise increases the risk of SUI during periods of physical activity. There is also consistent evidence that physically active females and elite athletes experience higher levels of SUI than control populations [125-130]. On the other hand, the presence of UI may prevent women from taking exercise [131]. There is no evidence that strenuous exercise predisposes athletes to the development of SUI later in life [132]. Lower levels of UI have been observed in cohorts of women who undertake moderate exercise, but it remains unclear whether taking exercise can prevent development of UI [133, 134].

4.1.2.2.2.1 The elderly

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime including PFMT and weight loss, was effective in improving UI in women. It is not clear which component of such a scheme is most important [98, 135, 136].

4.1.2.2.3 Summary of evidence for physical excercise

Summary of evidence	**LE**
Female athletes may experience UI during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose for women to UI later in life.	3
Moderate exercise is associated with lower rates of UI in middle-aged or older women.	2b

UI = urinary incontinence.

4.1.2.3 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated.

4.1.2.3.1 Question

In adults with UI, what is the effect of modifying fluid intake compared to not modifying fluid intake on symptoms and QoL?

4.1.2.3.2 Evidence

The few RCTs [119, 137, 138] provide inconsistent evidence. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women. An RCT [138] showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving antimuscarinics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [139].

4.1.2.3.3 Summary of evidence for fluid intake

Summary of evidence	**LE**
There is conflicting evidence on whether fluid modification improves UI.	2

UI = urinary incontinence.

4.1.2.4 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for UI in many epidemiological studies [140, 141]. There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index [142]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [143].

4.1.2.4.1 Question

In adults with UI, does weight loss lead to an improvement in symptoms of UI or QoL?

4.1.2.4.2 Evidence

All the available evidence relates to women. Three SRs plus two large RCTs concluded that weight loss was beneficial in improving UI [140, 141, 144]. Five further RCTs reported a similar beneficial effect on incontinence

following surgical weight reduction programmes [145-149]. Two large studies in women with diabetes, for whom weight loss was the main lifestyle intervention, showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [145, 150]. There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese [151-155].

4.1.2.4.3 Summary of evidence for obesity and weight loss

Summary of evidence	LE
Obesity is a risk factor for UI in women.	1b
Non-surgical weight loss in overweight and obese women improves UI.	1a
Surgical weight loss improves UI in obese women.	1b
Weight loss in obese women improves UI.	1b
Weight loss in obese adults with diabetes mellitus reduces the risk of developing UI.	1b

UI = urinary incontinence.

4.1.2.5 Smoking

Smoking cessation is now a generalised public health measure and has been shown to be weakly associated with improving urgency frequency and UI [116, 156].

4.1.2.5.1 Question

In adults with UI, does smoking cessation improve patient outcomes regarding either urinary symptoms or QoL compared to continued smoking?

4.1.2.5.2 Evidence

The effect of smoking cessation on UI was described as uncertain in a NIHR review [157].

4.1.2.5.3 Summary of evidence for smoking cessation

Summary of evidence	LE
There is no evidence that smoking cessation will improve the symptoms of UI.	4

UI = urinary incontinence.

4.1.2.6 Recommendations for lifestyle interventions

Recommendations	Strength rating
Encourage overweight and obese adults with UI to lose weight and maintain weight loss.	Strong
Advise adults with UI that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	Strong
Review type and amount of fluid intake in patients with UI.	Weak
Provide smoking cessation strategies to patients with UI who smoke.	Strong

UI = urinary incontinence.

4.1.2.7 Research priority

Which lifestyle modifications are effective for the cure or sustained improvement of UI?

4.1.3 ***Behavioural and Physical therapies***

Terminology relating to behavioural and physical therapies remains confusing because of the wide variety of ways in which treatment regimens and combinations of treatments have been delivered in different studies [158]. The terms are used to encompass all treatments which require a form of self-motivated personal retraining by the patient and also include techniques which are used to augment this effect.

Approaches include bladder training (BT) and PFMT, but terms such as bladder drill, bladder discipline and bladder re-education and behaviour modification are also used. Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy as well. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package.

4.1.3.1 Prompted voiding

The term 'prompted voiding' implies that carers, rather than the patient, initiate the decision to void and this applies largely to an assisted care setting.

Two SRs (nine RCTs) [159, 160] confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [160]. Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs, finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [161].

4.1.3.2 Bladder Training

A programme of patient education along with a scheduled voiding regimen with gradually adjusted voiding intervals. Specific goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore patient confidence in controlling bladder function. The ideal form or intensity of a BT programme for UI is unclear. It is also unclear whether or not BT can prevent the development of UI.

4.1.3.2.1 Questions

In adults with UI:

- Is BT better than no treatment for cure or improvement of UI?
- Is BT better than other conservative treatments for cure or improvement of UI?
- Does BT, as an adjunct to other conservative treatments, cure or improve UI?
- Are the benefits of BT durable in the longer term?
- Are there any patient groups for whom BT is more effective?

4.1.3.2.2 Evidence

There have been three SRs on the effect of BT compared to standard care [53, 157, 162] confirming that BT is more effective than no treatment in improving UUI. The addition of BT to anticholinergic therapy did not improve UI compared to antimuscarinics alone but it did improve frequency and nocturia [163].

This review identified seven RCTs in which BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI [163].

Bladder training alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women [164]. Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short term. Whatever the method of training used, any benefit of BT on UI is likely to be of short duration unless the BT programme is practised repeatedly. No adverse events have been reported with BT. Biofeedback combined with BT increased continence rates and improved MUI in two RCTs [162].

4.1.3.2.3 Summary of evidence for bladder training

Summary of evidence	**LE**
Bladder training is effective for improvement of UI in women.	1b
The effectiveness of BT diminishes after the treatment has ceased.	2
The comparative benefit of BT and drugs for the improvement of UUI remains uncertain.	2
The combination of BT with antimuscarinic drugs does not result in greater improvement of UI but may improve frequency and nocturia.	1b
Bladder training is better than pessary alone.	1b
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b

BT = bladder training; UI = urinary incontinence; UUI = urgency urinary incontinence.

For recommendations see section 4.1.3.5.

4.1.3.3 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training is used to improve function of the pelvic floor, improving urethral stability. There is some evidence that improving pelvic floor function may inhibit bladder contraction in patients with OAB [165]. Pelvic floor muscle training may be used to prevent UI, e.g. in childbearing women before birth, in men about

to undergo radical prostatectomy, or as part of a planned recovery programme after childbirth or surgery. Most often, PFMT is used to treat existing UI, and may be augmented with biofeedback (using visual, tactile or auditory stimuli), surface electrical stimulation (ES) or vaginal cones.

4.1.3.3.1 Question

In adult men and women suffering from UI, does treatment with PFMT, given either alone or augmented with biofeedback, ES or vaginal cones, improve or cure UI or improve QoL, compared to no treatment, sham treatment or other conservative treatments, e.g. bladder training, ES or vaginal cones?

4.1.3.3.2 Evidence

In a recent UK Health Technology Appraisal (HTA), the role of PFMT in the care of women with SUI was analysed in a direct comparison of treatments using a mixed treatment comparison model, which compared different 'packages' of care [157]. This extensive meta-analysis reviewed data from 37 interventions and 68 direct comparisons, while the mixed treatment comparisons examined combinations of fourteen different types of intervention from 55 separate trials. The mixed treatment comparison used both indirect and direct comparisons and may provide more accurate estimates of effect. Where relevant, the Health Technology Appraisal has influenced the evidence and recommendations in these Guidelines. The Agency for Healthcare Research and Quality (AHRQ) review of nonsurgical treatment of UI in adult women also included indirect comparison methods as well as conventional meta-analysis [162].

4.1.3.3.3 Efficacy of PFMT in SUI, UUI and MUI in women

This question has been addressed by several SRs [157, 162, 166], all report inconsistency between studies because of poor reporting of technique and different outcome measures. Meta-analysis showed that PFMT was effective for cure or improvement of incontinence, and improvement in QoL. The effect applies in women with SUI, UUI and MUI though the effect in MUI is lower than in women with pure SUI. A Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [167]. No other consistent differences between techniques were found.

With regard to the durability of PFMT, another RCT reported fifteen-year follow-up outcomes of an earlier RCT, showing that long-term adherence to treatment was poor and half of patients had progressed to surgery [168]. Numerous SRs have addressed the question of whether the effects of PFMT and BT are additive [157, 162, 169]. These reviews are confounded by differences in patient selection and have arrived at conflicting conclusions leaving uncertainty about the extent to which one treatment may augment the other. Similarly, there remains uncertainty about the additional value of biofeedback with SRs reaching differing conclusions [162, 169].

Comparison of PFMT to other treatments was extensively reviewed by both AHRQ and the 2010 UK HTA [157, 162], which considered additional non-randomised data as part of a mixed treatment comparison. The UK HTA resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the HTA, using a revised methodology, supporting the general principle that greater efficacy was achieved by adding together different types of treatment and by increasing intensity.

Efficacy of PFMT in childbearing women

Two SRs [170, 171] reviewed RCTs in pregnant or postpartum women, which included PFMT in one arm of the trial. Treatment of UI with PFMT in the postpartum period increased the chances of continence at 12 months' postpartum.

4.1.3.3.4 PFMT in the elderly

The effect of PFMT in women with SUI does not seem to decrease with increased age: in trials with older women with SUI it appeared both primary and secondary outcome measures were comparable to those in trials focused on younger women [135, 164, 172].

4.1.3.3.5 PFMT in men (post radical prostatectomy)

A 2015 Cochrane review concluded that there was no overall benefit at twelve months post-surgery for men who received post-operative PFMT for the treatment of post-prostatectomy urinary incontinence (PPI) and that the benefits of conservative treatment of PPI remain uncertain [173]. A meta-analysis within this review showed that a greater proportion of men were dry from between three and twelve months suggesting that PFMT may speed recovery of continence. A subsequent study adds to this evidence [174].

Two additional RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [175, 176]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [177].

One RCT compared PFMT to no treatment in men undergoing trans-urethral resection of the prostate (TURP). There was no demonstrable difference in the incidence of post-operative incontinence up to twelve months [178].

4.1.3.3.6 Summary of evidence for pelvic floor muscle training

Summary of evidence	**LE**
Pelvic floor muscle training (PFMT) for women with UI	
Pelvic floor muscle training is better than no treatment for improving UI and QoL in women with SUI and MUI.	1
Higher-intensity, supervised treatment regimes, and the addition of biofeedback, confer greater benefit in women receiving PFMT.	1
Short-term benefits of intensive PFMT are not maintained at fifteen-year follow-up.	2
Pelvic floor muscle training commencing in the early postpartum period improves UI in women for up to twelve months.	1
Pelvic floor muscle training for post-prostatectomy UI	
Pelvic floor muscle training appears to speed the recovery of continence following radical prostatectomy.	1b
Pelvic floor muscle training does not cure UI in men post radical prostatectomy or transurethral prostatectomy.	1b
There is conflicting evidence on whether the addition of bladder training, ES or biofeedback increases the effectiveness of PFMT alone.	2
Pre-operative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b

ES = electrical stimulation; MUI = mixed urinary incontinence; PFMT = pelvic floor muscle training; QoL=quality of life; SUI = stress urinary incontinence; UI = urinary incontinence.

For recommendations see section 4.1.3.5.

4.1.3.3.7 Electrical stimulation

The details and methods of delivery of ES vary considerably. Electrical stimulation of the pelvic floor can also be combined with other forms of conservative therapy, e.g. PFMT and biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their pelvic floor muscles. Electrical stimulation is also used in patients with OAB and UUI, for detrusor inhibition. It has been suggested that ES probably targets the pelvic floor directly in SUI and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

4.1.3.3.8 Question

In adults with UI, does treatment with ES improve or cure symptoms of UI or QoL compared to no/sham treatment or antimuscarinics?

4.1.3.3.9 Evidence

Most evidence on ES refers to women with SUI. The topic has been included in two HTAs [157, 162] and three SRs [53, 179, 180]. The reviews include analysis of fifteen trials and use different comparison methods, but differ in their assessment of whether ES is more effective than sham stimulation and whether ES adds to the benefit of PFMT alone. Studies were considered to be of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters [173].

A subanalysis in a SR on one small low quality RCT in which ES had been compared to oxybutynin and PFMT in patients with UI, showed no difference in incontinence outcomes [181].

A Cochrane review of ES in men with UI (six RCTs) concluded that there was some evidence that ES enhanced the effect of PFMT in the short-term but not after six months. Electrical Stimulation was also more effective than sham stimulation at six, but not twelve months. There were, however, more adverse effects (pain or discomfort) with ES [182].

Electromagnetic stimulation has been promoted as treatment for UI but weak evidence of the short-term and long-term effects has been found in SRs [183, 184].

4.1.3.3.10 Summary of evidence for electrical stimulation

Summary of evidence	LE
In adults with UI, ES may improve UI compared to sham treatment and antimuscarinics.	2
Electrical stimulation may add benefit to PFMT in the short-term.	2

ES = electrical stimulation, PFMT = pelvic floor muscle training; UI = urinary incontinence.

For recommendations see section 4.1.3.5.

4.1.3.4 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done percutaneously with a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS). Treatment cycles typically consist of twelve weekly treatments of 30 minutes.

4.1.3.4.1 Question

In adults suffering from UUI, what is the clinical effectiveness of PTNS compared to sham treatment or alternative treatment such as antimuscarinic drugs?

4.1.3.4.2 Evidence

P-PTNS

The reviewed studies included two twelve-week RCTs of PTNS against sham treatment [185, 186], one comparing PTNS to tolterodine, and a three-year extension trial utilising a maintenance protocol in patients with UUI [187, 188]. The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who did not have adequate improvement or could not tolerate anti-muscarinic therapy. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women. In men there is insufficient evidence to reach a conclusion about efficacy.

T-PTNS

A small RCT compared transcutaneous PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [189]. Women in the T-TPNS group were more likely to achieve improvement at the end of therapy.

4.1.3.4.3 Summary of evidence for posterior tibial nerve stimulation

Summary of evidence	LE
Percutaneous posterior tibial nerve stimulation appears effective for improvement of UUI in women who have had no benefit from antimuscarinic medication.	2b
A maintenance programme of P-PTNS has been shown to be effective up to three years.	1b
Percutaneous Posterior tibial nerve stimulation has comparable effectiveness to tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
There is limited evidence for effectiveness of T-PTNS.	2a
There is no evidence that P-PTNS cures UI.	2b

P-PTNS = Percutaneous posterior tibial nerve stimulation; T-PTNS = transcutaneous posterior tibial nerve stimulation; UI=urinary incontinence; UUI=urge urinary incontinence.

4.1.3.5 Recommendations for behavioural and physical therapies

Recommendations	Strength rating
Offer prompted voiding for adults with UI who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with UUI or MUI.	Strong
Offer supervised intensive PFMT, lasting at least 3 months, as a first-line therapy to all women with SUI or MUI (including the elderly and post-natal).	Strong

Offer instruction on PFMT to men undergoing radical prostatectomy to speed recovery from UI.	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Do not offer ES with surface electrodes (skin, vaginal, anal) alone for the treatment of stress UI.	Strong
Do not offer magnetic stimulation for the treatment of UI or overactive bladder in adult women.	Strong
Consider PTNS as an option for improvement of UUI in women who have not benefited from antimuscarinic medication.	Strong

ES = electrical stimulation; MUI = mixed urinary incontinence; PFMT = pelvic floor muscle training; PTNS = percutaneous tibial nerve stimulation; SUI = stress urinary incontinence; UI = urinary incontinence; UUI = urge urinary incontinence.

*4.1.4 **Conservative therapy in mixed urinary incontinence***

About one-third of women with UI have MUI with symptoms of both SUI and UUI, and this becomes more common with increasing age. In terms of evidence base, many studies include patients with MUI, but it is rare for these studies to provide a separate analysis of patients with MUI.

4.1.4.1 Question

In adults with MUI, is the outcome of conservative therapy different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.1.4.2 Evidence

No specific SRs were found that addressed the above question. However, a Cochrane report on PFMT [166] concluded that training was less likely to result in a cure in patients with MUI than in patients with pure SUI, though it is not clear from the report how this conclusion was reached.

A small RCT (n = 71) compared delivery of PFMT, with or without an instructive audiotape. It showed equal efficacy for different types of UI [190].

Following a RCT of PFMT, a review of 88 women available for follow-up at five years found that outcomes were less satisfactory in women with MUI than in women with pure SUI [191].

4.1.4.3 Summary of evidence and recommendations for conservative therapy in mixed urinary incontinence

Summary of evidence	**LE**
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Electrical stimulation is equally effective for MUI and SUI.	1b

Recommendation	**Strength rating**
Treat the most bothersome symptom first in patients with MUI.	Weak

MUI = mixed urinary incontinence; SUI = stress urinary incontinence.

4.2 Pharmacological management

*4.2.1 **Antimuscarinic drugs***

Antimuscarinic (anticholinergic) drugs are currently the mainstay of treatment for UUI. They differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation.

The evaluation of cure or improvement of UI is made harder by the lack of a standard definition of improvement and the failure to use cure as a primary outcome. In general, SRs note that the overall treatment effect of drugs is usually small but larger than placebo.

Dry mouth is the commonest side effect, though constipation, blurred vision, fatigue and cognitive dysfunction may occur [162].

The immediate release (IR) formulation of oxybutynin is the archetype drug in the treatment of UUI. Oxybutynin IR provides maximum dosage flexibility, including an off-label ‘on-demand’ use. Immediate-release drugs have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system (TDS) and gel developed for oxybutynin gives a further alternative formulation.

4.2.1.1 Question

In adults with UUI, are antimuscarinic drugs better than placebo for improvement or cure of UUI and for the risk of adverse effects?

4.2.1.2 Evidence

Seven SRs of individual antimuscarinic drugs vs. placebo were reviewed for this section [162, 192-197] as well as studies published since these reviews up until April 2016. Most studies included patients with a mean age of 55-60 years. Both female and male subjects were included in different studies but results cannot be generalised across sexes. Only short-term rates for improvement or cure of UUI are reported. The evidence reviewed was consistent, indicating that ER and IR formulations of antimuscarinics offer clinically significant short-term cure and improvement rates for UUI compared to placebo. On balance, IR formulations tend to be associated with more side effects compared to ER formulations [196].

Cure of UI was deemed to be the most important outcome measure. Risk of adverse events was best represented by withdrawal from a trial because of adverse events, although this does not reflect practice. Table 2 shows a summary of the findings from a SRs [162]. In summary, every drug where cure of UI was available shows superiority compared to placebo in achieving UI, but the absolute size of effect is small. There is limited evidence that patients who do not respond to a first-line antimuscarinic treatment may respond to a higher dose or a different antimuscarinic agent [198, 199].

Table 2: Summary of cure rates and discontinuation rates of antimuscarinic drugs from RCTs which reported these outcomes [162]

Drug	**No. of studies**	**Patients**	**Relative risk (95% CI) (of curing UI)**	**Number needed to treat (95% CI) (to achieve one cure of UI)**
Cure of incontinence				
Fesoterodine	2	2,465	1.3 (1.1-1.5)	8 (5-17)
Oxybutynin (includes IR)	4	992	1.7 (1.3-2.1)	9 (6-16)
Propiverine (includes IR)	2	691	1.4 (1.2-1.7)	6 (4-12)
Solifenacin	5	6,304	1.5 (1.4-1.6)	9 (6-17)
Tolterodine (includes IR)	4	3,404	1.2 (1.1-1.4)	12 (8-25)
Trospium (includes IR)	4	2,677	1.7 (1.5-2.0)	9 (7-12)
Discontinuation due to adverse events				
			Relative Risk (95% CI) (of discontinuation)	**NNT (95% CI) (of one discontinuation)**
Darifenacin	7	3,138	1.2 (0.8-1.8)	
Fesoterodine	4	4,433	2.0 (1.3-3.1)	33 (18-102)
Oxybutynin (includes IR)	5	1,483	1.7 (1.1-2.5)	16 (8-86)
Propiverine (includes IR)	2	1,401	2.6 (1.4-5)	29 (16-77)
Solifenacin	7	9,080	1.3 (1.1-1.7)	78 (39-823)
Tolterodine (includes IR)	10	4,466	1.0 (0.6-1.7)	
Trospium (includes IR)	6	3,936	1.5 (1.1-1.9)	56 (30-228)

CI = confidence interval; NNT = number to treat; UI = urinary incontinence.

4.2.1.2.1 Darifenacin

The cure rates for darifenacin were not included in the AHRQ review. Continence rates were 29-33% for darifenacin compared to 17-18% for placebo [162].

4.2.1.2.2 Transcutaneous oxybutynin

Transdermal oxybutynin has shown a significant improvement in the number of incontinence episodes and micturitions per day vs. placebo and other oral formulations but continence was not reported as an outcome [162].

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured [162, 200].

4.2.2 ***Comparison of antimuscarinic agents***

Head-to-head comparison trials of the efficacy and side effects of different antimuscarinic agents are of interest for decision making in practice.

4.2.2.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI, and/or a greater improvement in QoL, and/or a lesser likelihood of adverse effects compared to an alternative antimuscarinic drug?

4.2.2.2 Evidence

There are over 40 RCTs and eight SRs [162, 181, 192, 194, 197, 201-203]. Nearly all the primary studies were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.

In general, these studies have been designed for regulatory approval. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real life practice is questionable. Most trials were of low or moderate quality [194]. The 2012 AHRQ review included a specific section addressing comparisons of antimuscarinic drugs (Table 2).

Fesoterodine

Results of an RCT of fesoterodine 4 vs. 8 mg suggested a larger therapeutic effect on UUI with the higher dose but with more adverse events [198].

No antimuscarinic agent improved QoL more than another agent [194]. Dry mouth is the most prevalent adverse effect. Good evidence indicates that, in general, higher doses of any drug are likely to be associated with higher rates of adverse events. Also, ER formulations of short-acting drugs and longer-acting drugs are generally associated with lower rates of dry mouth than IR preparations [194, 201]. Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily [194, 201]. Overall, oxybutynin ER has higher rates of dry mouth than tolterodine ER, although the incidence of moderate or severe dry mouth were similar. Transdermal oxybutynin had a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to an adverse skin reaction [194]. Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [194]. Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily [204-206]. In general, similar discontinuation rates were observed, irrespective of differences in the occurrence of dry mouth (doses have been given were the evidence relates to a specific dose level typically from trials with a dose escalation element).

4.2.2.3 Summary of evidence for antimuscarinic agents

Summary of evidence	**LE**
There is limited evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI.	1b
Higher doses of antimuscarinic drugs are more effective to cure or improve UUI, but with a higher risk of side effects.	1b
Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release ones, although similar discontinuation rates are reported in clinical trials.	1b
Dose escalation of antimuscarinic drugs may be appropriate in selected patients to improve treatment effect although higher rates of adverse events can be expected.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b

UUI=urge urinary incontinence.

4.2.3 ***Antimuscarinic drugs vs. conservative treatment***

The choice of drug vs. conservative treatment of UUI is an important question.

4.2.3.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to conservative treatment?

4.2.3.2 Evidence

More than 100 RCTs and high-quality reviews are available [163, 181, 194, 195, 207, 208]. Most of these studies were independent. A US HTA [181] found that trials were of a low- or moderate-quality. The main focus of the review was to compare the different drugs used to treat UUI. In one study, multicomponent behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient satisfaction for behavioural vs. drug treatment. In men with storage LUTS no difference in efficacy was found between oxybutynin and behavioural therapy [209].

The combination of BT and solifenacin in women with OAB conferred no additional benefit in terms of continence [210]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [211].

One RCT [212] reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation (T-PTNS) or oxybutynin. One study compared tolterodine ER to transvaginal/anal ES without differences in UI outcomes [213].

4.2.3.3 Summary of evidence and recommendations for antimuscarinic drugs

Summary of evidence	**LE**
There is no consistent evidence to show superiority of drug therapy over conservative therapy for treatment of UUI.	1b
Behavioural treatment has higher patient satisfaction than drug treatment.	1b
There is insufficient evidence as to the benefit of adding PFMT to drug treatment for UUI.	1b

Recommendations	**Strength rating**
Offer antimuscarinic drugs for adults with UUI who failed conservative treatment.	Strong
Consider extended release formulations of antimuscarinics drugs, whenever possible.	Strong
If an antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative antimuscarinic formulation, or mirabegron, or a combination.	Strong
Encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for UUI.	Strong

PFMT = pelvic floor muscle training; UUI = urgency urinary incontinence.

*4.2.4 **Antimuscarinic agents: adherence and persistence***

Most studies on antimuscarinic medication are short term (twelve weeks). Adherence in clinical trials is considered to be much higher than in clinical practice [214].

4.2.4.1 Question

Do patients with UUI adhere to antimuscarinic drug treatment and persist with prescribed treatment in clinical practice?

4.2.4.2 Evidence

This topic has been reviewed for the development of these Guidelines [215]. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49-84% [216, 217]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at twelve months, and particularly high (68-95%) for oxybutynin.

Five articles reported 'median days to discontinuation' as between < 30 days and 50 days [218-222]. In a military health system where free medication was provided, the median time to discontinuation extended to 273 days [219].

Data on adherence/persistence from open-label extension populations are questionable as these patients are self-selected to be compliant. A Longitudinal Disease Analyser database study has indicated an increasing discontinuation rate from 74.8% at one year to 87% at three years [223].

Several of the RCT trials tried to identify the factors associated with low/lower, adherence or persistence of antimuscarinics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), higher adherence rates were observed when drugs were provided at no cost to the patient [219].

Other reasons for poor adherence included:

- IR vs. ER formulations;
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African-Americans and other ethnic minorities are more likely to discontinue or switch treatment).

In addition, the data source influenced the adherence figures.

4.2.4.3 Summary of evidence for adherence to antimuscarinic treatment

Summary of evidence	**LE**
Adherence to antimuscarinic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2
Most patients will stop antimuscarinic agents within the first three months.	2

*4.2.5 **Mirabegron***

Mirabegron is the first clinically available beta3 agonist, available from 2013. Beta3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Mirabegron has undergone evaluation in industry-sponsored phase 2 and phase 3 trials [224-227]. Three SRs assessing the clinical effectiveness of mirabegron [224, 225, 228] reported that mirabegron at doses of 25, 50 and 100 mg, results in significantly greater reduction in incontinence episodes, urgency episodes and micturition frequency/24 hours than placebo, with no difference in the rate of common adverse events [224]. The placebo dry rates in most of these trials are between 35-40%, and 43 and 50% for mirabegron. In all trials the statistically significant difference is consistent only for improvement but not for cure of UI. Similar improvement in frequency of incontinence episodes and micturitions/24 hours was found in people who had previously tried and those who had not previously tried antimuscarinic agents. One SR showed that mirabegron is similarly efficacious as most antimuscarinics in reducing UUI episodes [229].

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to placebo [224, 227, 230].

In a twelve-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterodine ER 4 mg, the improvement in efficacy seen at twelve weeks was sustained at twelve-month evaluation in all groups. The reported dry rates at twelve months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [230]. *Post-hoc* analyses of RCTs showed that clinical improvement observed in parameters of OAB severity translates to an improvement in HRQoL and efficacy is maintained in patients with more severe degree of UI [231, 232].

No risk of QTc prolongation on electrocardiogram [233] and raised intraocular pressure [234] were observed up to 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in rate of side effects at different doses of mirabegron [230]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to antimuscarinics [235]. Patients on certain concurrent medications (i.e. metroprolol) should be counselled that, due to common metabolism pathways, their medication dosage may need to be adjusted. In the case of patients taking metoprolol, blood pressure should be monitored after starting mirabegron and, if necessary, metoprolol dosing changed.

Evaluation of urodynamic parameters in men with combined bladder outlet obstruction (BOO) and OAB concluded that mirabegron (50 or 100 mg) did not adversely affect voiding urodynamic parameters compared to placebo [236].

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [230]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (OAB-q and PPBC) [231, 237].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg, demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [238].

4.2.5.1 Summary of evidence and recommendations for mirabegron

Summary of evidence	**LE**
Mirabegron is better than placebo and as efficacious as antimuscarinics for improvement of UUI symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	**Strength rating**
Offer antimuscarinic drugs or mirabegron to adults with UUI who failed conservative treatment.	Strong

UUI = urgency urinary incontinence.

4.2.6 ***Antimuscarinic and beta3 agonist agents, the elderly and cognition***

Trials have been conducted in elderly people with UI. Considerations in this patient group include the multifactorial aetiology of UI in the elderly, comorbidities such as cognitive impairment, the effect of co-medications and the risk of adverse events.

The effects of antimuscarinic agents on cognition have been studied in more detail.

4.2.6.1 Question

What is the comparative efficacy, and risk of adverse effects, particularly the cognitive impact, of treatment with antimuscarinic medication in elderly men and women with UUI?

4.2.6.2 Evidence

Two SRs focusing on elderly patients are available [239, 240]. A community-based cohort study found a high incidence of cognitive dysfunction [241]. Other SRs have included sections on the efficacy and safety of antimuscarinics in elderly patients [162, 194]. A SR in 2012 found inconclusive evidence as to the impact of antimuscarinics on cognition [242].

Two recent longitudinal cohort studies in patients using drugs with antimuscarinic effect showed a deterioration in cognitive function, alteration in CNS metabolism and an association with brain atrophy [243, 244]. In general, the long-term impact of antimuscarinic agents specifically approved for OAB treatment on specific patient cohorts is poorly understood [245-248].

4.2.6.2.1 Oxybutynin

There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [245, 247, 249-253]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use of antimuscarinic medication including oxybutynin [243].

More rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction [254].

4.2.6.2.2 Solifenacin

One pooled analysis [255] has shown that solifenacin does not increase cognitive impairment in the elderly. No age-related differences in the pharmacokinetics of solifenacin in different age groups was found, although more frequent adverse events in subjects over 80 years of age were observed. No cognitive effect on healthy elderly volunteers was shown [253]. In a subanalysis of a large trial, solifenacin 5-10 mg improved symptoms and QoL in people ≥ 75 years who had not responded to tolterodine [256]. In patients with mild cognitive impairment, ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [252, 257].

4.2.6.2.3 Tolterodine

No change in efficacy or side effects related to age have been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [245]. Two RCTs in the elderly found a similar efficacy and side effect profile to younger patients [258-261]. *Post-hoc* analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [262].

4.2.6.2.4 Darifenacin

Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that darifenacin was effective with no risk of cognitive change, measured as memory scanning tests, compared to placebo [263, 264]. Another study on darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [247].

4.2.6.2.5 Trospium chloride

Trospium does not appear to cross the blood brain barrier in significant amounts in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two (EEG) studies in healthy volunteers showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [265, 266]. No evidence as to the comparative efficacy and side effect profiles of trospium in different age groups in available. However, there is some evidence that trospium does not impair cognitive function [248, 267] and that it is effective compared to placebo in the elderly [268].

4.2.6.2.6 Fesoterodine

Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of the 8 mg but not the 4 mg dose in over 75-year olds [216]. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported [206, 216, 269]. A more recent RCT showed efficacy of fesoterodine in the vulnerable elderly with no differences in cognitive function at twelve weeks [270].

4.2.6.2.7 Anti-incontinence drugs in the elderly

RCTs comparing duloxetine and placebo included women up to 85 years, but no age stratification of the results is available [195, 271, 272].

4.2.6.2.8 Mirabegron

Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [273].

4.2.6.2.9 Applicability of evidence to general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of antimuscarinic side effects may be the most helpful [241]. When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [274]. No consensus exists as to the best mental function test to detect changes in cognition [254, 275].

4.2.6.2.10 Anticholinergic load

A number of medications have anticholinergic effects and their cumulative effects on cognition should be considered [276].

4.2.6.2.11 Question

In older people suffering from UI, what is the effect of anticholinergic burden (defined by anticholinergic cognitive burden scale) on cognitive function?

4.2.6.2.12 Evidence

No studies were identified specifically in older people with UI, but evidence was available from observational cohort studies relating to the risk in a general population of older people. Lists of drugs with anticholinergic properties are available from two sources [276, 277].

Two SRs of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [278, 279].

Longitudinal studies in older people over two to four years have found increased rate of decline in cognitive function for patients on anticholinergics or drugs with anticholinergic effects [243, 244, 280, 281].

4.2.6.3 Summary of evidence and additional recommendations for use of antimuscarinic drugs in the elderly

Summary of evidence	LE
Antimuscarinic drugs are effective in elderly patients.	1b
Mirabegron has been shown to be efficacious and safe in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly patients.	2
Solifenacin, darifenacin, fesoterodine and trospium have been shown not to cause cognitive dysfunction in elderly people in short-term studies.	1b

Recommendations	Strength rating
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	Strong

4.2.6.4 Research priorities

- All drug trials should report cure rates for UI based on a bladder diary.
- What is the relative incidence of cognitive side effects of antimuscarinic drugs?

4.2.7 ***Drugs for stress urinary incontinence***

Duloxetine inhibits the presynaptic re-uptake of neurotransmitters, serotonin (5-HT) and norepinephrine (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurones, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

4.2.7.1 Questions

- In adults with SUI, does duloxetine cure or improve UI and/or improve QoL compared to no treatment?
- In adults with SUI, does duloxetine result in a greater cure or improvement of UI, or a greater improvement in QoL, or a lesser likelihood of adverse effects, compared to any other intervention?

4.2.7.2 Evidence

Duloxetine was evaluated as a treatment for female SUI or MUI in three SRs [195, 271, 272].

Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in I-QoL was not found in the study using I-QoL as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [282], duloxetine reduced leakage compared to PFMT or no treatment.

Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment.

Two open-label studies with a follow-up of one year or more evaluated the long-term effect of duloxetine in controlling SUI; however, both had high discontinuation rates [283, 284].

All studies had a high patient withdrawal rate, which was caused by a lack of efficacy and high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue, amongst other causes [283, 284].

A SR showed significant efficacy for duloxetine compared to placebo in women with UI but with increased risk of adverse events [272].

4.2.7.3 Summary of evidence and recommendations on drugs for SUI

Summary of evidence	LE
Duloxetine, 40 mg twice daily improves SUI in women.	1a
Duloxetine causes significant gastrointestinal and central nervous system side effects leading to a high rate of treatment discontinuation, although these symptoms are limited to the first weeks of treatment.	1a

Recommendations	Strength rating
Offer Duloxetine in selected patients with symptoms of SUI when surgery is not indicated.	Strong
Duloxetine should be initiated and withdrawn using dose titration because of high risk of adverse event.	Strong

SUI = stress urinary incontinence.

*4.2.8 **Oestrogen***

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [285-287]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

4.2.8.1 Questions

- In women with UI, does vaginal (local) oestrogen cure or improve UI compared to no treatment or other active treatment?
- In women with UI, does oral (systemic) oestrogen cure or improve UI compared to no treatment?

4.2.8.2 Evidence

Vaginal oestrogens

A Cochrane SR looked at the use of oestrogen therapy in postmenopausal women [285] given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases [288].The Cochrane review (search date cut off June 2012) found that vaginal oestrogen treatment improved symptoms of UI in the short term [285]. The review found small, low quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, ES and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes although more women preferred the ring device. No adverse effects of vaginal administration of oestradiol for vulvovaginal atrophy over two years was seen in one trial [289].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. The ideal treatment duration and the long-term effects are uncertain. A standardised review of local oestrogen showed improvement of UI over placebo with vaginal rings favoured subjectively over pessaries; no significant difference between vaginal and oral oestrogen treatments was found [290].

One RCT in postmenopausal women showed benefit in adding intravaginal oestriol to vaginal ES and PFMT [291].

Systemic oestrogens

Studies of HRT with non-urogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo [292-295]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [296]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [53, 297, 298].

4.2.8.3 Summary of evidence and recommendations for oestrogen therapy

Summary of evidence	LE
Vaginal oestrogen therapy improves UI for post-menopausal women in the short term.	1a
Neoadjuvant or adjuvant use of local oestrogens are ineffective as an adjunct to surgery for UI.	2
Systemic hormone replacement therapy using conjugate equine oestrogens in previously continent women increases the risk of developing UI and worsens pre-existing UI.	1a

Recommendations	Strength rating
Offer long-term vaginal oestrogen therapy to post-menopausal women with UI and symptoms of vulvo-vaginal atrophy.	Strong
In women with a history of breast cancer, the treating oncologist should be consulted.	Weak
For women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or experience worsening UI, discuss alternative hormone replacement therapies.	Strong
Advise women who are taking systemic oestradiol who suffer from UI that stopping the oestradiol is unlikely to improve their incontinence.	Strong

UI = urinary incontinence.

*4.2.9 **Desmopressin***

Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone). It can be taken orally, nasally or by injection. Desmopressin is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.

4.2.9.1 Questions

- In adults with UI, does desmopressin cure or improve UI and/or improve QoL compared to no treatment?
- In adults with UI, does desmopressin result in a lesser likelihood of adverse effects, compared to any other intervention?

4.2.9.2 Evidence

4.2.9.2.1 Improvement of incontinence

Few studies have examined the use of desmopressin exclusively for the treatment of UI. No evidence was found that demonstrated any effect of desmopressin on nocturnal incontinence, though evidence does exist for it reducing nocturnal polyuria, particularly in children [299]. One RCT compared desmopressin to placebo with daytime UI as an outcome measure, with improved continence shown during the first four hours after taking desmopressin in women [300].There is no evidence reporting desmopressin cure rates for UI and no evidence that compares desmopressin with other non-drug treatments for UI.

4.2.9.2.2 Monitoring for hyponatraemia

The use of desmopressin carries a risk of developing hyponatraemia (please refer to the EAU Guidelines on Male LUTS [30]).

4.2.9.3 Summary of evidence and recommendations for desmopressin

Summary of evidence	LE
The risk of UI is reduced within four hours of taking oral desmopressin, but not after four hours.	1b
Continuous use of desmopressin does not improve or cure UI.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	Strength rating
Consider offering desmopressin to patients requiring occasional short-term relief from daytime UI and inform them that this drug is not licensed for this indication.	Strong
Monitor plasma sodium levels in patients on desmopressin.	Strong
Do not use desmopressin for long-term control of UI.	Strong

UI = urinary incontinence.

*4.2.10 **Drug treatment in mixed urinary incontinence***

4.2.10.1 Question

In adults with MUI, is the outcome of a drug treatment different to that for the same treatment in patients with either pure SUI or UUI?

4.2.10.2 Evidence

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI, but not SUI suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [301]. In another

study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [302]. Similar results were found for solifenacin [303, 304].

Duloxetine
In one RCT of duloxetine vs. placebo in 588 women, subjects were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups [305].

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations [306].

4.2.10.3 Summary of evidence and recommendations for drug treatment in mixed urinary incontinence

Summary of evidence	**LE**
Limited evidence suggests that antimuscarinic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and UUI in patients with MUI.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with MUI.	Weak
Offer antimuscarinic drugs or beta3 agonists to patients with urgency-predominant MUI.	Strong
Consider offering duloxetine for patients with MUI unresponsive to other conservative treatments and who are not seeking cure.	Strong

MUI = mixed urinary incontinence; SUI=stress urinary incontinence; UUI=urge urinary incontinence.

4.3 Surgical management

In line with the recommendations from the UK National Institute for Healthcare and Clinical Excellence (NICE) [53] the Panel agreed that surgeons and centres performing surgery should:
- be trained in the field of incontinence and for each surgical procedure they perform/offer;
- not be trained by someone who is not surgically qualified;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for long-term follow-up.

This section considers surgical options for:
- Women with uncomplicated SUI: This means no history of previous surgery, no neurogenic LUT dysfunction, no bothersome genitourinary prolapse, and women not considering further pregnancy.
- Women with complicated SUI: Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology [2].
- Associated genitourinary prolapse has been included in these Guidelines in terms of treating incontinence, but no attempt has been made to comment on treatment of prolapse itself.
- Men with SUI: mainly men with post-prostatectomy incontinence without neurological disease affecting the LUT.
- Patients with refractory DO and low compliance bladders.

Although the outcome of surgical procedures should be considered in terms of cure, it is also important to consider any associated complications, adverse events and costs. The outcome parameters used to evaluate surgery for SUI have included:
- continence rate and number of incontinence episodes;
- patient-reported outcome measures;
- general and procedure-specific complications;
- generic, specific (UI) and correlated (sexual and bowel) QoL.

In this context it has to be taken into account that a number of products may no longer be available and therefore the recommendations may not be transferable to current devices. The Panel makes a strong recommendation that new devices are only used as part of a structured research programme and their outcomes monitored in a registry.

4.3.1 ***Women with uncomplicated stress urinary incontinence***

4.3.1.1 Mid-urethral slings

Early clinical studies identified that non-autologous slings should be made from monofilament, non-absorbable material, typically polypropylene, and constructed as a 1-2 cm wide mesh with a relatively large pore size (macroporous). Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

Safety of mid-urethral slings

A population-based study performed in Scotland on over 16,000 women operated on for SUI showed a similar rate of complications between mesh and non-mesh surgery confirming the safety of mesh procedure for UI [307]. However, a recent study of over 92,000 patients followed in the National Health Service (UK) showed a significant (9.8%) rate of complications using a more broad definition and following patients for a longer period of time. These findings suggest that, as with any SUI surgery, mid-urethral sling (MUS) surgery can be associated with complications and proper informed consent is mandatory.

4.3.1.1.1 Questions

In women with SUI, what is the effectiveness in curing SUI and adverse effects for:

- mid-urethral synthetic sling insertion compared to Burch colposuspension?
- one method of insertion of a MUS compared to another method?
- one direction of insertion of a MUS compared to another direction of insertion?
- colposuspension compared to autologous fascial sling.

4.3.1.1.2 Evidence

For the purpose of these Guidelines, a new meta-analysis was performed.

A Cochrane review of open retropubic colposuspension in the treatment on UI was published in 2016 [308]. Overall, colposuspension is associated with a continence rate of 85-90% at 1 to 5 years post-operatively and about 70% of patients can expect to be dry after five years. Comparison of colposuspension vs. MUS showed non difference in subjective or objective evaluation of incontinence rates at any time point (one to five years and five years and more time points). A subanalysis of autologous fascialslings showed better effectiveness compared to colposuspension at one to five years follow-up. In a RCT of Burch colposuspension vs. autologous fascial slings, continence rates decreased substantially over time in both arms. At five years, continence rate of colposuspension was 24.1% compared to 30.8% for fascial slings, satisfaction remained higher in the sling group (83% vs. 73%) and was related to the continence status [309]. Adverse events rates were similar for the two treatment groups with Burch 10% and sling 9% although post-operative obstruction was found exclusively in the sling group.

In general, open retropubic colposuspension does not seem to be associated with higher morbidity and complications compared to MUS. Pelvic organ prolapse is more common after colposuspension and voiding dysfunction occurs more often after MUS [308].

Transobturator route vs. retropubic route

A Cochrane meta-analysis of mid-urethral sling procedures for SUI in women was performed in 2017 spanning January 1947 to June 2014 [310]. Moderate quality evidence from 55 studies showed variable, but comparable, subjective cure rates between retropubic and transobturator slings (62-98% in the transobturator arms and 71-97% in the retropubic arms) in the short term (up to one year). No difference in the objective cure rate in the short term was found. A lower number of studies provide medium (one to five years) and long-term (over five years) follow-up with no difference in the subjective cure rates in the mid- and long-term. In the long term, a subjective cure rate of 43-92% in the transobturator group and of 51-88% in the retropubic group was found.

Although the adverse event rates are low, the retropubic approach was associated with a higher rate of bladder perforation (4.5% vs. 0.6%) and voiding dysfunction; vascular and visceral injury, mean operative time, operative blood loss and hospital stay were lower in the transobturator groups.

Transobturator surgery was associated with a lower risk of voiding dysfunction but groin pain was more frequent (6.4% vs. 0.6%). The opposite occurred for suprapubic pain (0.8% in the transobturator and 2.9% in the retropubic groups, respectively). The overall vaginal erosion risk was low and comparable in both groups (2.1% in retropubic and 2.4% in transobturator surgery). Re-do surgery for UI was more common in the transobturator group (RR = 8.79, 95% CI: 3.36-23) however the data is limited and of low quality

In retropubic surgery, the bottom-to-top route was 10% more efficacious than top-to-bottom in terms of subjective cure and it was associated with less voiding dysfunction, bladder perforations and vaginal erosion.

Analysis of the TOMUS trial (a randomised equivalence trial of retropubic vs. transobturator MUS for the treatment of SUI in women) confirms equivalence of objective cure rates at 12 but not at 24 months (77.3% and 72.3% objective cure rate for retropubic and transobturator surgery). Subjective cure rates are inconclusive for equivalence. Patient satisfaction (86.3% vs. 88.1%), frequency of *de novo* UUI (0% vs. 0.3%) and mesh exposure (4.4% vs. 2.7%) did not differ significantly between the retropubic and transobturator groups. Subjective and objective treatment success continues to decrease over time and equivalence of the retropubic and the transobturator routes cannot be confirmed at 24 and 60 months with retropubic demonstrating a slight benefit, however satisfaction remained high in both arms [311]. The cumulate rate of serious adverse events was nearly twice as high in the retropubic group compared with the transobturator group at 24 months, but they occurred much less often in the second year of follow-up [312].

An economic evalution of retropubic vs. transobsturator tapes suggests that the latter may be cost-effective and cost-saving compared to the standard tension-free vaginal tape (TVT) approach over a five years period [313].

Ten years data are available from a RCT of TVT, xenograft and autologous fascial slings. Dry rates were 31.7%, 50.8% and 15.7% at ten years, for TVT, autologous and Pelvicol™ fascial slings, respectively, down from 55%, 48% and 22% measured at one year follow-up. Re-operation rates at ten years were 3.2% in the TVT group, none in the autologous fascial sling arm and 13.1% in the Pelvicol group [314]. Satisfaction rates were 69.3%, 70.1%, 52.6% for TVT, autologous and Pelvicol fascial slings, respectively.

Long-term results of a RCT comparing TVT vs. inside-out trans-obturator tape (TOT) showed a 79.3% and a 69.4% objective cure rate at 95 months, however patient-reported cure rates were 74.1% and 61.3%, respectively. The long-term complication rates for TVT and TVT-O were 43.1% and 27.4% respectively ($p = 0.07$). [315].

Surgery in obese women

There is no agreement as to the outcome of incontinence surgery in obese women. Secondary analysis of a RCT on retropubic and transobturator tapes in the treatment of women with SUI suggests that obese women experience inferior outcome compared to non-obese women. Stratification of patients according to BMI (< 30 and ≥ 30) shows significant difference in objective dry rates (negative pad test) at one (85.6% vs. 67.8%) and five years (87.4% vs. 65.9%) and subjective cure (absence of SUI symptoms) at one (85.8% vs. 70.7%) and five years (76.7% vs. 53.6%, respectively). Between one and five years, 6.7% and 16.3% of patients initially dry (negative pad test) after surgery developed a positive pad test, respectively [316, 317].

Conversely, short-term outcome of single-incision MiniArc sling showed comparable objective cure rates (negative cough stress test) at two years (86% and 81% in non-obese and obsese women, respectively); similar improvement of the Urinary Distress Inventory 6 and Incontinence Impact questionnaire 7 was observed in non-obese and obese women [318].

Long-term outcome of MUS (≥ 5 years)

Long-term follow-up of MUS is rarely available from RCTs and more often from cohort studies. Evaluation of the long-term (nine years) outcome of the E-TOT study using postal questionnaires showed a 71.6% patient-reported success rate (very/much improved) on the Patient's Global Impression of Improvement (PGI-I) scale. The nine-years success rates are lower than observed in the first year (80%) but comparable with the three-year follow-up (73.1%). Overall, 8% of patients had re-do surgery, tape extrusion/erosion rate was 4.5%, and groin pain/discomfort was reported in 4.32%, with only 1.4% requiring treatment [319].

Long-term efficacy of transobturator mid-urethral slings was confirmed by the ten-year follow-up of a large patient cohort with 92% cure rate (160 of 168 implanted patients were available for evaluation). *De novo* OAB developed in 14% of patients at ten years. History of failure of previous anti-incontinence procedures was the only predictor of recurrence of SUI (hazard ratio: 5.34; 95% CI: 2.61–11.9; $p = 0.009$) [320].

Long-term follow-up of patients treated with TVT showed a sustained response with 95.3%, 97.6%, 97.0% and 87.2% of patients being cured or improved at 5, 7, 11 and 17 years, respectively [321].

Another long-term cohort study of retropubic tension-free vaginal tape showed a 89.9% objective cure rate, a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported to be highly satisfied with the surgery [322].

Insertion using a skin-to-vagina direction vs. a vagina-to-skin direction

A Cochrane review of MUS operations for female SUI showed no difference in the short and medium-term

subjective cure rates in medial-to-lateral vs. lateral-to-medial approaches based on moderate quality evidence [310]. Voiding dysfunction seems to be more frequent in the medial-to-lateral group but this approach is associated with a lower frequency of vaginal perforations (RR 0.25, 95% CI: 0.12-0.53; 3 trials). Because of the low quality of the evidence it is unclear whether the lower frequency of vaginal perforations of the medial-to-lateral approach is responsible for the observed lower rate of vaginal tape erosions.

A meta-analysis of RCTs demonstrated no significant difference in efficacy between lateral-to-medial vs. medial-to-lateral approaches, but vaginal perforations were less frequent in the medial-to-lateral group (2.6% vs. 11.8%, OR: 0.21, p = 0.0002) [323].

The five-year data of a prospective, non-randomised study of the two techniques showed a very high objective success rate (82.6 vs. 82.5%, respectively) with no difference between the two approaches [324].

In a secondary analysis of the E-TOT study (a study of transobturator tension-free vaginal tapes in the treatment of women with urodynamic MUI), no difference in the patient-reported success rates was found between the inside-out and the outside-in groups (63.2% and 65.5%, respectively; OR 1.11, 95% CI: 0.33-3.70, P > 0.999) at 9 years follow-up [325].

4.3.1.2 Adjustability

4.3.1.2.1 Questions

- In women with SUI, does an adjustable sling cure SUI and improve QoL or does it cause adverse outcome(s)?
- How does an adjustable sling compare with other surgical treatments for SUI?

4.3.1.2.2 Evidence

There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence. The available devices have differing designs, making it difficult to draw general conclusions about adjustable slings as a class of procedure.

4.3.1.3 Single-incision slings

4.3.1.3.1 Questions

- In women with SUI, do single-incision slings cure UI or improve QoL, or cause adverse outcomes?
- How does a single-incision sling compare to other surgical treatments for SUI?

4.3.1.3.2 Evidence

Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operations. It should also be noted that some devices have been withdrawn from the market (e.g. TVT Secur®, Minitape, MiniArc©), and yet evidence relating to these may be included in current meta-analyses. There was evidence to suggest single-incision slings are quicker to perform and cause less post-operative thigh pain, but there was no difference in the rate of chronic pain. There was insufficient evidence for direct comparisons between single-incision slings, and reach any conclusions about differences.

The most recent meta-analyses [326, 327] and a re-analysis of the Cochrane review data by the Panel (excluding TVT Secur® data) have demonstrated that there was no difference in efficacy between available single-incision devices and conventional mid-urethral slings at one year. However, not all single-incision devices have been subjected to RCT evaluation and it may be unsafe to assume that they are collectively technically similar devices.

Generalisability of evidence to adult women with SUI

Analysis of the population studied in trials included in this meta-analysis suggests that the evidence is generalisable to women who have predominantly SUI, and no other clinically severe LUT dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI. The results of the EAU Panel meta-analysis [328] were consistent with those of the Cochrane SR [329], except that in the EAU Panel meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The EAU Panel finding is consistent with an additional SR and meta-analysis [330] and the difference may result from the Panel's decision to only consider trial data with at least twelve months of follow-up.

Sexual function after mid-urethral tape surgery
A SR of the effect of female sexual function following mid-urethral slings suggested contradictory results, overall more papers show an improvement, or no change, in sexual function because of a reduction in coital incontinence, anxiety and avoidance of sex. Dyspareunia was the most common cause of worsening of sexual life [331].

A meta-analysis of outcome measures in trials of sling procedures suggests that single-incision slings are associated with a significantly higher improvement in sexual life compared to standard mid-urethral procedures [332].

SUI surgery in the elderly
An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 [333]. An RCT assessing risk factors for the failure of TVT vs. transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at one year [334]. In a sub-analysis of a trial cohort of 655 women at 2 years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI: 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo re-treatment for SUI (OR 3.9, 95% CI: 1.3-11.48). There was no difference in time to post-operative normal voiding [335].

Another RCT comparing immediate TVT vs. no surgery (delayed TVT) in older women, confirmed efficacy of surgery in terms of QoL and satisfaction, but with complications in the surgical arm [336].

A cohort study evaluating 181 women undergoing TVT-O surgery, found that women over 70 years had similar outcomes when compared to women under 70 years old in terms of cure rates (92.5% vs. 88.3% p = 0.40), voiding dysfunction, vaginal erosion and groin pain at a median follow-up of 24 months [337].

A SR of the efficacy of treatments of UI in older patients suggests that MUS are successful in older patients (≥ 65 years) with 5.2-17.6% reporting persistent SUI after surgery. No difference in the frequency of *de novo* UUI, persistent UUI and persistant SUI was found in older patients [338].

4.3.1.3.3 Summary of evidence for mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS provides equivalent patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Mid-urethral synthetic slings inserted by either the transobturator or retropubic route provide equivalent patient-reported outcome at five years.	1a
Mid-urethral synthetic slings inserted by the retropublic routes has higher objective patient-reported cure rates at 8 years.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond ten years.	2b
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a
Long-term analysis showed no difference in terms of efficacy for the skin-to-vagina compared to vagina-to-skin directions up to nine years.	2a
The top-to-bottom direction in the retropubic approach is associated with a higher risk of post-operative voiding dysfunction.	1b
Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard MUS.	4
The comparative efficacy of single-incision slings against conventional MUS is uncertain.	1b
Operation times for insertion of single-incision MUS are shorter than for standard retropubic slings.	1b
Blood loss and immediate post-operative pain are lower for insertion of single-incision slings compared with conventional mid-urethral slings.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional MUS.	1b
Incontinence surgery has similar outcomes in older patients (≥ 65 years).	2a

The risk of failure from surgical repair of SUI, or suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4
Incontinence surgery may be safely performed in obese women, however, outcomes may be inferior.	2b
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following SUI surgery.	2a
Improvement in sexual life is higher with single incision slings than with standard MUS.	1a

MUS = mid-urethral sling; SUI = stress urinary incontinence; TVT = tension-free vaginal tape.

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVT-S) device and although this device is no longer available, many women still have the device in place.

4.3.1.4 Open and laparoscopic surgery for stress urinary incontinence

Open colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

4.3.1.4.1 Question

In women with SUI, what is the effectiveness of open and laparoscopic surgery, compared to other surgical procedures, measured in terms of cure or improvement of incontinence or QoL, or the risk of adverse events?

4.3.1.4.2 Evidence

Four SRs were found, which covered the subject of open surgery for SUI, including 46 RCTs [2, 339-341]. Risk of re-operation for Burch colposuspension is estimated to 6% within 5 years [342] and 10.8% (95% CI: 9.3–12.3) within 9 years [343] .

Open colposuspension

The Cochrane review [308] included 55 trials in which 5,417 women had open colposuspension. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Consequently, for this review we have only considered the absolute effect of colposuspension, but have not reviewed all of these comparisons. No additional trials have been reported since this review.

Within the first year, complete continence rates of approximately 85-90% were achieved for open colposuspension, while failure rates for UI were 17% up to five years and 21% over five years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development, at five years, of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) compared to TVT (23% and 32%, respectively) but with a lower risk of voiding dysfunction compared to sling surgery. The rate of cystocoele was similar in colposuspension (37%) and with TVT (41%). The Cochrane review concluded that open colposuspension is an effective treatment for SUI and 70% of women can expect to be dry at five years after surgery.

Autologous fascial sling

The Cochrane review [340, 344] described 26 RCTs, including 2,284 women undergoing autologous sling procedure in comparison to other operations [345].

There were seven trials of autologous fascial sling vs. colposuspension. Except for one very high-quality study [52] showing superiority of fascial sling, most of the studies were of variable quality, with a few very small studies and short follow-up. The meta-analysis showed that fascial sling and colposuspension had a similar cure rate at one year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In twelve trials of autologous fascial sling vs. mid-urethral synthetic slings, the procedures showed similar efficacy. However, use of the synthetic sling resulted in shorter operating times and lower rates of complications, including voiding difficulty. Six trials compared autologous fascial slings with other materials of different origins, with results favouring traditional autologous fascial slings. *Post-hoc* analysis of an RCT comparing the autologous fascial sling to Burch colposuspension showed inferior outcomes for women who suffered pre-operative urgency [335].

Laparoscopic colposuspension

The Cochrane review reported on twelve trials comparing laparoscopic colposuspension to open colposuspension. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic colposuspension. However, laparoscopic colposuspension had a lower risk of complications and shorter duration of hospital stay and may be slightly more cost-effective when compared with open colposuspension after 24 months follow-up.

In eight RCTs comparing laparoscopic colposuspension to MUS, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at eighteen months. Complication rates were similar for the two procedures and operating times were shorter for the MUS. Comparisons of colposuspension to mid-urethral sling are covered in section 4.3.1.1.

Single-port laparoscopic Burch can be an alternative treatment for scarless surgery, though data confirming efficacy is limited [346].

4.3.1.4.3 Summary of evidence for open and laparoscopic surgery for stress urinary incontinence

Summary of evidence	**LE**
Autologous fascial sling is more effective than colposuspension for improvement of SUI.	1b
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and post-operative UTI.	1b
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a

POP = pelvic organ prolapse; SUI = stress urinary incontinence ; UTI = urinary tract infection.

4.3.1.5 Bulking agents

The concept of this procedure originates from the idea that intra or periurethral injection of an agent able to solidify under the submucosa or around the urethra, respectively, will form artificial cushions which increase the resistance to urine flow and facilitate continence.

4.3.1.5.1 Question

In women with SUI, does injection of a urethral bulking agent cure SUI or improve QoL, or cause adverse outcomes?

4.3.1.5.2 Evidence

A Cochrane review identified 14 randomised or quasi-randomised controlled trials of treatment for urinary incontinence in which at least one management arm involved periurethral or transurethral injection therapy [347]. Following this review, five additional reviews investigated the effect of injectables for the treatment of female SUI [348-352] but one review included results from RCTs only [352], independently of the injected material. Altogether, 1,814 patients were included from fourteen trials of seven different types of intraurethral injection: glutaraldehyde cross-linked collagen (Contigent©), a porcine dermal implant (Permacol©), solid silicone elastomer (Macroplastique©), autologous fat, pyrolytic carbon (Durasphere©), calcium hydroxylapatite (Coaptite©), hydrogel (Bulkamid©) and dextran polymer (Zuidex©). The heterogeneity of the populations, the variety of materials used and the lack of long-term follow-up limit guidance of practice. Most of the studies show a tendency for a short-term improvement in urinary incontinence, with the exception of a RCT which could not find difference between saline and fat injection [353]. The short-term analysis from the RCT does not give information about the effect of repeated injections.

A recent SR of 26 studies with 12 months follow-up showed objective success rates using urodynamics, 24-h pad tests, cough tests and voiding diaries ranging from 25.4% to 73.3%. A SR of 23 studies using Macroplastique© including 958 patients showed 75% improvement and 43% dry patients at less than 6 months but 64% improvements and 36% cures at more than 18 months [349]. A review of 514 elderly women with SUI treated with various agents showed a reduced pad weight in 73% at one year follow-up independently of the material injected [354]. Proximal urethral injection showed better outcome than mid-urethral injections [355]. Intra-urethral injections or peri-urethral injections produce similar outcomes, although the latter is associated with a higher risk of temporary urinary retention [347]. One study treated patients who had received radiotherapy with injection of Bulkamid© and reported around 25% cure at short term follow-up [356].

Bulking agent injection is safe, the most frequent adverse event being UTI. However, autologous fat or hyaluronic acid should not be used due to the risk of fatal embolism and local abscess formation, respectively [347, 352].

Comparison with open surgery
Two RCTs compared collagen injection to conventional surgery for SUI (autologous sling vs. silicon particles and collagen vs. other surgical procedures/bulking agents). The studies reported greater efficacy but higher complication rates for open surgery. In comparison, collagen injections showed inferior efficacy but equivalent levels of satisfaction and fewer serious complications [53, 357].

Another trial found that a peri-urethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection [358]. A recent small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [359].

4.3.1.5.3 Summary of evidence for bulking agents

Summary of evidence	**LE**
Peri-urethral injection of bulking agent may provide short-term improvement and cure (twelve months), in women with SUI.	1b
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
The peri-urethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

4.3.1.6 Recommendations for women with uncomplicated stress urinary incontinence

Recommendations	**Strength rating**
Offer a MUS to women with uncomplicated SUI	Strong
Inform women of the unique complications associated with each individual procedure.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong
Inform women undergoing colposuspension that there is a longer duration of surgery, hospital stay and recovery, as well as a high risk of development of pelvic organ prolapse and voiding dysfunction post-operatively.	Strong
Inform older women with SUI about the increased risks associated with surgery, including the lower probability of success.	Weak
Inform women that any vaginal surgery may have an impact on sexual function, which is generally positive.	Weak
Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.	Strong
Only offer adjustable MUS as a primary surgical treatment for SUI as part of a structured research programme.	Strong
Offer bulking agents to women with SUI who request a low-risk procedure with the understanding that repeat injections are likely and long-term durability is not established.	Strong

MUS = mid-urethral sling; SUI = stress urinary incontinence.

*4.3.2 **Complicated stress urinary incontinence in women***
This section will address surgical treatment for women who have had previous surgery for SUI, which has failed, or those women who have undergone previous radiotherapy affecting the vaginal or urethral tissues. Neurogenic LUT dysfunction is reviewed by the EAU Guidelines on Neuro-Urology [2]. Women with associated genitourinary prolapse are included in this edition (see section 4.3.3).

4.3.2.1 Colposuspension or sling following failed surgery
There may be persistent or recurrent SUI, or the development of *de novo* UUI. This means that careful evaluation including urodynamics becomes an essential part of the work-up of these patients.

4.3.2.1.1 Question

In women who have had failed surgery for SUI, what is the effectiveness of any second-line operation, compared to any other second-line operation, in terms of cure or improvement of UI, QoL or adverse events?

4.3.2.1.2 Evidence

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons.

The 4th International Consultation on Incontinence includes a review of this topic [1] up to 2008, and the subject has also been reviewed by Ashok [360] and Lovatsis *et al.* [361]. A further literature review has been carried out since that time by the Panel.

Cochrane reviews of individual operative techniques have not included separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol to address this issue [362]. Only one RCT was found (abstract only) comparing TVT to laparoscopic colposuspension in women with recurrent SUI. This small study found similar cure rates and adverse events in the short term for both procedures [363].

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have shown conflicting evidence of relative effectiveness [78, 335, 364, 365]. One large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for fascial sling [366].

Several cohort studies have reported outcomes for TVT specifically for primary and secondary cases. Evidence on the effectiveness of second-line retropubic tapes conflicts with some series showing equivalent outcomes for primary and secondary cases [367, 368], whilst other research has shown inferior outcomes for secondary surgery [369, 370]. Other confounding variables make meaningful conclusions difficult.

Systematic review of older trials of open surgery for SUI suggest that the longer-term outcomes of redo open colposuspension may be poor compared to autologous fascial slings [371]. Successful results have been reported from mid-urethral slings after various types of primary surgery, while good outcomes are reported for both repeat TVT and for 'tightening' of TVT, but data are limited to small case series only.

Systematic meta-analysis of retropubic (TVT) vs. transobsturator (TOT) MUS in the treatment of recurrent SUI showed no difference in terms of patient-reported or objective cure/improvement after a mean follow-up of eighteen months. In one RCT no difference between Burch colposuspension and TVT could be observed in either patient-reported or objective cure/improvement rates [372].

A large cohort study (112 pts) of mid-urethral slings for recurrent SUI showed an overall subjective success rate (cured/improved) of 76.8% at 21 months with no significant differences between the retropubic and transobturator routes [373].

4.3.2.1.3 Summary of evidence for colposuspension or sling following failed surgery for stress urinary incontinence

Summary of evidence	**LE**
There is conflicting evidence whether prior surgery for SUI or prolapse results in inferior outcomes from repeat operations for SUI.	2
Most procedures will be less effective when used as a second-line procedure.	2
In women who have had more than two procedures for SUI, the results of open colposuspension are inferior to autologous fascial sling.	2
Tension-free vaginal tape (TVT) and TOT have similar outcomes in patients with recurrent SUI.	1a
Burch colposuspension has similar patient-reported or objective cure rates when compared to TVT.	1b

SUI = stress urinary incontinence; TOT = trans-obturator tape; TVT = tension-free vaginal tape.

4.3.2.2 External compression devices

External compression devices are still widely used in the treatment of recurrent SUI after the failure of previous surgery and if there is thought to be profound intrinsic failure of the sphincter mechanism, characterised by very low leak point pressures or low urethral closure pressures. This should be confirmed by urodynamic evaluation.

The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT©) device and the artificial urinary sphincter (AUS). Using ultrasound or fluoroscopic guidance, the ACT© device is inserted by placement of two inflatable spherical balloons on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. More recently, an adjustable artificial urinary sphincter (Flowsecure™) has been introduced. It has the potential added benefit of 'conditional occlusion', enabling it to respond to rapid changes in intra-abdominal pressure.

4.3.2.2.1 Questions

- In women with SUI, does insertion of an external compressive device cure SUI, improve QoL or cause adverse outcomes?
- How do external compression devices compare to other surgical treatments for SUI?

4.3.2.2.2 Evidence

The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [115]. However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices. A recent consensus report has standardised the terminology used for reporting complications arising from implantation of materials into the pelvic floor region [20].

Artificial urinary sphincter (AUS)

A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women [374].

There are a few case series in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from one month to 25 years [375-378]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cures in 59-88%. Common side effects included mechanical failure requiring revision (up to 42% at ten years) and explantation (5.9-15%). In a retrospective series of 215 women followed up for a mean of six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [378]. Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation [376].

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design, has been introduced to clinical use. A series of 100 patients reported 28% explantation at four years but the device has undergone redesign and more up-to-date evidence is awaited [379]. Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [380, 381].

Adjustable compression device (ACT©)

There are four case series (n = 349), with follow-up ranging from five to 84 months [382-385]. Reported outcome ranged from 47% objective cure to 100% subjective improvement. However, most patients required adjustment to achieve continence and 21% required explantation.

4.3.2.2.3 Summary of evidence for external compression devices

Summary of evidence	**LE**
Implantation of an artificial sphincter can improve or cure incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the adjustable compression therapy (ACT©) device may improve complicated UI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT©.	3
Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

4.3.2.3 Recommendations for complicated stress urinary incontinence

Recommendations	Strength rating
Management of complicated SUI should only be offered in expert** centres.	Weak
The choice of surgery for recurrent SUI should be based on careful evaluation of the individual patient including multichannel urodynamics and imaging as appropriate.	Weak
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated SUI.	Weak
Inform women receiving AUS or ACT© that although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Weak

ACT© = Adjustable compression device; AUS = artificial urinary sphincter; SUI = stress urinary incontinence; UI = urinary incontinence.

*** Expert centres refers to the comments on surgeon volume in the introduction to the surgical chapter.*

*4.3.3 **Women with both stress urinary incontinence and pelvic organ prolapse***

There is a clear association between the presence of POP and SUI. Although the subject of prolapse is not part of the remit of these Guidelines, the extent to which it impacts on the management of SUI will be addressed. The aim is to assess the options available to women who require surgery for POP and who have associated UI (either symptomatic or after reduction of prolapse), and to assess the value of prophylactic anti-incontinence surgery in women with no evidence of UI.

4.3.3.1 Questions

1. In women with POP and UI, does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?
2. In continent women with POP, does combined surgery for POP and SUI reduce the incidence of post-operative *de novo* UI compared to POP surgery alone?
3. In women with POP and occult SUI, (i.e. seen only on prolapse reduction stress testing/ urodynamics), does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?
4. In women with POP and OAB, does surgery for POP improve OAB symptoms?
5. In adults with POP, what is the reliability, the diagnostic accuracy and predictive value of a prolapse reduction test to identify patients at risk from *de novo* SUI following prolapse repair?

4.3.3.2 Evidence

A Cochrane review in 2013 included sixteen trials concerning bladder function after surgery for pelvic organ prolapse [386]. After prolapse surgery 434 of 2,125 women (20.4%) reported new subjective SUI, in sixteen trials. New voiding dysfunction was reported in 109 of 1,209 (9%) women, in twelve trials. A recent SR and metanalysis assessing prolapse surgery with or without stress incontinence surgery found that combination surgery reduces the risk of post-operative SUI, but short-term voiding difficulties and adverse events were more frequent after combination with a MUS [387].

1. In women with POP does combined surgery for POP and SUI reduce the incidence of post operative UI compared to POP surgery alone?

In summary, it is difficult to generalise the results of trials using very different procedures to treat both POP and UI. It seems that with a combined procedure the rate of SUI post-operatively is lower. Studies using mid-urethral slings have generally shown more significant differences in UI outcomes with combined procedures than when other types of anti-incontinence procedure have been used. Individual patient characteristics may play the most important role in shaping treatment decisions. It must be taken into account that, although more women may be dry after combined surgery, the risks of repeat surgery, should it become necessary, may outweigh the potential benefits.

There are two well-designed RCTs relating to the prevalence of post-operative SUI in women (continent or incontinent) who underwent prolapse surgery with and without an anti-incontinence procedure. Both of these trials involved women with POP who did not complain of symptoms of SUI regardless of objective findings.

One trial compared abdominal sacrocolpopexy with and without Burch colposuspension [363], the other compared vaginal repair with and without a mid-urethral sling [364]. In both trials addition of anti-

incontinence surgery reduced the risk of SUI at twelve months. In one trial there was a higher rate of adverse events reported in the combined surgery group [364]. This was also the finding of the Cochrane review and meta-analysis.

The most recent RCT by van der Ploeg including 7 trials found that significantly more women in the combined therapy group reported the absence of post-operative SUI [387]. They concluded that women undergoing POP surgery should be counselled about the possibility of combination surgery. They should know that there is strong evidence that post-operative SUI is less frequent after combining prolapse and anti-incontinence surgery relative to prolapse surgery only. However, the number needed to treat to prevent one SUI is probably considerable. The rate of adverse events is likely to be higher with combined surgery. Further evaluation was undertaken according to subgroups (with or without UI prior to surgery).

Women with POP and SUI

Three trials addressed post-operative SUI in patients who had SUI pre-operatively. Borstad *et al.*, in a multicentre trial, randomised women with POP and SUI to have a TVT at the time of prolapse repair or three months later, if they still had SUI (n = 53). One year after surgery there was no difference between the groups regarding continence; however, 44% of the women without initial TVT never required surgery and 29% were dry [388].

In contrast, Costantini *et al.* followed-up women with POP and SUI randomised to abdominal POP repair with or without Burch colposuspension (after a median of 97 months), finding that additional SUI surgery did not improve outcome [389]. On the contrary, a higher number of patients had *de novo* storage symptoms when a Burch colposuspension was performed.

The most recent RCT by van der Ploeg *et al.* found that more women in the combined therapy group reported the absence of UI (62% vs. 30%) and SUI (78% vs. 39%) [390]. Seventeen percent of women undergoing POP surgery alone required an additional MUS. Severe complications were more common in the MUS group 16% vs. POP surgery only 6%.

2. Women with POP asymptomatic for SUI

A pooled anlaysis of all studies (5) in continent women shows a reduction in both objective and subjective post-operative SUI after combined surgery with a reduced need for subsequent anti-incontinence surgery [387]. The number needed to treat (NNT) was six to prevent one woman developing *de novo* subjective SUI after POP repair, and 20 to prevent one woman undergoing an additional MUS.

3. Women with POP and occult SUI

A recent RCT by van der Ploeg *et al* found adressing occult incontinence found that women with occult SUI had a higher risk of reporting SUI after POP surgery than women without occult SUI [391]. Thirteen percent of women undergoing POP surgery aloneneeded an additional MUS. This is in line with the outcomes reported in the earlier SR. The NNT to prevent one woman with occult SUI from developing *de novo* subjective SUI after POP repair was three [387].

4. Women with POP and OAB

There are three case series evaluating patients with concomitant OAB and pelvic organ prolapse which assess incontinence/OAB symptom scores post-surgical repair. Costantini *et al.* assessed the effect of posterior repair on OAB/DO and reported a 70-75% improvement rate in both parameters along with a 93% anatomic success rate [392]. Kummeling *et al.* assessed the effect of a modified laparoscopic sacrocolpopexy on urodynamic parameters and reported an improvement with no evidence to support a concomitant prophylactic colposuspension [393]. Lee *et al.* assessed the value of pre-operative urodynamic study and bladder outlet obstruction index (BOOI) in predicting the degree of OAB symptoms post anterior prolapse repair. They reported a significant correlation between low pre-operative BOOI and improvement in OAB symptom scores post-operative [394].

5. Prolapse reduction stress test (PRST)

Data concerning PRST were made available from the CARE trial, where significant differences were noted in the detection of urodynamic stress incontinence with prolapse reduction among the various methods studied, ranging from 6% (pessary) to 30% (speculum). Manual, swab and forceps showed detection rates of 16%, 20% and 21%, respectively [395]. In the study by Duecy, about one third of women were diagnosed with occult SUI using a pessary while two thirds were diagnosed with manual reduction of the prolapse [396]. In a further study occult SUI was only detected by a pessary test in 19% of patients, not by urodynamics, history or clinical examination [397].

4.3.3.3 Summary of evidence for women with both stress urinary incontinence and pelvic organ prolapse

Summary of evidence	LE
Women with pelvic organ prolapse and urinary incontinence	
Surgery for pelvic organ prolapse (POP) + SUI shows a higher rate of cure of UI in the short term than POP surgery alone.	1a
There is conflicting evidence on the relative long-term benefit of surgery for POP + SUI vs. POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1a
Continent women with pelvic organ prolapse	
Are at risk of developing UI post-operatively.	1a
The addition of a prophylactic anti-incontinence procedure reduces the risk of post-operative UI.	1a
The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events.	1a
Women with pelvic organ prolapse and overactive bladder	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of overactive bladder.	2

4.3.3.4 Recommendations for women with both stress urinary incontinence and pelvic organ prolapse

Recommendations for women requiring surgery for bothersome pelvic organ prolapse who have symptomatic or unmasked SUI	Strength rating
Offer simultaneous surgery for pelvic organ prolapse and SUI.	Strong
Inform women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome pelvic organ prolapse who do not have symptomatic or unmasked SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of surgery for SUI may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	Strong

POP = pelvic organ prolapse; SUI = stress urinary incontinence; UI = urinary incontinence.

*4.3.4 **Urethral diverticulum***

A female urethral diverticulum is a sac-like protrusion made up by the entire urethral wall or only by the urethral mucosa situated between the periurethral tissues and the anterior vaginal wall. Urethral diverticula give rise to a variety of symptoms that include pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or urinary incontinence.

4.3.4.1 Question

In a woman with the clinical suspicion of having a urethral diverticulum, what is the best test to confirm the diagnosis?

4.3.4.2 Evidence

No robust diagnostic accuracy studies address this question. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than voiding cystourethrography (VCUG) [398]. In a case series of 60 subjects Pathi, *et al.* reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI is 100%, 83%, 92% and 100%, respectively [399]. Dwarkasing *et al.* also reports 100% specificity and sensitivity of MRI in a case series of 60 patients [400]. However, in a case series of 41 patients, a study reported 25% discrepancy between MRI and surgical findings [401].

4.3.4.3 Question

In a woman who has a bothersome urethral diverticulum, what is the relative effectiveness of available surgical treatments?

4.3.4.4 Surgical treatment

No RCTs were found. Surgical removal is the most commonly reported treatment in contemporary case series. However, recurrence may occur; Han *et al.* found a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within one year [402], Ingber *et al.* found a 10.7% recurrence rate in 122 women

undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [403]. SUI may occur in up to 20% of women after diverticulectomy, requiring additional correction [404-407]. *De novo* SUI seems to be more common in proximal and in large size (> 30 mm) diverticula.

Diverticula may undergo neoplastic alterations (6%) including invasive adenocarcinomas [408].

4.3.4.5 Summary of evidence and recommendation for urethral diverticulum

Summary of evidence	LE
Magnetic resonance imaging has good sensitivity and specificity for the diagnosis of urethral diverticula; however, there is a risk of misdiagnosis and missing potential intraluminal neoplastic change.	3
Surgical removal of symptomatic urethral diverticula provides good long-term results; however, women should be counselled of the risk of recurrence and de novo SUI.	3

Recommendations	Strength rating
Symptomatic urethral diverticula should be completely surgically removed.	Strong

SUI = stress urinary incontinence.

*4.3.5 **Men with stress urinary incontinence***

In men who fail conservative treatment (see chapter 4.1.3.3.5) other treatments can be considered.

4.3.5.1 Drug therapy

Three RCTs suggest an earlier recovery of continence in men receiving duloxetine either alone [409], or in addition to PFMT, for post prostate surgery SUI [410, 411].

4.3.5.1.1 Summary of evidence for drug therapy in men with stress urinary incontinence

Summary of evidence	LE
Duloxetine, either alone or combined with conservative treatment, can hasten recovery of continence but does not improve continence rate following prostate surgery, but can be associated with significant, albeit often transient, side effects.	1b

4.3.5.2 Bulking agents in men

Injection of bulking agents has been used to try and improve the coaptation of a damaged sphincter zone. Initial reports showed limited efficacy in treating incontinence following radical prostatectomy [412, 413].

4.3.5.2.1 Question

In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.2.2 Evidence

Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials [414, 415]. However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI [414]. A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria [416]. A prospective, randomised study compared the AUS to silicone particles (Macroplastique™) in 45 patients. Eighty-two per cent of patients receiving an AUS were continent compared to 46% receiving silicone particles. In patients with severe incontinence, outcome was significantly worse after silicone bulking injection.

4.3.5.2.3 Summary of evidence for bulking agents in men

Summary of evidence	LE
There is no evidence that bulking agents cure post-prostatectomy incontinence.	2a
There is weak evidence that bulking agents can offer temporary, short-term, improvement in QoL in men with post-prostatectomy incontinence.	3
There is no evidence that one bulking agent is superior to another.	3

QoL = quality of life

4.3.5.3 Fixed male sling

In addition to external compression devices and bulking agents, slings have been introduced to treat post-prostatectomy incontinence. Fixed slings are positioned under the urethra and fixed by a retro-pubic or transobturator approach. The tension is adjusted during the surgery and cannot be re-adjusted post-operatively.

For the restoration of continence by these male slings, two concepts are now being proposed:

- continence restoration by urethral compression (InVance®, I-stop TOMS©);
- continence restoration by repositioning the bulb of urethra (AdVance©) [417].

In principle, the AUS can be used for all degrees of post-prostatectomy incontinence, while male slings are advocated for mild-to-moderate UI. However, the definitions of mild and moderate UI are not clear. The definition of cure, used in most studies, was no pad use or one security pad per 24 hours. Some authors used a stricter criterion of less than 2 g urine loss in a 24-hour pad test [418].

4.3.5.3.1 Question

In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.3.2 Evidence

Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available [419-421]. There are a large number of uncontrolled case series concerning men implanted with several types of slings [422, 423].

For the repositioning sling (AdVance©), the benefit after a mean follow-up of three years has been published on 136 patients [424]. Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between three months and three years. Subjective cure rates for the device vary between 8.6% and 73.7%, with a mean of 49.5%. Pelvic radiotherapy was a negative prognostic factor [422]. Post-operative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%) [418, 424-426]. The overall failure rate was about 20%.

The previously available 'InVance®' device has now been removed from the market in some countries.

The strategy of intraoperative placement of an autologous vas deferens sling below the vesico-urethral anastomosis during robotic-assisted radical prostatectomy (RARP) has been explored with the intention to improve early return of continence. Two RCTs [427, 428] showed an advantage of sling vs. no sling at one month follow-up, and another study [429] showed an advantage of a 6-branch vs. a 2-branch sling at one month follow-up. However, a larger RCT [n = 195] showed that continence rate and near-continence rate were similar at six months with 66 vs. 65% and 88 vs. 87%, respectively [430].

4.3.5.3.3 Summary of evidence for fixed male sling

Summary of evidence	LE
There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
There is no evidence that intraoperative placement of an autologous sling during RARP improves return of continence at 6 months.	1b
Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

RARP = robotic assisted radical prostatectomy.

4.3.5.4 Adjustable slings in males

Adjustability in male sling surgery attempts to adjust the tension of the sling post-operatively. Three main systems have been used in men: the Remeex® system, the Argus® system and the ATOMS® system.

4.3.5.4.1 Question

In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure or improve SUI, improve QoL, or cause adverse outcomes?

4.3.5.4.2 Evidence

There are no RCTs. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success. Some have been published only as conference abstracts. For the Remeex® system, only two abstracts, with conflicting findings, have been published. One study followed nineteen patients for nearly seven years and reported 70% success, with no explants, infections or erosions. The second study followed fourteen patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [431].

Argus® system

Data on the Argus® system has been reported for 404 men, but only four series have reported on more than 50 patients [432, 433], with the longest follow-up being 2.4 years. Success rates varied between 17% and 91.6%, with a mean of 57.6% predominantly reporting a subjective cure. The number of implants requiring re-adjustment was reported as between 22.9% and 41.5% [433]. Infection of the device occurred in 5.4-8% [432]. Erosions were reported in 5-10% [434]. Urethral perforations occurred in 2.7-16% [432]. Pain at the implant site was usually only temporary, but chronic pain has been reported [432, 434]. These complications resulted in explantation rates of 10-15% [433].

The ATOMS® system consists of a mesh implant with an integrated adjustable cushion, which uses a titanium port left in the subcutaneous tissue of the lower abdomen or scrotum for adjustment of cushion volume. Initial reports show objective cure rates of 60.5% and improvement rates of 23.7% but with the need for up to nine post-operative adjustments [435, 436].

4.3.5.4.3 Summary of evidence for adjustable slings in males

Summary of evidence	**LE**
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is limited evidence that early explantation rates are high.	3
There is no evidence that adjustability offers additional benefit over other types of sling.	3

SUI = stress urinary incontinence.

4.3.5.5 Compression devices in males

External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen [419]. The artificial urinary sphincter (AUS) is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation are from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Men considering insertion of an AUS should understand that if the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognised complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection. The non-circumferential compression devices consist of two balloons placed close to the vesico-urethral anastomotic site. The balloons can be filled and their volume can be adjusted post-operatively through an intra-scrotal port. Men who develop cognitive impairment or lose manual dexterity will have difficulty operating an AUS.

4.3.5.5.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.5.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, there are three SRs [416, 421, 437] presenting limited evidence, of generally poor quality, except for one RCT comparing AUS with bulking

agents [412]. A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy [419].

Trigo Rocha *et al.* published a prospective cohort study on 40 patients with a mean follow-up of 53 months, showing that from all urodynamic parameters only low bladder compliance had a negative impact on the outcome [438]. Another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [439].

The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking [440]. The dual-cuff placement was introduced to treat patients who remained incontinent with a single 4 cm cuff in place. However, it has not improved control of UI, while the availability of a 3.5 cm cuff may have eliminated the need for a dual cuff [441, 442]. Patients who experienced complete continence after AUS implantation had a higher erosion risk [443]. One small series reported results of AUS implantation after failure of previous AdVance© sling, showing no difference in efficacy between secondary and primary implantation [444].

Non-circumferential compression device (ProAct®)

There have been trials to treat post-prostatectomy SUI by insertion of a device consisting of balloons with adjustable volume external to the proximal bulbar urethra. A prospective cohort study (n = 128) described the functional outcome as 'good' in 68%, while 18% of the devices had to be explanted [445]. A subgroup of radiotherapy patients only had 46% success and a higher percentage of urethral erosions.

A quasi-randomised trial comparing a non-circumferential compression device (ProAct®) with bone-anchored male slings found that both types of device resulted in similar improvement of SUI (68% vs. 65%, respectively) [446]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [421, 447-450]. A questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence [451]. Other designs of artificial sphincter remain the subject of ongoing evaluation though they may have been introduced onto the market.

4.3.5.5.3 Summary of evidence for compression devices in males

Summary of evidence	LE
There is evidence that primary AUS implantation is effective for cure of SUI in men.	2b
Long-term failure rate for AUS is high although device replacement can be performed.	3
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
The usefulness of tandem-cuff placement is uncertain.	3
There is insufficient evidence to state whether one surgical approach for cuff placement is superior to another.	3
Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.	3
The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.	3
The rate of explantation of the AUS because of infection or erosion remains high (up to 24% in some series).	3
Mechanical failure is common with the AUS.	3
Revision and re-implantation of AUS is possible after previous explantation or for mechanical failure.	3

AUS = artificial urinary sphincter; SUI = stress urinary incontinence.

4.3.5.6 Recommendations for men with stress urinary incontinence

Recommendations	Strength rating
Offer duloxetine only to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events and that its use is off label for this indication in most European countries.	Weak
Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of incontinence symptoms.	Weak
Do not offer bulking agents to men with severe post-prostatectomy incontinence.	Weak
Offer fixed slings to men with mild-to-moderate* post-prostatectomy incontinence.	Weak

Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.	Weak
Offer AUS to men with moderate-to-severe post-prostatectomy incontinence.	Weak
Implantation of AUS or ProACT© for men should only be offered in expert centres.	Weak
Warn men receiving AUS or ProACT© that, although cure can be achieved, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Weak
Do not offer non-circumferential compression device (ProACT©) to men who have had pelvic radiotherapy.	Weak

** The terms "mild" and "moderate" post-prostatectomy incontinence remain undefined.*
ACT© = artificial compression device; AUS = artificial urinary sphincter.

*4.3.6 **Surgical interventions for refractory detrusor-overactivity***

4.3.6.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX®) 100 U dissolved in 10 mL of saline and injected in 20 points of the bladder wall above the trigone (0.5 mL per injection site) is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both genders, despite the small number of males included in the registration trials [452, 453]. Surgeons must realise that other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxin A and incobotulinum toxin A, are not licensed for use in UUI. Doses for onabotA are not transposable to the other brands of botulinum toxin A. The continued efficacy of repeat injections is the rule but discontinuation rate may be high. The most important adverse events related to onabotA 100 U injection detected in the regulatory trials were UTI and an increase in PVR that may require clean intermittent catheterisation [454].

4.3.6.1.1 Question

In adults with UUI, is bladder wall injection of onabotA better than no treatment for cure or improvement?

4.3.6.1.2 Evidence

Following a dose ranging study in which the 100 U of onabotA was established as the ideal dose, two phase III trials randomised (1:1) 1,105 OAB incontinent patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline, the population had on average more than five episodes of UUI, around twelve micturitions per day and a small PVR. At week twelve, in patients treated with onabotA, UUI episodes/day were halved and the number of micturitions/day reduced by more than two. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [455].

Quality of life was substantially improved in the onabotA arm, as shown by the more than 60% of positive responses in the Treatment Benefit Scale questionnaire at week twelve, which was double the positive responses in the saline arm. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly [456], though the success rate might be lower and the PVR (> 150 mL) higher in this group.

The median time to request re-treatment in the pooled analysis of the two RCTs was 24 weeks [454, 455]. Follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months [457].

A recent RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed similar rates of improvement in UUI over the course of six months [458]. However, patients receiving onabotA were not only more likely to have cure of UUI (27% vs. 13%, p = 0.003), but also had higher rates of urinary retention during the initial two months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking antimuscarinics were more likely to have dry mouth.

Identification of DO in urodynamics does not influence the outcome of onabotulinum toxin A injections in patients with UUI [61].

4.3.6.1.3 Summary of evidence and recommendations for bladder wall injection of botulinum toxin A

Summary of evidence	LE
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI and QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteriuria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to solifenacin for cure of UUI, but rates of improvement were equivalent.	1b

Recommendations	Strength rating
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with UUI refractory to conservative therapy (such as PFMT and/or drug treatment).	Strong
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to self-catheterise (ensure that they are willing and able to do so).	Strong

PFMT = pelvic floor muscle training PVR = post-void residual; QoL = quality of life; UUI = urgency urinary incontinence; UTI = urinary tract infection.

4.3.6.2 Sacral nerve stimulation (neuromodulation)

In the first stage of a two-stage implantation, an electrode is placed percutaneously under fluoroscopic control in the sacral foramen alongside a sacral nerve, usually S3. In earlier techniques, a temporary wire electrode was used. More recently, a permanent tined electrode has been used for a longer test phase. Patients, in whom selected symptoms of UUI are reduced by more than 50% during the test phase, are candidates for the full implant, including the pulse generator, and reported results only apply to this sub population.

4.3.6.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

4.3.6.2.2 Evidence

All randomised studies suffer from the limitation that assessors and patients were not blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. A Cochrane review of the literature until March 2008 [459] identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared to 1.6% of the control group [460]. The other RCT [461] achieved similar results, although these patients had already been included in the first report [460]. However, Weil *et al.* [461] showed that the effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions.

The results of seventeen case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation, were reviewed [462]. After a follow-up duration of between one and three years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50-90% improvement, and another 25% demonstrated < 50% improvement. Two case series describing the outcome of sacral nerve neuromodulation, with a mean or median follow-up of at least four years [463, 464] reported continued success (> 50% improvement on original symptoms) in patients available for follow-up. Cure rates for UUI were 15% [464]. A RCT comparing a strategy of onabotulinum toxinA injection of 200 U, repeated as required, against a strategy of test and permanent sacral nerve neuromodulation [465] (ROSETTA trial) showed lower cure rates with SNM: at six months, 20% in the onabotulinumtoxinA group and 4% in the sacral neuromodulation group had complete resolution of UUI ($p < .001$). Forty-six percent in the onabotulinumtoxinA group and 26% in the sacral neuromodulation group had at least a 75% reduction in the number of episodes of UUI ($p < .001$). This 4% cure rate is also lower than the 6 months cure rate in another RCT of sacral neuromodulation vs. standard medical therapy which reported a 39% continence rate in the sacral neuromodulation group at 6 months; however, the mean (SD) baseline leaks per day (2.4 [± 1.7]) for the sacral

neuromodulation group in the study were lower than in the ROSETTA trial (5.3 [± 2.7]), reflecting a less severe population [466].

Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33-41% [463, 464]. In a subanalysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with or without urodynamic DO [467].

4.3.6.2.3 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	**LE**
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.	1b
Sacral nerve neuromodulation is not more effective than OnabotulinumA toxin 200 U injection at 6 months.	1b
In those patients who have been implanted, at long-term, 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured.	3
The use of tined, permanent electrodes in a staged approach results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendations	**Strength rating**
Offer sacral nerve modulation to patients who have UUI refractory to antimuscarinic therapy.	Strong

UUI = urgency urinary incontinence.

4.3.6.3 Cystoplasty/urinary diversion

4.3.6.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be used if it has the appropriate mesenteric length. One study did not find any difference between bivalving the bladder in the sagittal or in the coronal plane [468, 469]. The procedure can be done, with equal success by open or robot techniques, although the robotic consumes considerably more operative time [470].

There are no RCTs comparing bladder augmentation to other treatments for patients with UUI. Most often, bladder augmentation is used to correct neurogenic DO or small-capacity, low-compliant, bladders caused by fibrosis, chronic infection such as tuberculosis, radiation or chronic inflammation from interstitial cystitis.

The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [471]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. It seems that the results for patients with idiopathic DO (58%) appeared to be less satisfactory than for patients with neurogenic UUI (90%).

Adverse effects were common and have been summarised in a review over five to seventeen years of more than 267 cases, 61 of whom had non-neurogenic UUI [472]. In addition, many patients may require clean intermittent self-catheterisation to obtain adequate bladder emptying (Table 3). It is unclear if mucolytic agents will reduce mucus accumulation. The only RCT that was identified comparing various mucolytic agents did not find significant benefits with the use of N-acetylcysteine, aspirin, or ranitidine. In one small study (n = 40), the use of subcutaneous octreotide immediately before, and for 15 days after surgery was reported to yield significant reductions in mucus production, the need for bladder irrigation to clear blockages, and the mean duration of hospital stay [473]

Depending on the relative costs of Onabotulinum Toxin A and augmentation cytoplasty, the latter can be cost effective within five years if the complication rate is low and duraton of effect of Onabotulinum Toxin A < 5 months [474].

Table 3: Complications of bladder augmentation

Short-term complications	**Affected patients (%)**
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	**Affected patients (%)**
Clean intermittent self-catheterisation	38
Urinary tract infection	70% asymptomatic 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.3.6.3.2 Detrusor myectomy (bladder auto-augmentation)

Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal 'bulge' or pseudo-diverticulum. It was initially described as an alternative to bladder augmentation in children [475].

Two case series [476, 477] in adult patients with idiopathic and neurogenic bladder dysfunction, demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum. This technique is rarely, if ever, used nowadays.

4.3.6.3.3 Urinary diversion

Urinary diversion remains a reconstructive option for patients with intractable incontinence after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation. These patients may be offered irreversible urinary diversion surgery. Options include ileal conduit urinary diversion, orthotopic neobladder and heterotopic neobladder with Mitrofanoff continent catheterisable conduit. There is insufficient evidence to comment on which procedure leads to the most improved QoL.

A small study compared ileal with colonic conduits and concluded that there were no differences in the relative risks of UUT infection and uretero-intestinal stenosis. However, there are no studies that have specifically examined these techniques in the treatment of intractable UUI [468]. Therefore, careful consideration on which operation is undertaken will depend on patient factors and informed patient choice.

4.3.6.3.4 Summary of evidence and recommendations for cystoplasty/urinary diversion

Summary of evidence	**LE**
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and long-term severe complications.	3
The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.	3
Detrusor myectomy is ineffective in adults with UI.	3

Recommendations	Strength rating
Offer augmentation cystoplasty to patients with UI who have failed all other treatment options.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they need lifelong surveillance.	Weak
Do not offer detrusor myectomy as a treatment for UI.	Weak
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of UI and who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

DO = detrusor overactivity; UI = urinary incontinence.

*4.3.7 **Surgery in patients with mixed urinary incontinence***

4.3.7.1 Question

In adults with MUI, is the outcome of surgery different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.3.7.2 Evidence

Many RCTs include both patients with pure SUI or pure UUI and patients with MUI. However, very few RCTs report separate outcomes for MUI and pure UI groups.

Post-hoc analysis of the SISTER trial showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency [335]. A similar *post-hoc* review of another RCT comparing transobturator and retropubic mid-urethral slings showed that the greater the severity of pre-operative urgency, the more likely that treatment would fail [78]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO). Another RCT with 93 patients with MUI showed a statistical improvement in continence and QOL in the group that had TVT and Botox rather than with either treatment alone [478].

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing mid-urethral sling insertion, overall satisfaction rates were lower for women with mixed symptoms and detrusor overactivity on pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [479]. A comparison of two parallel cohorts of patients undergoing surgery for SUI, with and without DO, found inferior outcomes in women with MUI [480].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI [481]. In a study with 1,113 women treated with transvaginal obturator tape, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency predominant MUI [482].

In a prospective, multicentre, comparative trial, 42 women who had a TVT for mixed UI had a greater improvement in urgency and QOL scores than 90 women who had a TOT. There were no significant differences in the cure and satisfaction rates between the two groups [483].

Overall, the outcome for women with pre-existing urgency incontinence remains uncertain.

4.3.7.3 Summary of evidence and recommendations for surgery in patients with mixed urinary incontinence

Summary of evidence	LE
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	1b
The response of pre-existing urgency symptoms to SUI surgery is unpredictable.	3

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with MUI.	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for SUI alone.	Strong
Inform women with MUI that one single treatment may not cure UI; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Strong

MUI = mixed urinary incontinence; SUI = stress urinary incontinence; UI = urinary incontinence.

4.3.7.4 Research priorities

Research trials should define accurately what is meant by 'mixed urinary incontinence'.
There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

*4.3.8 **Surgery for urinary incontinence in the elderly***

There are no RCTs comparing surgical treatment in older vs. younger women although subgroup analyses of some RCTs have included a comparison of older with younger cohorts.

A RCT of 537 women comparing retropubic to transobturator tapes, showed that cure rates decreased and failure increased with each decade over the age of 50 [333]. A RCT assessing risk factors for failure of TVT vs. TOT in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at one year [334]. In a subanalysis of the SISTER trial cohort of 655 women at 2 years of follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI: 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo re-treatment for SUI (OR 3.9, 95% CI: 1.3-11.48). There was no difference in time to normal post-operative voiding [335].

Another RCT compared immediate TVT vs. delayed TVT in older women, confirming significant efficacy for the women operated upon, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) [336].

A cohort study of 256 women undergoing inside-out TOT reported similar efficacy in older vs. younger women, but there was a higher risk of *de novo* urgency in older patients [330].

Cohort studies have shown the effectiveness of onabotulinum toxin A injections in the elderly and frail elderly [456, 484], although a comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group.

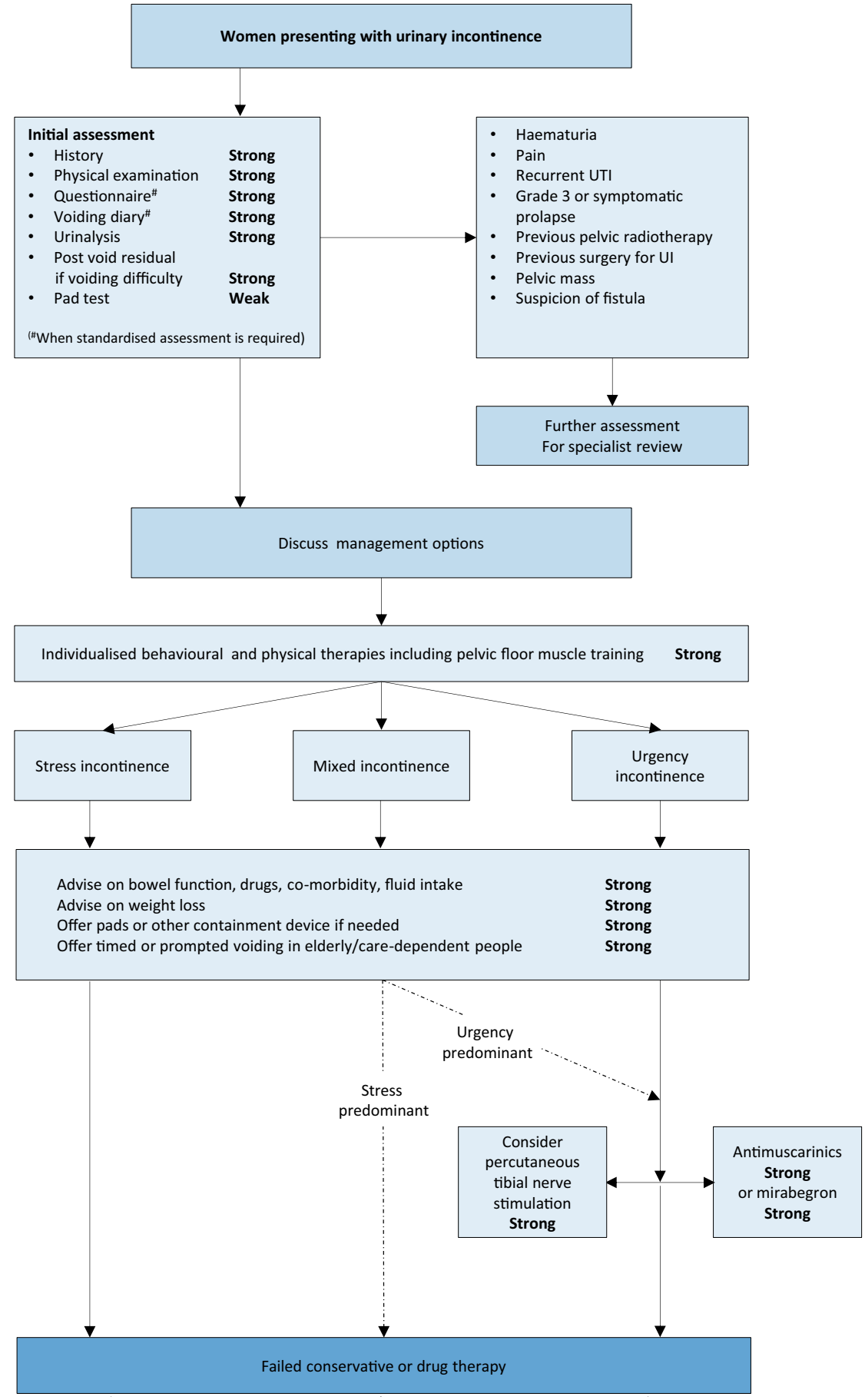
4.3.8.1 Summary of evidence and recommendation for surgery for urinary incontinence in the elderly

Summary of evidence	LE
Older women benefit from surgical treatment for incontinence.	1
The risk of failure from surgical repair of SUI, or of suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendations	Strength rating
Inform older women with UI about the increased risks associated with surgery (including onabotA injection), together with the lower probability of benefit.	Weak

SUI = stress urinary incontinence; UI = urinary incontinence.

Figure 1: Management and treatment of women presenting with urinary incontinence



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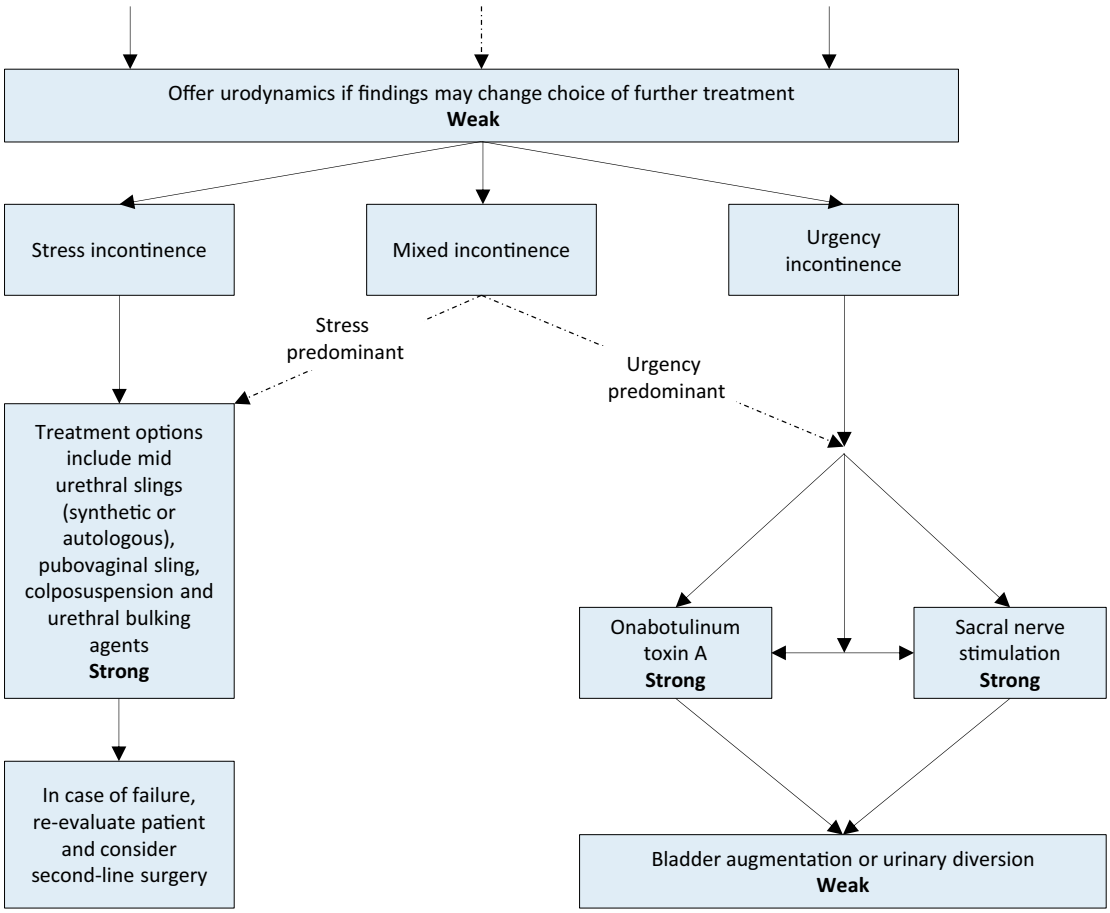
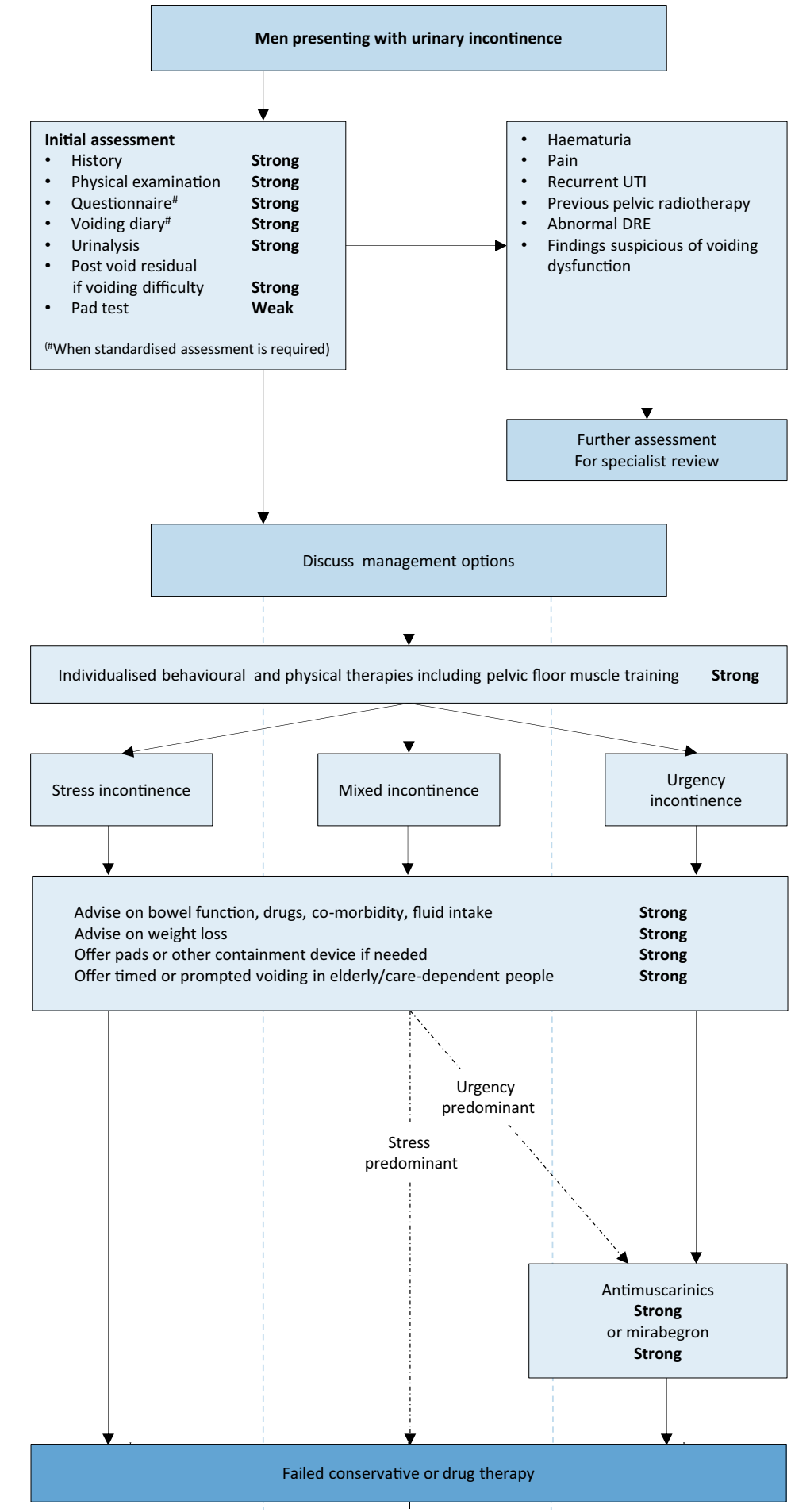

Offer urodynamics if findings may change choice of further treatment
Weak
Stress incontinence
Mixed incontinence
Urgency incontinence
Stress predominant
Urgency predominant
Treatment options include mid urethral slings (synthetic or autologous), pubovaginal sling, colposuspension and urethral bulking agents
Strong
Onabotulinum toxin A
Strong
Sacral nerve stimulation
Strong
In case of failure, re-evaluate patient and consider second-line surgery
Bladder augmentation or urinary diversion
Weak

Figure 2: Management and treatment of men presenting with urinary incontinence



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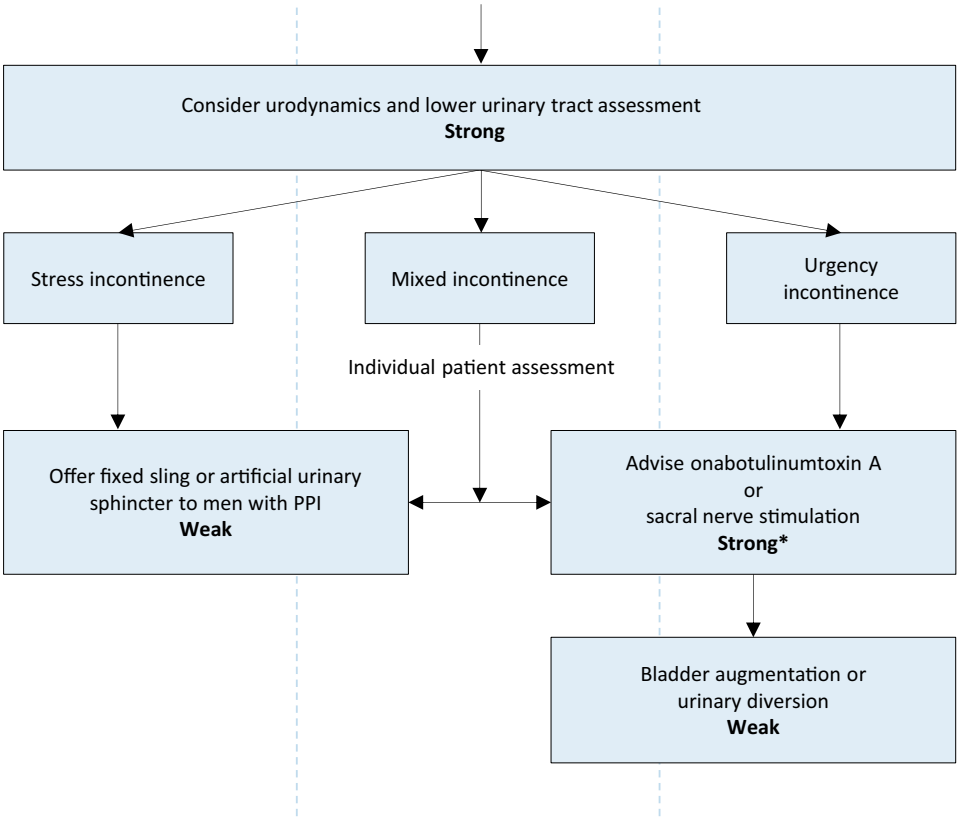

*Available evidence refers mainly to women

APPENDIX A: NON OBSTETRIC URINARY FISTULA

A.2 Introduction

The evidence relating to diagnosis and treatment of urinary fistulae is generally poor and this review inevitably relies largely on numerous case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of non-obstetric fistulae have been described in detail during the recent International Consultations on Incontinence [485, 486]. Most non-obstetric fistulae are iatrogenic in origin, with causes including pelvic surgery (particularly hysterectomy for benign or malignant conditions, caesarean section and obstetric injuries). The risks during pelvic surgery increase relative to the complexity of the resection, the extent of primary disease and when there has been prior radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

A.3 Diagnosis of fistula

Clinical diagnosis

Leakage of urine is the hallmark sign of a fistula. The leakage is usually painless, may be intermittent if it is position dependent, or may be constant. Unfortunately, intra-operative diagnosis of a GU or GI injury is made in only about half of the cases that result in fistula [487].

The diagnosis of vesicovaginal fistula (VVF) usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid or placement of a tampon into the vagina to identify staining may facilitate the diagnosis of a VVF. A double-dye test to differentiate between a ureterovaginal and VVF may be useful in some cases [488]. Testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this to the serum creatinine level will confirm urinary leakage.

Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides optimal diagnostic information regarding fistulae and may be preferred for urinary - intestinal fistulae [489].

A.4 Management of vesicovaginal fistula

A.3.1 ***Conservative management***

Before epithelialisation is complete an abnormal communication between viscera will tend to close spontaneously, provided that the natural outflow is unobstructed or if urine is diverted. Combining available data gives an overall spontaneous closure rate of 13% ± 23% [490], though this applies largely to small fistulae [486]. Hence, immediate management should be by urinary catheterisation or diversion.

A.3.2 ***Surgical management***

Timing of surgery

Findings from uncontrolled case series suggest no difference in success rates for early or delayed closure of VVF.

A.3.2.1 Surgical approaches

Vaginal procedures

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [491] and the more commonly used dissection and repair in layers or ‘flapsplitting’ technique [492]. There are no data comparing their outcomes.

Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed in the vault and are inaccessible through the vagina. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure is favoured by many urologists and is particularly useful for fistula repair following Caesarean section. There are no RCTs comparing abdominal and vaginal approaches. Results of secondary and subsequent repairs are not as good as primary repair [493].

A single RCT compared trimming of the fistula edge with no trimming [494]. There was no difference in success rates but failed repairs in trimmed cases ended up with larger recurrences than untrimmed cases, which were smaller.

Laparoscopic and Robotic

Very small series (single figures) have been reported using these techniques, but whilst laparoscopic repair is feasible with and without robotic assistance, it is not possible to compare outcomes with alternative surgical approaches.

Tissue Interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischemic or obstetrical fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Post-operative management

There is no high-level evidence to support any particular practice in post-operative management but most reported series used catheter drainage for at least ten days and longer periods in radiation-associated fistulae (up to three weeks).

A.4 Management of radiation fistula

Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [495]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include, on the one hand, permanent urinary and/or faecal diversion [496, 497] or alternatively preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. This may in some cases extend life perhaps inappropriately, and where life expectancy is deemed to be very short, ureteric occlusion might be more appropriate.

A.5 Management of ureteric fistula

General principles

Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and also recognise injury promptly when it occurs. Immediate repair of any intra-operative injury should be performed observing the principles of debridement, adequate blood supply and tension-free anastomosis with internal drainage using stents [490]. Delayed presentation of upper tract injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system. Whilst there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis, and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< two weeks) or delayed (> three months) surgical repair when required [498]. Functional and anatomical imaging should be used to follow up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

Ureterovaginal fistula

Ureterovaginal fistula occurring in the early post-operative phase predominantly after hysterectomy is the most frequent presentation of UUT fistulae in urological practice. An RCT in 3,141 women undergoing open or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [499].

Endoscopic management is sometimes possible [500] by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [501].

If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, re-implantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration.

A.6 Management of urethrovaginal fistula

Aetiology

Whilst they are rare, most urethrovaginal fistulae in adults have an iatrogenic aetiology. Causes include surgical treatment of stress incontinence with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction in adults. Irradiation and even conservative treatment of prolapse with pessaries can lead to the formation of fistulae.

A.6.1 ***Diagnosis***

Clinical vaginal examination, including the three swab test, is often sufficient to diagnose the presence of a urethrovaginal fistula. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, voiding cystourethrography (VCUG) or ultrasound can be useful. 3D MRI or CT scan is becoming utilised more widely to clarify anatomy [502, 503].

A.6.2 ***Surgical repair***

Choice of surgery will depend on the size, localisation and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between vaginal wall and urethra, watertight closure of urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

A.6.2.1 Vaginal approach

Goodwin described in his series that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, but that an abdominal approach only leads to a successful closure in 58% of cases. A vaginal approach required less operating time, had less blood loss and a shorter hospitalisation time.

Most authors describe surgical principles that are identical to those of vesicovaginal fistula repair: primary closure rates of 53-95.4% have been described. Pushkar *et al.* described a series of 71 women, treated for urethrovaginal fistula. 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, stress incontinence developed in 52%. The stress incontinent patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [504].

Flaps and neourethra.

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra [505, 506]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases a transpubic approach has been used [507]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbocavernosus tissue can be incorporated in the pedicled flap and probably offers a better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome stress incontinence would occur post-operatively [508, 509].

Martius flap

While in obstetrical fistula repair it was not found to have any benefit, in a large retrospective study in 440 women the labial bulbocavernosus muscle/fat flap by Martius is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistulae where additional bulking with well vascularised tissue is needed [510]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [511]. The indications for Martius flap in the repair of all types of fistulae remain unclear.

Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [512, 513].

A.6.2.2 Abdominal approach

A retropubic retrourethral technique has been described by Koriatim [514]. This approach allows a urethrovesical flap tube to be fashioned to form a continent neo-urethra.

A.7 Summary of evidence and recommendations for management of urethrovaginal fistula

Summary of evidence	**LE**
Spontaneous closure of surgical fistulae does occur, although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of vesicovaginal fistulae by vaginal, abdominal, transvesical and transperitoneal approaches.	3

A period of continuous bladder drainage is crucial to successful fistula repair but there is no high-level evidence to support one regime over another.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting.	3
Post-radiation fistula	
Successful repair of irradiated fistulae requires prior urinary diversion and the use of non-irradiated tissues to effect repair.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethrovaginal fistula	
Urethrovaginal fistula repair may be complicated by stress incontinence, urethral stricture and urethral shortening necessitating long-term follow-up.	3

Recommendations	Strength rating
General	
Surgeons undertaking complex pelvic surgery should be competent at identifying, preserving and repairing the ureter.	Weak
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Weak
Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs post-operatively, or if drainage fluid contains high levels of creatinine.	Weak
Suspect uretero-arterial fistula in patients presenting with haematuria with a history of relevant surgery.	Weak
Use three dimensional imaging techniques to diagnose and localise urinary fistulae.	Weak
Manage upper urinary tract fistulae by conservative or endoluminal technique where such expertise and facilities exists.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient.	Weak
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair.	Weak
If a vesicovaginal fistula is diagnosed within six weeks of surgery, consider indwelling catheterisation for a period of up to twelve weeks after the causative event.	Weak
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Where concurrent ureteric re-implantation or augmentation cystoplasty are required, the abdominal approach is necessary.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: 10-14 days for simple and/or postsurgical fistulae; 14-21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition grafts when repair of radiation associated fistulae is undertaken.	Weak
In patients with intractable UI from radiation-associated fistula, where life expectancy is very short, consider performing ureteric occlusion.	Weak
Repair persistent ureterovaginal fistula by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	Weak
Consider palliation by nephrostomy tube diversion and endoluminal distal ureteric occlusion for patients with ureteric fistula associated with advanced pelvic cancer and poor performance status.	Weak
Urethrovaginal fistulae should preferably be repaired by a vaginal approach.	Weak

UI = urinary incontinence

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6. CONFLICT OF INTEREST

All members of the Urinary Incontinence Guidelines Panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline/.

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7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Neuro-Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Neuro-Urology Guidelines aim to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These Guidelines reflect the current opinion of experts in this specific pathology and represent a state-of-the art reference for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures advised throughout these Guidelines follow the recommendations for investigations of the lower urinary tract (LUT) as published by the International Continence Society (ICS) [1-3]. Readers are advised to consult other EAU Guidelines that may address different aspects of the topics discussed in this document.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Neuro-Urology Guidelines Panel consists of an international multidisciplinary group of neuro-urological experts. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/neuro-urology/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation with the full text version. A guideline summary has also been published in European Urology [4]. All are available through the EAU website: http://www.uroweb.org/guideline/neurourology/.

1.4 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014, and 2017. This 2020 document represents a limited update of the 2019 publication. The literature was assessed for all chapters.

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that coordinates the activity of the urinary bladder and bladder outlet. The part of the nervous system that regulates LUT function is disseminated from the peripheral nerves in the pelvis to highly specialised cortical areas. Any disturbance of the nervous system involved, can result in neuro-urological symptoms. The extent and location of the disturbance will determine the type of LUT dysfunction, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. Since symptoms and long-term complications do not correlate [5], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high risk of subsequent complications. The risk of developing upper urinary tract (UUT) damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida [6]. In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

2.1 Introduction

For the 2020 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Neuro-Urology Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 31st 2018 and 1st April 2019. A total of 754 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/neuro-urology/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [7, 8]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [10]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications ensuing from panel-led systematic reviews have all been peer-reviewed. The 2015 Neuro-Urology Guidelines were subject to peer review prior to publication.

3. THE GUIDELINE

3.1 Epidemiology, aetiology and pathophysiology

*3.1.1 **Introduction***

Neuro-urological symptoms may be caused by a variety of diseases and events affecting the nervous system controlling the LUT. The resulting neuro-urological symptoms depend predominantly on the location and the extent of the neurological lesion. There are no exact figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of these for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence. This reflects the variability in the cohort (e.g. early or late stage disease) and the frequently small sample sizes, resulting in a low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

Suprapontine and pontine lesions and diseases		
Neurological Disease	**Frequency in General Population**	**Type and Frequency of Neuro-Urological Symptoms**
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [11], 10% of cardiovascular mortality.	Nocturia - overactive bladder (OAB) - urgency urinary incontinence (UUI) - detrusor overactivity (DO), other patterns less frequent [12]. 57-83% of neuro-urological symptoms at 1 month post-stroke, 71-80% spontaneous recovery at 6 months [13]. Persistence of urinary incontinence (UI) correlates with poor prognosis [14].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%).	6.4% of adults > 65 yrs [15].	OAB - UUI – DO 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [16]. Incontinence 3 times more frequent in geriatric patients with dementia than without [17].
Parkinsonian syndrome (PS) Idiopathic Parkinson's disease (IPD): 75-80% of PS.	Second most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [18].	Urinary symptoms affect 50% at onset, with urgency and nocturia being the most common. Patients with urinary symptoms at presentation have worse disease progression in Parkinson's disease [19].
Non-IPD: Parkinson's-plus (18%): - Multiple system atrophy (MSA), - Progressive supranuclear palsy, - Corticobasal degeneration, - Dementia with Lewy bodies. Secondary Parkinson's (2%)	MSA is the most frequent non-IPD PS.	Infections account for a major cause of mortality in MSA [20]. Impaired detrusor contractility with post-void residual (PVR) > 150 mL seems to be the urodynamic finding distinguishing MSA from IPD [21-23].
Brain tumours	26.8/100,000/yr in adults (> 19 yrs), (17.9 benign, 8.9 malignant) [24].	Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [25].
Cerebral palsy	Cerebral palsy: 3.1-3.6/1,000 in children aged 8 yrs [26].	46% of patients with cerebral palsy suffer from UI, with 85% of patients having abnormal urodynamic studies (NDO most common 59%). Upper tract deterioration is rare (2.5%) [27].
Traumatic brain injury	235/100,000/yr [28].	44% storage dysfunction, 38% voiding dysfunction, 60% urodynamic abnormalities [29].
Normal pressure hydrocephalus	0.5% of the population > 60, up to 2.9% of those > 65 [30].	Classic triad of gait and cognitive disturbance along with UI. Incontinence affects 98-100% of patients [30].

Lesions and diseases between caudal brainstem and sacral spinal cord		
Spinal cord injury (SCI)	Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million [31].	Neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) (up to 95%) and detrusor underactivity (up to 83%) depending on the level of the lesion [32].
Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [33].	Bladder function is impaired in up to 96% of SB patients [34]. Over 50% of patients are incontinent [35]. Patients with open and closed defects can have equally as severe neurogenic lower urinary tract dysfunction [36].
Lesions and diseases of the peripheral nervous system		
Lumbar spine Degenerative disease Disk prolapse Lumbar canal stenosis	Male (5%) and female (3%) > 35 yr have had a lumbosciatic episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [37]. Detrusor underactivity (up to 83%) [32]. Tarlov cysts: early sensation of filling (70%), NDO (33%), urethral instability (33%) and stress urinary incontinence (SUI) (33%) [38].
Iatrogenic pelvic nerve lesions	Rectal cancer. Cervical cancer (multimodal therapy, radiotherapy and surgery). Endometriosis surgery.	After abdomino-perineal resection: 50% urinary retention. After total mesorectal excision: 10-30% voiding dysfunction [39].
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy causing neuro-urological symptoms: alcohol abuse; lumbosacral zona and genital herpes; Guillain Barré syndrome.	Worldwide, prevalence of pharmacologically treated diabetes 8.3% [40].	Urgency/frequency +/- incontinence [41]. Hyposensitive and detrusor underactivity at later phase [41].
Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [42].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [43]. DO: 86% [43]. DSD: 35% [43]. Detrusor underactivity: 25% [43].

3.2 Classification systems

3.2.1 Introduction

Relevant definitions can be found in the general ICS standardisation reports [2, 3, 44]. Supplementary online Tables S1 and S2 list the definitions from these references, partly adapted, and other definitions considered useful for clinical practice: https://uroweb.org/guideline/neuro-urology/?type=appendices-publications.

3.3 Diagnostic evaluation

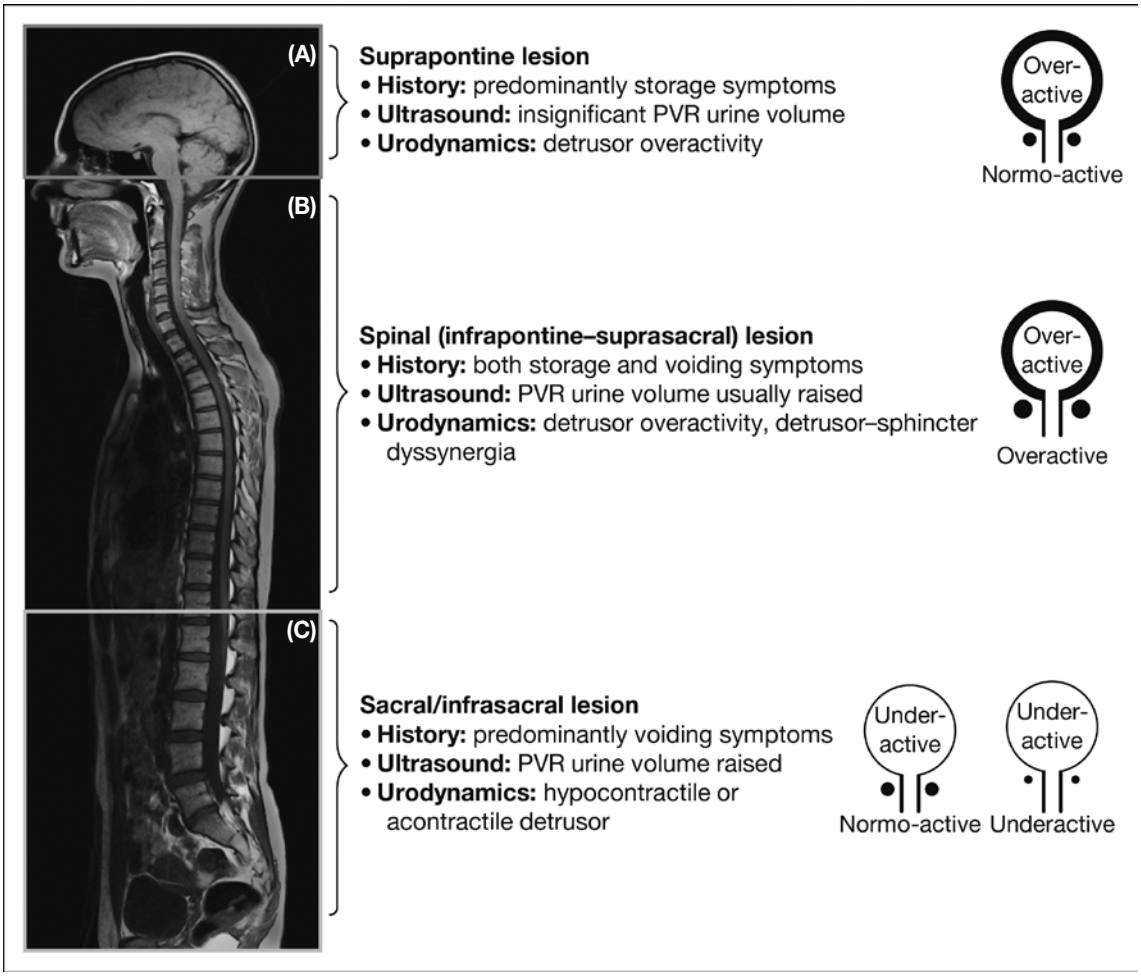
3.3.1 Introduction

The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

*3.3.2 **Classification systems***

The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system for use in daily clinical practice to decide on the appropriate therapeutic approach is provided in Figure 1 [6].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel (A) denotes the region above the pons, panel (B) the region between the pons and the sacral cord and panel (C) the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. Figure adapted from Panicker et al. [6] with permission from Elsevier.
PVR = post-void residual.

*3.3.3 **Timing of diagnosis and treatment***

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders [45]. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [46, 47]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [48, 49]. Early intervention can prevent irreversible deterioration of the LUT and UUT [50]. Long term follow up (life-long) is mandatory to assess risk of UUT damage, renal failure and bladder cancer [51-53].

*3.3.4 **Patient history***

History taking should include past and present symptoms and disorders (Table 4). It is the cornerstone of evaluation, as the answers will aid selection of diagnostic investigations and treatment options.

- In non-traumatic neuro-urological patients with an insidious onset, a detailed history may find that the condition started in childhood or adolescence [54].
- Urinary history consists of symptoms associated with both urine storage and voiding.
- Bowel history is important because patients with neuro-urological symptoms may also have related neurogenic bowel dysfunction [55].

- Sexual function may be impaired because of the neuro-urological condition [56].
- Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) requiring further investigation.
- Patients with SCI usually find it difficult to report urinary tract infection (UTI)-related symptoms accurately [57, 58].
- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive of an underlying neurological disease or condition.
- Ambulatory status after acute SCI does not predict presence or absence of unfavourable urodynamic parameters [59].

Table 4: History taking in patients with suspected neuro-urological disorder

Past history
Childhood through to adolescence and into adulthood
Hereditary or familial risk factors
Specific female: menarche (age); this may suggest a metabolic disorder
Obstetric history
History of diabetes
Diseases, e.g. multiple sclerosis, parkinsonism, encephalitis, syphilis
Accidents and operations, especially those involving the spine and central nervous system
Present history
Present medication
Lifestyle (smoking, alcohol and drugs); may influence urinary, sexual and bowel function
Quality of life
Specific urinary history
Onset of urological history
Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy
Bladder sensation
Initiation of micturition (normal, precipitate, reflex, strain, Credé)
Interruption of micturition (normal, paradoxical, passive)
Enuresis
Mode and type of voiding (catheterisation)
Frequency, voided volume, incontinence, urgency episodes
Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area
Specific male: erection, (lack of) orgasm, ejaculation
Specific female: dyspareunia, (lack of) orgasm
Bowel history
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digitation)
Neurological history
Acquired or congenital neurological condition
Mental status and comprehension
Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
Spasticity or autonomic dysreflexia (especially in lesions at or above level Th 6)
Mobility and hand function

3.3.4.1 Bladder diaries

Bladder diaries provide data on the number of voids, voided volume, pad weight and incontinence and urgency episodes [3, 60]. Although a 24-hour bladder diary (recording should be done for three consecutive days) is reliable in women with UI [61, 62], no research has been done on bladder diaries in neuro-urological patients. Nevertheless, bladder diaries are considered a valuable diagnostic tool.

*3.3.5 **Patient quality of life questionnaires***

An assessment of the patient's present and expected future quality of life (QoL) is important to evaluate the effect of any therapy. Quality of life is an essential aspect of the overall management of neuro-urological patients, for example when evaluating treatment related changes on a patient's QoL [63]. The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI [64, 65] and MS [66], as does the presence or absence of urinary and faecal incontinence [67]. Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neuro-urological patient in determining patient QoL [68].

In recent years a proliferation in the number of questionnaires to evaluate symptoms and QoL has been seen. Condition-specific questionnaires can be used to assess symptom severity and the impact of symptoms on QoL. A patient's overall QoL can be assessed using generic questionnaires. It is important that the questionnaire of choice has been validated in the neuro-urological population, and that it is available in the language that it is to be used in.

3.3.5.1 Available Questionnaires

Three condition-specific questionnaires for urinary or bowel dysfunction and QoL have been developed specifically for adult neuro-urological patients [69]. In MS and SCI patients the Qualiveen [70, 71] is validated and can be used for urinary symptoms. A short form of the Qualiveen is available [70, 71] and it has been translated into various languages [72-77]. Although several objective and subjective tools have been used to assess the influence of neurogenic bladder on QoL in SCI, the Quality life index-SCI and Qualiveen are the only validated condition-specific outcomes that have shown consistent sensitivity to neurogenic bladder [78]. The Neurogenic Bladder Symptom Score (NBSS) has been validated in neurological patients to measure urinary symptoms and their consequences [79, 80]. The QoL scoring tool related to Bowel Management (QoL-BM) [81] can be used to assess bowel dysfunction in MS and SCI patients.

In addition, sixteen validated questionnaires that evaluate QoL and asses urinary symptoms as a subscale or question in neuro-urological patients have been identified [82, 83] (Table 5). The condition-specific Incontinence-Quality of Life (I-QoL) questionnaire which was initially developed for the non-neurological population has now also been validated for neuro-urological patients [84].

A patient's overall QoL can be assessed by generic HRQoL questionnaires, the most commonly used being the I-QOL, King's Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12) [69]. In addition, the quality-adjusted life year (QALY), quantifies outcomes, by weighing years of life spent in a specified health state, adjusted by a factor representing the value placed by society or patients on their specific health state [85].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for validated questionnaires have been assessed [69].

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [86]	MS	X		X
FILMS [87]	MS	X	X	
HAQUAMS [88]	MS	X	X	X
I-QOL [84]	MS, SCI	X		X
MDS [89]	MS	X	X	
MSISQ-15 / MSISQ-19 [90, 91]	MS	X	X	X
MSQLI [92]	MS	X	X	X
MSQoL-54 [93]	MS	X	X	X
MSWDQ [94]	MS	X	X	
NBSS [95]	MS, SCI, Congenital neurogenic bladder	X		
QoL-BM [81]	SCI		X	
Qualiveen/SF-Qualiveen [71, 96]	MS, SCI	X		X
RAYS [97]	MS	X		X
RHSCIR [98]	SCI	X	X	X
Fransceschini [97]	SCI	X	X	X

3.3.6 ***Physical examination***

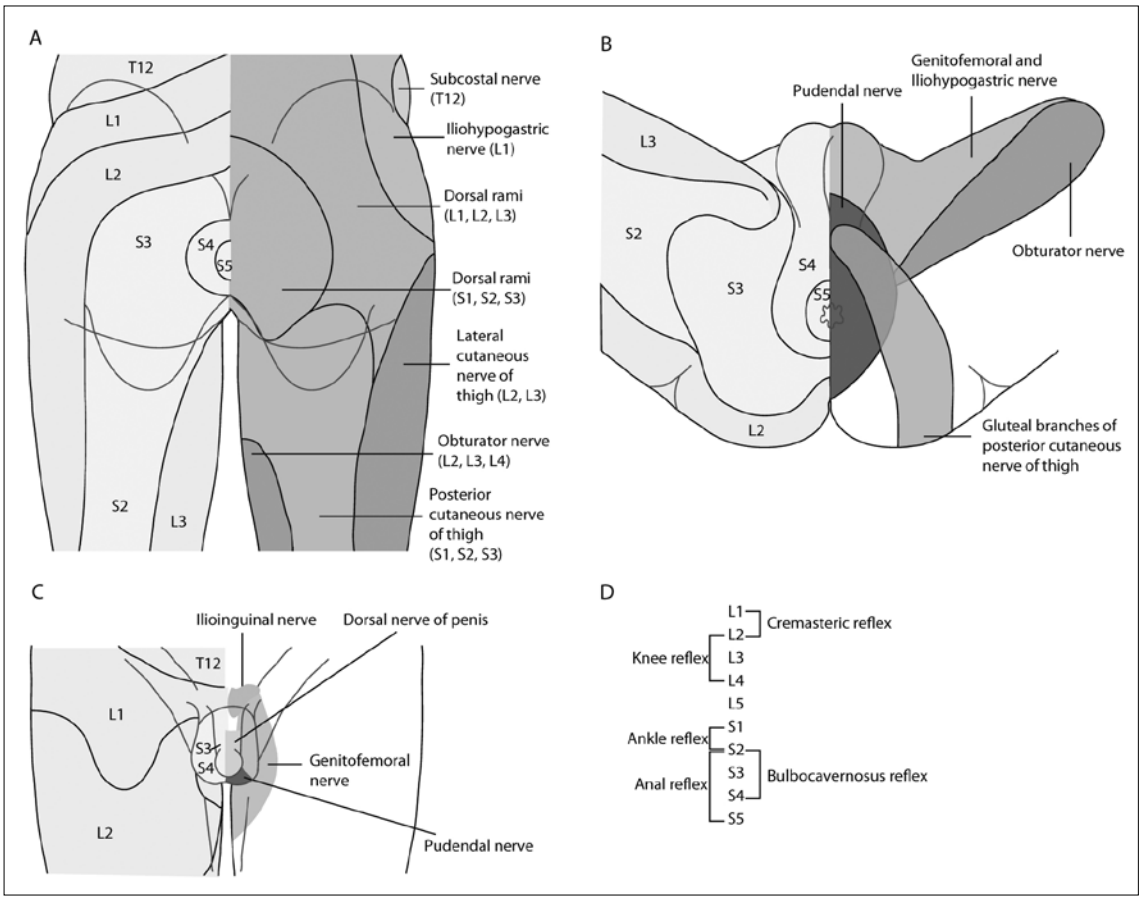
In addition to a detailed patient history, attention should be paid to possible physical and intellectual disabilities with respect to the planned investigations [99, 100]. Neuro-urological status should be described as completely as possible (Figure 2) [6]. Patients with a high spinal cord lesion or supraspinal neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested [6]. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2) [6, 101]. It is essential to have this clinical information to reliably interpret later diagnostic investigations.

Additionally, urinalysis, blood chemistry, ultrasonography, residual and free flowmetry and incontinence quantification should be performed as part of the routine assessment of neuro-urological patients [6, 102].

3.3.6.1 Autonomic dysreflexia

Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction. It generally manifests at or above level Th 6. The stimulus can be distended bladder or bowel. For example, iatrogenic stimuli during cystoscopy or urodynamics can trigger AD [103]. It can also be secondary to sexual stimulation or a noxious stimulus, e.g. infected toe nail or pressure sore. Autonomic dysreflexia is defined by an increase in systolic blood pressure > 20 mmHg from baseline [104] and can have life-threatening consequences if not properly managed.

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of the lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum [105] (B), male external genitalia [106] (C) and root values of lower spinal cord reflexes (D). Figure adapted from Panicker et al. [6] with parts A-C adapted from Standring [107], both with permission from Elsevier.

Table 6: Neurological items to be specified

Sensation S2-S5 (both sides)
Presence (increased/normal/reduced/absent)
Type (light touch/pin prick)
Affected dermatomes
Reflexes (increased/normal/reduced/absent)
Bulbocavernous reflex
Perianal/anal reflex
Knee and ankle reflexes
Plantar responses (Babinski)
Anal sphincter tone
Presence (increased/normal/reduced/absent)
Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
Prostate palpation
Descensus (prolapse) of pelvic organs

3.3.6.2 Summary of evidence and recommendations for history taking and physical examination

Summary of evidence	**LE**
Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders to prevent irreversible changes within the LUT.	4
An extensive general history is the basis of evaluation focusing on past and present symptoms including urinary, sexual, bowel and neurological functions.	4
Assessment of present and expected future QoL is an essential aspect of the overall management of neuro-urological patients and is important to evaluate the effect of any therapy.	2a
Quality of life assessment should be completed with validated QoL questionnaires for neuro-urological patients.	1a
Bladder diaries provide data on the number of voids, voided volume, pad weight and incontinence and urgency episodes.	3

Recommendations	**Strength rating**
History taking	
Take an extensive general history, concentrating on past and present symptoms.	Strong
Take a specific history for each of the four mentioned functions - urinary, bowel, sexual and neurological.	Strong
Pay special attention to the possible existence of alarm signs (e.g. pain, infection, haematuria, fever) that warrant further specific diagnosis.	Strong
Assess quality of life when evaluating and treating the neuro-urological patient.	Strong
Use available validated tools including the Qualiveen and I-QoL for urinary symptoms and the QoL-BM for bowel dysfunction in multiple sclerosis and spinal cord injury patients. In addition, generic (SF-36 or KHQ) questionnaires can be used.	Strong
Use MSISQ-15 and MSISQ-19 to evaluate sexual function in multiple sclerosis patients.	Strong
Physical examination	
Acknowledge individual patient disabilities when planning further investigations.	Strong
Describe the neurological status as completely as possible, sensations and reflexes in the urogenital area must all be tested.	Strong
Test the anal sphincter and pelvic floor functions.	Strong
Perform urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging.	Strong

I-QoL = Incontinence Quality of Life Instrument; QoL-BM = Quality of Life Bowel Management scoring tool; KHQ = King's Health Questionnaire; SF-36 = Short Form 36-item Health Survey Questionnaires; MSISQ 15/19 = Multiple Sclerosis Intimacy and Sexuality Questionnaire 15/19 question version.

3.3.7 ***Urodynamics***

3.3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the function and dysfunction of the LUT. In neuro-urological patients, invasive urodynamic investigation is even more challenging than in general patients. Any technical source of artefacts must be critically considered. It is essential to maintain the quality of the urodynamic recording and its interpretation [1]. Same session repeat urodynamic investigations are crucial in clinical decision making, since repeat measurements may yield completely different results [108].

In patients at risk of AD, it is advisable to measure blood pressure during the urodynamic study [109, 110]. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to the ICS technical recommendations and standards [1, 111].

3.3.7.2 Urodynamic tests

Free uroflowmetry and assessment of residual urine: Provides a first impression of the voiding function and is compulsory prior to planning any invasive urodynamics in patients able to void. For reliable information, it should be repeated at least two to three times [1]. Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and residual urine. Care must be taken when assessing the results in patients unable to void in a normal position, as both flow pattern and rate may be modified by inappropriate positions.

Filling cystometry: This test is the only method for quantifying the patient's filling function. The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and is even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline. Possible pathological findings include DO, low bladder compliance, abnormal bladder sensations, incontinence, and an incompetent or relaxing urethra. There is some evidence that a bladder capacity < 200 mL and detrusor pressures over 75 cm H_2O are independent risk factors for UUT damage in patients with SCI [51].

Detrusor leak point pressure [112]: Appears to have no use as a diagnostic tool. Some positive findings have been reported [113-115], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [116, 117].

Pressure flow study: Reflects the coordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more effective if combined with filling cystometry and video-urodynamics. Lower urinary tract function must be recorded during the voiding phase. Possible pathological findings include detrusor underactivity, bladder outlet obstruction (BOO), DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [118, 119], non-relaxing urethra, or non-relaxing bladder neck [120, 121]. Pressure-flow analysis mainly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties and has limited value in patients with neuro-urological disorders.

Electromyography (EMG): Reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [122].

Urethral pressure measurement: Has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [123].

Video-urodynamics: Is the combination of filling cystometry and pressure flow studies with imaging. It is the optimum procedure for urodynamic investigation in neuro-urological disorders [5]. Possible pathological findings include all those described in the cystometry and the pressure flow study sections, and any morphological pathology of the LUT and reflux to the UUT [124].

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which predominantly uses the natural filling of the urinary tract to reproduce the patient's normal activity. Although this type of study might be

considered when conventional urodynamics does not reproduce the patient's symptoms, its role in the neuro-urological patient still needs to be determined [125, 126].

Triggered tests during urodynamics: Lower urinary tract function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') will discriminate between upper and lower motor neuron lesions [127, 128]. Patients with upper motor neuron lesions develop a detrusor contraction if the detrusor is intact, while patients with lower motor neuron lesions do not. However, the test does not seem to be fully discriminative in other types of patients [129].

Previously, a positive bethanechol test [130] (detrusor contraction > 25 cm H_2O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol [131], but there was no published follow-up. Currently, there is no indication for this test.

3.3.7.3 Specialist uro-neurophysiological tests

The following tests are advised as part of the neurological work-up [132]:

- electromyography (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
- nerve conduction studies of pudendal nerve;
- reflex latency measurements of bulbocavernosus and anal reflex arcs;
- evoked responses from clitoris or glans penis;
- sensory testing on bladder and urethra.

Other elective tests, for specific conditions, may become obvious during the work-up and urodynamic investigations.

3.3.7.4 Summary of evidence and recommendations for urodynamics and uro-neurophysiology

Summary of evidence	**LE**
Urodynamic investigation is the only method that can objectively assess the (dys-)function of the LUT.	2a
Video-urodynamics is the optimum procedure for urodynamic investigation in neuro-urological disorders.	4
Specific uro-neurophysiological tests are elective procedures and should only be carried out in specialised settings.	4

Recommendations	**Strength rating**
Perform a urodynamic investigation to detect and specify lower urinary tract (dys-)function, use same session repeat measurement as it is crucial in clinical decision making.	Strong
Non-invasive testing is mandatory before invasive urodynamics is planned.	Strong
Use video-urodynamics for invasive urodynamics in neuro-urological patients. If this is not available, then perform a filling cystometry continuing into a pressure flow study.	Strong
Use a physiological filling rate and body-warm saline.	Strong

3.3.8 ***Renal function***

In many patients with neuro-urological disorders, the UUT is at risk, particularly in patients who develop high detrusor pressure during the filling phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity [133, 134]. Patients with SCI or SB have a higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as MS and Parkinson's disease (PD) [135].

Caregivers must be informed of this risk and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. In patients with poor muscle mass cystatin C based glomerular filtration rate (GFR) is more accurate in detecting chronic kidney disease than serum creatinine estimated GFR [136, 137]. There are no high level evidence publications available which show the optimal management to preserve renal function in these patients [138].

3.4 Disease management

*3.4.1 **Introduction***

The primary aims for treatment of neuro-urological symptoms, and their priorities, are [139, 140]:

- protection of the UUT;
- achievement (or maintenance) of urinary continence;
- restoration of LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity and possible complications [140].

Renal failure is the main mortality factor in SCI patients who survive the trauma [141, 142]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [143-145] and has consequently become the top priority in the treatment of patients with neuro-urological symptoms [139, 140].

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance), treatment is aimed primarily at conversion of an overactive, high-pressure bladder into a low-pressure reservoir despite the resulting residual urine [139]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTIs [146, 147]. However, complete continence cannot always be obtained.

*3.4.2 **Non-invasive conservative treatment***

3.4.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure and incontinence. Methods to improve the voiding process should therefore be practiced.

Bladder expression: The downwards movement of the lower abdomen by suprapubic compression (Credé) or by abdominal straining (Valsalva) leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction [148, 149]. The latter may increase bladder outlet resistance and lead to inefficient emptying. The high pressures created during these procedures are hazardous for the urinary tract [150, 151]. Therefore, their use should be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [140].

Long-term complications are unavoidable for both methods of bladder emptying [149]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence [151].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with a upper motor neuron lesion can elicit a reflex detrusor contraction [151]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [152]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [153]. All assisted bladder emptying techniques require low outlet resistance. Even then, high detrusor pressures may still be present. Hence, patients need dedicated education and close urodynamic and urological surveillance [151, 154, 155].

Note: In the literature, including some of the references cited here, the concept "reflex voiding" is sometimes used to cover all three assisted voiding techniques described in this section.

External appliances: Social continence may be achieved by collecting urine during incontinence, for instance using pads. Condom catheters with urine collection devices are a practical method for men [140]. The penile clamp is absolutely contraindicated in case of NDO or low bladder compliance because of the risk of developing high intravesical pressure and pressure sores/necrosis in cases of altered/absent sensations.

3.4.2.2 Neuro-urological rehabilitation

3.4.2.2.1 Bladder rehabilitation including electrical stimulation

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. Strong contraction of the urethral sphincter and/or pelvic floor, as well as anal dilatation, manipulation of the genital region, and physical activity inhibit micturition in a reflex manner [140, 156]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [116]. Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction [157]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [140, 158]. Evidence

for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on small non-comparative studies with high risk of bias.

Peripheral temporary electrostimulation: Tibial nerve stimulation and transcutaneous electrical nerve stimulation (TENS) might be effective and safe for treating neurogenic LUT dysfunction, but more reliable evidence from well-designed randomised controlled trials (RCTs) is required to reach definitive conclusions [158-160]. In post-stroke patients TENS has been shown to effectively improve urodynamic findings and QoL [161-163].

Peripheral temporary electrostimulation combined with pelvic floor muscle training and biofeedback: In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [164, 165]. This treatment combination seems to be more effective than either therapy alone [166, 167]. However, the combination of intravaginal electrostimulation and pelvic floor muscle training was not superior to pelvic floor muscle training alone in reducing urinary incontinence in women with incomplete spinal cord injury [168].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder filling sensation in patients with incomplete SCI or myelomeningocele (MMC) [169]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [170, 171].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD and MS patients, this technique is still under investigation [172, 173].

Summary: To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation; however, there is a lack of well-designed studies.

3.4.2.3 Drug treatment

A single, optimal, medical therapy for neuro-urological symptoms is not always available. Commonly, a combination of different therapies (e.g. intermittent catheterisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with a suprasacral SCI or MS [151, 174-176].

3.4.2.3.1 Drugs for storage symptoms

Antimuscarinic drugs: Are the first-line choice for treating NDO, increasing bladder capacity and reducing episodes of UI secondary to NDO by the inhibition of parasympathetic pathways [140, 177-183]. Antimuscarinic drugs have been used for many years to treat patients with NDO [181, 182, 184], and the responses of individual patients to antimuscarinic treatment are variable. Despite a meta-analysis confirming the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO, a more recent integrative review has indicated that the information provided is still too limited for clinicians to be able to match trial data to the needs of individual patients with SCI, mainly due to the lack of use of standardised clinical evaluation tools such as the American Spinal Injury Association bladder diary and validated symptoms score [182, 185].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [178, 179, 186-189]. However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy. Despite this, NDO patients have generally shown better treatment adherence compared to idiopathic DO patients [190].

Choice of antimuscarinic agent: Oxybutynin [140, 178, 179, 181, 182, 191], trospium [182, 188, 192], tolterodine [193] and propiverine [182, 194] are established, effective and well tolerated treatments even in long-term use [181, 182, 195, 196]. Darifenacin [197, 198] and solifenacin [199] have been evaluated in NDO secondary to SCI and MS [182, 197-199] with results similar to other antimuscarinic drugs. A pilot study using solifenacin in NDO due to PD showed an improvement in UI [200]. Fesoterodine, an active metabolite of tolterodine, has also been introduced; to date there has been no published clinical evidence for its use in the treatment of neuro-urological disorders. Favourable results with the new drug imidafenacin have been reported in suprapontine as well as SCI patients [201, 202].

Side effects: Controlled-release antimuscarinics have some minor side effects, e.g. dry mouth [203]. It has been suggested that different ways of administration may help to reduce side effects [204]. Imidafenacine has been safely used in neurological patients with no worsening of cognitive function [201].

Beta-3-adrenergic receptor agonists
The role of mirabegron in neuro-urological patients is still unclear. In MS and SCI patients, with very short follow up, mirabegron has not demonstrated any significant effect on detrusor pressure or cystometric capacity despite the reported improvement in LUTS [205, 206]. A significant subjective improvement in OAB symptoms has also been reported using lower dosages of mirabegron in patients affected by CNS lesions without any negative effects on voiding function [207]. A standard dosage of 50 mg has been found effective with no worsening of cognitive function in patients with PD [208]. Combination therapy with mirabegron and desmopressin in MS patients has shown promising results; however, clinical experience is still very limited in neuro-urological populations [209].

Other drugs
In preliminary studies, improvements in daily incontinence rates, nocturia, daytime and 24 hour voids, as well as the low risk of adverse events, suggest that cannabinoids may be effective and safe in MS patients [210]. A concomitant improvement in OAB symptoms has been reported in male MS patients using daily tadalafil to treat neurogenic erectile dysfunction (ED) [211]. A systematic review found that desmopressin may be effective for treating nocturia in MS patients; however, adverse events were common, with the included studies being heterogeneous and of low quality [212].

3.4.2.3.2 Drugs for voiding symptoms
Detrusor underactivity: Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not frequently used in clinical practice [213]. Only preclinical studies have documented the potential benefits of cannabinoid agonists for improving detrusor contractility when administered intravesically [214, 215].

Decreasing bladder outlet resistance: α-blockers (e.g. tamsulosin, naftopidil and silodosin) seem to be effective for decreasing bladder outlet resistance, PVR and AD [216-218].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild SUI, but there are no high-level evidence studies in neurological patients [140].

3.4.2.4 Summary of evidence and recommendations for drug treatments

Summary of evidence	**LE**
Long-term efficacy and safety of antimuscarinic therapy for NDO is well documented.	1a
Mirabegron does not improve urodynamic outcomes in NDO patients.	1b
Maximise outcomes for neurogenic detrusor overactivity by considering a combination therapy.	3

Recommendations	**Strength rating**
Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity.	Strong
Prescribe α-blockers to decrease bladder outlet resistance.	Strong
Do not prescribe parasympathomimetics for underactive detrusor.	Strong

3.4.2.5 Minimally invasive treatment
3.4.2.5.1 Catheterisation
Intermittent self- or third-party catheterisation [219, 220] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [140]. Sterile IC, as originally proposed by Guttmann and Frankel [219], significantly reduces the risk of UTI and bacteriuria [140, 221, 222], compared with clean IC introduced by Lapides *et al.* [220]. However, it has not yet been established whether or not the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean IC, coated or uncoated catheters or by any other strategy [223].

Sterile IC cannot be considered a routine procedure [140, 222]. Aseptic IC is an alternative to sterile IC [224]. The use of hydrophilic catheters was associated with a lower rate of UTI [225].

Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients [140, 226-230]. The average frequency of catheterisations per day is four to six times [231] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of five

times showed a reduction of UTI [231]. Ideally, bladder volume at catheterisation should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI [140, 232-239]; therefore, both procedures should be avoided, when possible. Silicone catheters are preferred as they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [240].

3.4.2.5.2 Summary of evidence and recommendations for catheterisation

Summary of evidence	LE
Intermittent catheterisation is the standard treatment for patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI.	3

Recommendations	Strength rating
Use intermittent catheterisation, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of intermittent catheterisation.	Strong
Avoid indwelling transurethral and suprapubic catheterisation whenever possible.	Strong

3.4.2.5.3 Intravesical drug treatment

To reduce DO, antimuscarinics can also be administered intravesically [204, 241-244]. The efficacy, safety and tolerability of intravesical administration of 0.1% oxybutynin hydrochloride compared to its oral administration for treatment of NDO has been demonstrated in a recent randomised controlled study [204]. This approach may reduce adverse effects due to the fact that the antimuscarinic drug is metabolised differently [241] and a greater amount is sequestered in the bladder, even more than with electromotive administration [242].

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres for a period of a few months [245, 246]. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A injections in the detrusor [245].

Although preliminary data suggest that intravesical vanilloids might be effective for treating neurogenic LUT dysfunction, their safety profile appears to be unfavourable [247]. Currently, there is no indication for the use of these substances, which are not licensed for intravesical treatment.

3.4.2.5.4 Summary of evidence and recommendations for intravesical drug treatment

Summary of evidence	LE
A significant reduction in adverse events was observed for intravesical administration of oxybutynine compared to oral administration.	1a

Recommendation	Strength rating
Offer intravesical oxybutynin to neurogenic detrusor overactivity patients with poor tolerance to the oral route.	Strong

3.4.2.5.5 Botulinum toxin injections in the bladder

Botulinum toxin A causes a long-lasting but reversible chemical denervation that lasts for about nine months [248, 249]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS, SCI and PD in multiple RCTs and meta-analyses [250-252]. Urodynamic studies might be necessary after treatment in patients with maximal filling pressure of > 40 cm H_2O cm in order to monitor the effect of the injections on bladder pressure [253]. Repeated injections seem to be possible without loss of efficacy, even after initial low response rates, based on years of follow up [248, 254-257]. The clinical efficacy of botulinum toxin A injection in patients with low morbidity after failure of augmentation enterocystoplasty has been demonstrated [258]. A switch between different toxin variations may improve responsiveness [259]. The most frequent side

effects are UTIs, urinary retention and haematuria [260]. Intermittent catheterisation may become necessary, this is especially relevant in MS patients as they do not often perform IC prior to intravesical botulinum toxin injections. However, a lower dose of botulinum toxin A (100 U) may reduce the rate of clean IC in MS patients [261]. Rare complications include generalised muscle weakness and AD [260]. Current research focuses on different delivery approaches to injection such as liposome encapsulated botulinum toxin to decrease side effects [262]. Neuro-urological patients with an indwelling catheter and concomitant bladder pain and/or catheter bypass leakage could benefit from intravesical botulinum injections [263].

3.4.2.5.6 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the UUT. This can be achieved by chemical denervation of the sphincter or by surgical interventions (bladder neck or sphincter incision or urethral stent – Section 3.4.3.1). Incontinence may result and can be managed by external devices (Section 3.4.2.1).

Botulinum toxin A: This can be used to treat DSD effectively by injecting the sphincter at a dose that depends on the preparation used. The dyssynergia is abolished only for a few months, necessitating repeat injections. The efficacy of this treatment has been reported to be high with few adverse effects [264-266]. However, a recent Cochrane report concluded that, because of limited evidence, future RCTs assessing the effectiveness of botulinum toxin A injections also need to address the uncertainty about the optimal dose and mode of injection [267]. In addition, this therapy is not licensed.

Balloon dilatation: Favourable immediate results were reported [268], but there have been no further reports since 1994; therefore, this method is no longer recommended.

Increasing bladder outlet resistance: This can improve the continence condition. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders [140, 269, 270].

Urethral inserts: Urethral plugs or valves for the management of (female) stress incontinence have not been applied in neuro-urological patients. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor were disappointing [271].

3.4.2.5.7 Summary of evidence and recommendations for botulinum toxin A injections and bladder neck procedures

Summary of evidence	**LE**
Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS or SCI in multiple RCTs and meta-analyses.	1a
Bladder neck incision is indicated only for secondary changes (fibrosis) at the bladder neck.	4

Recommendations	**Strength rating**
Use botulinum toxin injection in the detrusor to reduce neurogenic detrusor overactivity in multiple sclerosis or spinal cord injury patients if antimuscarinic therapy is ineffective.	Strong
Bladder neck incision is effective in a fibrotic bladder neck.	Strong

*3.4.3 **Surgical treatment***

There is considerable heterogeneity in outcome parameters and definitions of cure used to report on outcome of surgical interventions for SUI in neuro-urological patients [272]. The heterogeneity of outcome reporting makes it difficult to interpret and compare different studies and therapies. A consistent comparison of the outcomes of therapy can only be made after standardisation of outcome parameters and definitions of cure or success; therefore, it would seem prudent to develop a core outcome set (COS) for use in UI research in neuro-urological patients [272]. Until such a COS is developed it would seem feasible to use both a subjective and objective outcome parameter and the combination of both to define cure [272]. Due to the importance of QoL for neuro-urological patients a disease-specific QoL questionnaire or a bother questionnaire validated for neuro-urological patients should be used as the subjective outcome parameter [272].

3.4.3.1 Bladder neck and urethral procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure. Procedures to treat sphincteric incontinence are therefore suitable only when the detrusor activity can be controlled and when no significant reflux is present. A simultaneous bladder augmentation and IC may be necessary [140].

Urethral sling: Various materials have been used for this procedure with enduring positive results. The procedure is established in women with the ability to self-catheterise [140, 273-276]. There is growing evidence that synthetic slings can be used effectively with acceptable medium to long-term results and minimal morbidity in neurological patients [277, 278]. Besides the pubovaginal sling, which has been considered the procedure of choice in this subgroup of patients, recent reports suggest that both the transobturator and the retropubic approaches may also be considered, with similar failure rates and a reduction in the need for IC. However, for both approaches a higher incidence of *de novo* urgency was reported [278, 279]. In men, both autologous and synthetic slings may also be an alternative [280-284].

Artificial urinary sphincter (AUS): This device was introduced by Light and Scott for patients with neuro-urological disorders [285]. It has stood the test of time and acceptable long-term outcomes can be obtained [286]. However, the complication rates and re-operation rates are higher than in non-neurogenic patient groups (up to 60%), so it is advisable that patients are conscientiously informed about the success rates as well as the complications that may occur after the procedure [287, 288]. In a case series with 25 years follow up only 7.1% of patients were revision free at 20 years [289]. Re-interventions are commonly due to infection, urethral atrophy or erosion and mechanical failure.

There is growing interest in the use of this device in women with development of laparoscopic and robot-assisted approaches which appear to reduce infection and erosion rates [290-293]. Long-term surgical and patient-reported outcomes are needed to determine the role of AUS placement in female patients with neurogenic SUI [294].

Adjustable continence device - ProACT/ACT®: The efficacy of this device has been reported mainly in post-prostatectomy incontinence. A marginally lower cure rate has been reported in neurological patients when compared to non-neurological patients [295]. A retrospective study in neuro-urological patients reported a low rate of efficacy and high complication rate for this device [296].

Functional sphincter augmentation: Transposing the gracilis muscle to the bladder neck [297] or proximal urethra [298], can enable the possible creation of a functional autologous sphincter by electrical stimulation [297-299]; therefore, raising the prospect of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter procedure [300] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [301] improved by Salle [302], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [140, 303].

Endoscopic techniques for treating anatomic bladder outlet obstruction [304]:

- Transurethral resection of the prostate is indicated in male patients with refractory LUT symptoms due to benign prostatic obstruction. Special consideration should be given to pre-operative abnormal sphincter function which can lead to *de novo* or persistent UI [305, 306].
- Bladder neck resection is indicated in patients with high PVR and when a prominent obstruction of the sclerotic ring in the bladder neck is identified during cystoscopy. The resection can be performed between the three or nine o'clock position or full circle [307].
- Urethrotomy is indicated in patients with urethral strictures. Cold knife or neodymium:YAG contact laser urethrotomy at the twelve o'clock position can be performed [308, 309]. In recurrent strictures, open surgery should be considered.
- Sphincterotomy has been shown to be an efficient technique for the resolution of AD, hydronephrosis and recurrent UTI, and for decreasing detrusor pressures, PVR and vesicoureteral reflux. It is irreversible and should be limited to men who are able to wear a condom catheter. By staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra [139, 140, 310]. The incision with less complications is the twelve o'clock sphincterotomy with cold knife [311] or neodymium:YAG laser [312]. Sphincterotomy needs to be repeated at regular intervals in many patients [313], but it is efficient and does not cause severe adverse effects [139, 268]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [314].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [139, 315]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [139].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [140]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [316, 317]. However, the costs [139], possible complications and re-interventions [318, 319] are limiting factors in their use [320-323].

3.4.3.2 Denervation, deafferentation, sacral neuromodulation

Sacral anterior root stimulation (SARS) is aimed at producing detrusor contraction. The technique was developed by Brindley [324] and is only applicable to complete lesions above the implant location, as its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called "post-stimulus voiding" occurs. This approach has been successful in highly selected patients [325-327]. Although it has been shown that detrusor pressure during SARS decreases over time, the changes do not seem to be clinically relevant during the first decade after surgery [328]. By changing the stimulation parameters, this method can also induce defecation or erection. A recent study reported that Charcot spinal arthropathy should be considered as a potential long-term complication of SARS, leading to spinal instability and to SARS dysfunction [329].

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing DO [330-332], but nowadays, it is used mostly as an adjuvant to SARS [325, 333-336]. Alternatives to rhizotomy are sought in this treatment combination [337-339].

Sacral neuromodulation [340] might be effective and safe for treating neuro-urological symptoms, but there is a lack of RCTs and it is unclear which neurological patients are most suitable [341-344].

3.4.3.3 Bladder covering by striated muscle

When the bladder is covered by striated muscle, that can be stimulated electrically, or ideally that can be contracted voluntarily, voiding function can be restored to an acontractile bladder. The rectus abdominis [345] and latissimus dorsi [346] have been used successfully in patients with neuro-urological symptoms [347, 348].

3.4.3.4 Bladder augmentation

The aim of auto-augmentation (detrusor myectomy) is to reduce DO or improve low bladder compliance. The advantages are: low surgical burden, low rate of long-term adverse effects, positive effect on patient QoL, and it does not preclude further interventions [139, 140, 349-352].

Replacing or expanding the bladder by intestine or other passive expandable coverage will improve bladder compliance and at least reduce the pressure effect of DO [353, 354]. Improved QoL and stable renal function has been reported during long-term follow-up [355]. Patients performing IC with augmentation cystoplasty had better urinary function and satisfaction with their urinary symptoms compared to patients performing IC with or without botulinum toxin treatment [356]. Long-term complications included bladder perforation (1.9%), mucus production (12.5%), metabolic abnormalities (3.35%), bowel dysfunction (15%), and stone formation (10%) [355].

The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed. Special attention should be paid to patients with pre-operative renal scars since metabolic acidosis can develop [357]. Bladder substitution with bowel after performing a supratrigonal cystectomy [354], to create a low-pressure reservoir, is indicated in patients with a severely thick and fibrotic bladder wall [140]. Intermittent catheterisation may become necessary after this procedure. The long-term scientific evidence shows that bladder augmentation is a highly successful procedure that stabilises renal function and prevents anatomical deterioration; however, lifelong follow-up is essential in this patient group given the significant morbidity associated with this procedure [355, 358].

3.4.3.5 Urinary diversion

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT and for the patient's QoL [140].

Continent diversion: This should be the first choice for urinary diversion. Patients with limited dexterity may prefer a stoma instead of using the urethra for catheterisation. For cosmetic reasons, the umbilicus is often used for the stoma site [359-364]. A systematic review of the literature concluded that continent catheterisable tubes/stomas are an effective treatment option in neuro-urological patients unable to perform intermittent self-catheterisation through the urethra [365]. However, the complication rates were significant with 85/213 post-operative events requiring re-operation [365]. Tube stenosis occurred in 4-32% of the cases. Complications related to concomitant procedures (augmentation cystoplasty, pouch) included neovesicocutaneous fistulae (3.4%), bladder stones (20-25%), and bladder perforations (40%). In addition, data comparing HRQoL before and after surgery were not reported [365].

Incontinent diversion: If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [140]. An ileal segment is used for the deviation in most cases [140, 366-369]. Patients gain better functional status and QoL after surgery [370].

Undiversion: Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence [140]. The patient must be carefully counselled and must comply meticulously with the instructions [140]. Successful undiversion can then be performed [371].

3.4.3.6 Summary of evidence and recommendations for surgical treatment

Summary of evidence	LE
Bladder augmentation is an effective option to decrease detrusor pressure and increase bladder capacity, when all less-invasive treatment methods have failed.	3
Urethral sling placement is an established procedure, with acceptable medium- to long-term results, in women with the ability to self-catheterise.	3
Artificial urinary sphincter insertion is a viable option, with acceptable long-term outcomes, in males. The complication and re-operation rates are higher in neuro-urological patients; therefore, patients must be adequately informed regarding the success rates as well as the complications that may occur following the procedure.	3

Recommendations	Strength rating
Perform bladder augmentation in order to treat refractory neurogenic detrusor overactivity.	Strong
Place an autologous urethral sling in female patients with neurogenic stress urinary incontinence who are able to self-catheterise.	Strong
Insert an artificial urinary sphincter in male patients with neurogenic stress urinary incontinence.	Strong

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [360]. There are no evidence-based cut-off values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing IC is present with $> 10^2$ cfu/mL, $> 10^4$ cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, ten or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant [360].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Male gender seems to be a risk factor for febrile UTI [372]. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [373]. Poor glycemic control has been established as a risk factor for UTI in women with type 1 diabetes [374]. However, the exact working mechanisms remain unknown. The presence of asymptomatic bacteriuria in SCI patients is higher than in the general population, and varies depending on bladder management. Prevalence of bacteriuria in those performing clean IC varies from 23-89% [375]. Sphincterotomy and condom catheter drainage has a 57% prevalence [376]. Asymptomatic bacteria should not be routinely screened for in this population [377].

Individuals with neuro-urological symptoms, especially those with SCI, may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. Other problems, such as AD, may develop or worsen due to a UTI [225]. The most common signs and symptoms suspicious of a UTI in those with neuro-urological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odour, discomfort or pain over the kidney or bladder, dysuria, or AD [225, 378]. New incontinence is the most specific symptom, whereas cloudy and foul smelling urine has the highest positive predictive value for UTI diagnosis [379].

3.5.2 ***Diagnostic evaluation***

Urine culture and urinalysis are the optimum tests for the diagnosis of UTI in neuro-urological patients. A dipstick test may be more useful to exclude than to prove UTI [380, 381]. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [382].

3.5.3 ***Disease management***

Bacteriuria in patients with neuro-urological disorders should not be treated. Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving the outcome [383]. Urinary tract infections in persons with neuro-urological disorders are by definition a complicated UTI; therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment as it depends on the severity of the UTI and the involvement of kidneys and the prostate. Generally, a five to seven day course of antibiotic treatment is advised, which can be extended up to fourteen days according to the extent of the infection [383]. The choice of antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g. fever, septicaemia, intolerable clinical symptoms, extensive AD), the choice of treatment should be based on local and individual resistance profiles [384]. In patients with afebrile UTI, an initial non-antibiotic treatment may be justified [385, 386].

3.5.3.1 Recurrent UTI

Recurrent UTI in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, by treating DO by botulinum toxin A injection in the detrusor [387], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [382].

3.5.3.2 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilised. In a meta-analysis the use of hydrophilic catheters was associated with a lower rate of UTI [225]. Bladder irrigation has not been proven effective [388].

Various medical approaches have been tested for UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice or probiotics for the prevention of UTI could not be demonstrated in RCTs [389, 390]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [391]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI [392]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI [393] and that recurrent UTIs are reduced [394]. Low-dose, long-term, antibiotic prophylaxis can reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [383].

Weekly cycling of antibiotic prophylaxis provided long-term positive results, but the results of this trial need to be confirmed in further studies [395]. Another possible future option, the inoculation of apathogenic *Escherichia coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data [396], cannot be recommended as a treatment option. There is initial evidence that homeopathic treatment can decrease UTI frequency [397]. In addition, intravesical gentamycin instillations can reduce UTI frequency without increasing the number of multi-resistant bacteria [398].

In summary, based on the criteria of evidence-based medicine, there is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations. Therefore, individualised concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine [399]. Prophylaxis in patients with neuro-urological disorders is important to pursue, but since there are no data favouring one approach over another, prophylaxis is essentially a trial and error approach.

*3.5.4 **Summary of evidence and recommendations for the treatment of UTI***

Summary of evidence	LE
Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving patient outcome.	1a
Low-dose, long-term, antibiotic prophylaxis does not reduce UTI frequency, but increases bacterial resistance.	2a
Recurrent UTI in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem. Improvement of bladder function as early as possible is mandatory.	3
There is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations.	3

Recommendations	Strength rating
Do not screen for or treat asymptomatic bacteriuria in patients with neuro-urological disorders.	Strong
Avoid the use of long-term antibiotics for recurrent urinary tract infections (UTIs).	Strong
In patients with recurrent UTI, optimise treatment of neuro-urological symptoms and remove foreign bodies (e.g. stones, indwelling catheters) from the urinary tract.	Strong
Individualise UTI prophylaxis in patients with neuro-urological disorders as there is no optimal prophylactic measure available.	Strong

3.6 Sexual function and fertility

These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [400, 401]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [402, 403]. In neuro-urological patients sexual problems can be identified at three levels: primary (direct neurological damage), secondary (general physical disabilities) and tertiary (psychosocial and emotional issues) sexual dysfunction [404]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [405], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction. Sexual dysfunction is associated with neurogenic LUT dysfunction in patients with MS [406] and SB [407]. Although various patient reported outcome measures (PROMs) are available to evaluate sexual function, the evidence for good PROMs is limited and studies with high methodological quality are needed [408].

*3.6.1 **Erectile dysfunction***

3.6.1.1 Phosphodiesterase type 5 inhibitors (PDE5Is)

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic ED [400, 401]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10 mg was shown to be more effective than sildenafil 50 mg. All currently available PDE5Is appear to be effective and safe, although there are no high level evidence studies in neuro-urological patients investigating the efficacy and side effects across different PDE5Is, dosages and formulations [409].

For MS patients two studies reported significant improvement in ED when using sildenafil and tadalafil. One study; however, showed no improvement in ED with sildenafil.

In PD normal erectile function was described in over half of the patients using sildenafil 100 mg and a significant improvement in IIEF-15 score was found compared to placebo. While most neuro-urological patients require long-term therapy for ED some have a low compliance rate or stop therapy because of side effects [410, 411], most commonly headache and flushing [401]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy [410, 411]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce erection. Since many patients with SCI use on-demand nitrates for the treatment of AD, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3.6.1.2 Drug therapy other than PDE5Is

Fampridine to treat neurogenic spasticity has been shown to be beneficial in improving ED in two domains of the IIEF-15 in SCI and MS patients, however, with a significant discontinuation rate due to severe adverse

events [412]. Sublingual apomorfine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [413]. In PD pergolide mesylate showed a significant improvement in IIEF-15 scores up to twelve months follow-up [414].

3.6.1.3 Mechanical devices

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [415-419].

3.6.1.4 Intracavernous injections and intraurethral application

Patients not responding to oral drugs may be offered intracavernous injections (alprostadil, papaverine and phentolamine) that have been shown to be effective in a number of neurological conditions, including SCI, MS, and diabetes mellitus [420-426], but their use requires careful dose titration and some precautions. Complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first-line therapeutic option in patients taking nitrate medications, as well as those with concerns about drug interactions with PDE5Is, or in whom PDE5Is are ineffective. The impact of intracavernous injections on ejaculation and orgasmic function, their early use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term are unclear [410]. Intra-urethral alprostadil application is an alternative, but a less effective, route of administration [422, 427].

3.6.1.5 Sacral neuromodulation

Sacral neuromodulation for LUT dysfunction may improve sexual function; however, high level evidence studies are lacking.

3.6.1.6 Penile prostheses

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. At a mean follow-up of seven years 83.7% of patients with SCI were able to have sexual intercourse [401]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [428-430].

3.6.1.7 Summary of evidence and recommendations for erectile dysfunction

Summary of evidence	**LE**
The long-term efficacy and safety of oral PDE5Is for the treatment of ED is well documented.	1b
Intracavernous vasoactive drug injections have been shown to be effective in a number of neurological conditions, including SCI and MS; however, their use requires careful dose titration and precautions.	3
Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular.	3
Reserve penile prostheses for selected patients, those in which all conservative treatments have failed, with neurogenic ED.	4

Recommendations	**Strength rating**
Prescribe oral phosphodiesterase type 5 inhibitors as first-line medical treatment in neurogenic erectile dysfunction (ED).	Strong
Give intracavernous injections of vasoactive drugs (alone or in combination) as second-line medical treatment in neurogenic ED.	Strong
Offer mechanical devices such as vacuum devices and rings to patients with neurogenic ED.	Strong

3.6.2 ***Male fertility***

Male fertility can be compromised in the neurological patient by ED, ejaculation disorder, impaired sperm quality or various combinations of these three disorders. Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, SB, MS and SCI [431]. Erectile dysfunction is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [431]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [432]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [433].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [434]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [431, 435, 436]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [437-439]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [440, 441]; patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition. In SCI patients the use of oral midodrine can improve sperm retrieval at vibrostimulation [442].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [443]. Surgical procedures, such as, microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful [444, 445]. Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection (ICSI), men with SCI now have a good chance of becoming biological fathers [446-448].

3.6.2.1 Sperm quality and motility

The following has been reported on sperm quality and motility:

- bladder management with clean IC may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression [449];
- in SCI patients sperm quality decreases at the early post traumatic phase demonstrating lower spermatozoid vitality (necrospermia), reduced motility (asthenospermia) and leucospermia [444];
- long-term valproate treatment for epilepsy negatively influences sperm count and motility [450];
- vibrostimulation produces samples with better sperm motility than electrostimulation [451, 452];
- electroejaculation with interrupted current produces better sperm motility than continuous current [453];
- freezing of sperm is unlikely to improve fertility rates in men with SCI [454].

3.6.2.2 Summary of evidence and recommendations for male fertility

Summary of evidence	**LE**
Vibrostimulation and transrectal electroejaculation have been shown to be effective for sperm retrieval in neuro-urological patients.	1b
Surgical procedures, such as, microsurgical epididymal sperm aspiration or testicular sperm extraction, may be used if vibrostimulation and electroejaculation are not successful.	3
In men with SCI at or above Th 6, AD might occur during sexual activity and ejaculation.	3

Recommendations	**Strength rating**
Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with spinal cord injury.	Strong
Perform microsurgical epididymal sperm aspiration, testicular sperm extraction and intracytoplasmic sperm injection after failed vibrostimulation and/or transrectal electroejaculation in men with spinal cord injury.	Strong
Counsel men with spinal cord injury at or above Th 6 and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	Strong

*3.6.3 **Female sexuality***

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life [455-458]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [459, 460].

The greatest physical barrier to sexual activity is UI. A correlation has been found between the urodynamic outcomes of low bladder capacity, compliance and high maximum detrusor pressure and sexual dysfunction in MS patients. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimise the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others [455, 461-463].

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Data on sildenafil for treating female sexual dysfunction are poor and controversial [401]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [464], there is a lack of high-level evidence studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive Th 11-L2 pin-prick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm is more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5), even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions [465-467].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [401].

Women with SCI reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services and were less likely to receive sexual information than men [465, 468, 469].

*3.6.4 **Female fertility***

There are few studies on female fertility in neurological patients. More than a third (38%) of women with epilepsy had infertility and the relevant predictors were exposure to multiple (three or more) antiepileptic drugs, older age and lower education [470].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately six months after SCI [471], there are no high-level evidence studies. About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury [472].

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, anaemia, and AD [473-477]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [472, 475-477].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [478, 479].

There is very little published data on women's experience of the menopause following SCI [480]. Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [481-483]. Clinical management should be individualised to optimise both the mother's reproductive outcomes and MS course [482-484].

3.6.4.1 Summary of evidence and recommendation for female sexuality and fertility

Summary of evidence	**LE**
Data on specific drugs for treating female sexual dysfunction are poor and controversial.	4
There are limited numbers of studies on female fertility in neurological patients, clinical management should be individualised to optimise both the mother's reproductive outcomes and medical condition.	4

Recommendations	**Strength rating**
Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women.	Strong
Take a multidisciplinary approach, tailored to individual patient's needs and preferences, in the management of fertility, pregnancy and delivery in women with neurological diseases.	Strong

3.7 Follow-up

*3.7.1 **Introduction***

Neuro-urological disorders are often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary to assess the UUT [138].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological symptoms, the interval between initial investigations and control diagnostics may vary and in many cases should not exceed one to two years. In high-risk neuro-urological patients this interval should be much shorter. Urinalysis should be performed only when patients present with symptoms [485]. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; about once every six months [6, 486]. In these patients, physical examination and urine laboratory should take place every year [6, 486]. In MS patients higher scores on the Expanded Disability Status Scale (EDSS) are associated with risk factors for UUT deterioration [53]. A urodynamic investigation should be performed as a diagnostic baseline, and repeated during follow-up, more frequently in high-risk patients [6, 486]. In addition, bladder wall thickness can be measured on

ultrasonography as an additional risk assessment for upper tract damage [487], although a 'safe' cut-off threshold for this has not been agreed [488]. The utility of DMSA for follow-up of neuro-urological patients has not been fully evaluated [489]. Any significant clinical change warrants further, specialised, investigation [6, 486]. However, there is a lack of high level evidence studies on this topic and every recommendation must be viewed critically in each individual neuro-urological patient [138].

The increased prevalence of muscle invasive bladder cancer in neuro-urological patients also warrants long-term follow-up [490]. The exact frequency of cystoscopy with or without cytology remains unknown, but presence of risk factors similar to the general population should trigger further investigation [485].

Adolescent patients with neurological pathology are at risk of being lost to follow-up during the transition to adulthood. It is important that a standardised approach during this transition is adopted to improve follow-up and specific treatment during adult life [491].

*3.7.2 **Summary of evidence and recommendations for follow-up***

Summary of evidence	**LE**
Neuro-urological disorders are often unstable and the symptoms may vary considerably, therefore, regular follow-up is necessary.	4

Recommendations	**Strength rating**
Assess the upper urinary tract at regular intervals in high-risk patients.	Strong
Perform a physical examination and urine laboratory every year in high-risk patients.	Strong
Any significant clinical changes should instigate further, specialised, investigation.	Strong
Perform urodynamic investigation as a mandatory baseline diagnostic intervention in high-risk patients at regular intervals.	Strong

3.8 Conclusions

Neuro-urological disorders have a multi-faceted pathology. They require an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about their future. The urologist can select from a wealth of therapeutic options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, close surveillance is necessary for the patient's entire life.

These Guidelines offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as non-invasive as possible.

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5. CONFLICT OF INTEREST

All members of the Neuro-urology working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Sexual and Reproductive Health

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and Objectives

The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines aim to provide a comprehensive overview of the medical aspects relating to sexual and reproductive health in adult males. These Guidelines cover the former EAU guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

It must be emphasised that guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Sexual and Reproductive Health Guidelines panel consists of an international multidisciplinary group of urologists, endocrinologists and a psychologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/sexualandreproductivehealth/.

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/sexualandreproductivehealth/.

1.4 Publication History

This document is a new Guideline which includes a comprehensive update of the 2018 versions of Male Sexual Dysfunction, Male Infertility and Male Hypogonadism, along with a number of new topics. Additional sections will be added in the coming year to address priapism and male contraception and vasectomy which were addressed in the 2018 versions.

2. METHODOLOGY

2.1 Methods

For the 2020 Sexual and Reproductive Health Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2013 and 2018 and restricted to English language publications. Detailed search strategies are available online: http://www.uroweb.org/guideline/sexualandreproductivehealth/.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative

management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Sections of the Sexual and Reproductive Health Guidelines were peer reviewed prior to publication. This is an ongoing process which will continue as the Guidelines is further refined in the coming year.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2021 update of the Sexual and Reproductive Health Guidelines. Systematic reviews planned for 2020 are:

- What is the effectiveness of non-surgical therapies in the treatment of ischaemic priapism in patients with sickle cell disease?
- What is the effectiveness of non-surgical therapies in the management of priapism in patients without sickle cell disease?

3. MALE HYPOGONADISM

3.1 Epidemiology and prevalence of male hypogonadism

Definition: Male hypogonadism is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production [5]. This is caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis. Several congenital or acquired disorders causing impaired action of androgens are also described [5]. Hypogonadism may adversely affect multiple organ functions and quality of life (QoL) [6]. Late-onset hypogonadism (LOH) is a clinical condition in the aging male, which, by definition, must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [5, 7]. It is a condition frequently diagnosed in the absence of an identifiable classical cause of hypogonadism, which becomes more prevalent with age, usually occurring, but not exclusively, in men over 40 years of age.

Male hypogonadism has also been called *Testosterone Deficiency*; the Panel has agreed to use the term *Male Hypogonadism*, which may better reflect and explain the underlying pathophysiology. Likewise, the Panel has further agreed to continue with the terminology *testosterone therapy* to indicate a therapy with testosterone. The present guidelines will specifically address the management of adult male hypogonadism also called LOH. Some insights related to congenital or pre-pubertal hypogonadism are also provided and summarised where applicable.

The prevalence of hypogonadism increases with age and the major causes are central obesity, co-morbidities (e.g., diabetes) and overall poor health [8]. In healthy aging men there is only a small gradual decline in testosterone; up to the age of 80 years, age accounts for a relatively low percentage of hypogonadism [8]. In men aged between 40-79 years the incidence of symptomatic hypogonadism varies between 2.1-5.7% [9-11]. The incidence of hypogonadism has been reported to be 12.3 and 11.7 cases per 1,000 people per year [9, 12].

There is a high prevalence of hypogonadism within specific populations, including patients with type 2 diabetes (T2DM), metabolic syndrome (MetS), obesity, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), renal disease and cancer [11]. Low testosterone levels are common in men with T2DM [13] and a high prevalence of hypogonadism (42%) has been reported in T2DM patients [14].

Klinefelter's syndrome, a trisomy associated with a 47,XXY karyotype, is the most prevalent genetic cause of primary hypogonadism (hypergonadotropic hypogonadism), with a global prevalence of 1/500-1,000 live male births [15-17]. However, less than 50% of individuals with Klinefelter syndrome are diagnosed in life [18].

3.1.1 Body Composition and Metabolic Profile

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to men with adequate testosterone levels [19]. Much evidence has documented that low testosterone is strongly associated with an increased visceral adiposity, but it also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. *In vitro* studies suggest that hypogonadism impairs glucose and triglyceride uptake into subcutaneous fat depots [19]. This enhances the uptake of glucose and triglycerides into ectopic fat depots as described above.

Testosterone therapy has been associated with a reduced percentage of body fat and an increase of lean body mass [20]. Data from a registry study has suggested that over a period of eight years, testosterone therapy with long-acting intramuscular testosterone undecanoate was associated with a substantial but gradual loss of weight along with a reduction in waist circumference [21]. Testosterone also reduces liver fat content and muscle fat stores [19].

*3.1.2 **Metabolic Syndrome/Type 2 Diabetes***

Metabolic Syndrome (MetS) is characterised by a number of specific components, including increased waist circumference, dyslipidaemia, hypertension, and impaired glucose tolerance. Hypogonadism is associated with central obesity, hyperglycaemia, insulin resistance and dyslipidaemia (low HDL-cholesterol, raised total and LDL-cholesterol and triglycerides), hypertension and a predisposition to T2DM, which are all components of MetS [22].

A number of randomised controlled trials (RCTs) have shown that testosterone therapy might improve insulin resistance, hyperglycaemia and lower cholesterol and LDL-cholesterol [23-27]. Evidence suggests that testosterone therapy in hypogonadal T2DM improves glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence from RCTs and meta-analyses studies [24, 28, 29]. Recently, a registry study reported that testosterone therapy is associated in time with remission of T2DM [28]. HDL-cholesterol may decrease, remain unchanged or increase with testosterone therapy. Testosterone therapy in men with MetS and low testosterone has also been shown to reduce mortality compared to untreated men [30, 31] although no conclusive evidence is available.

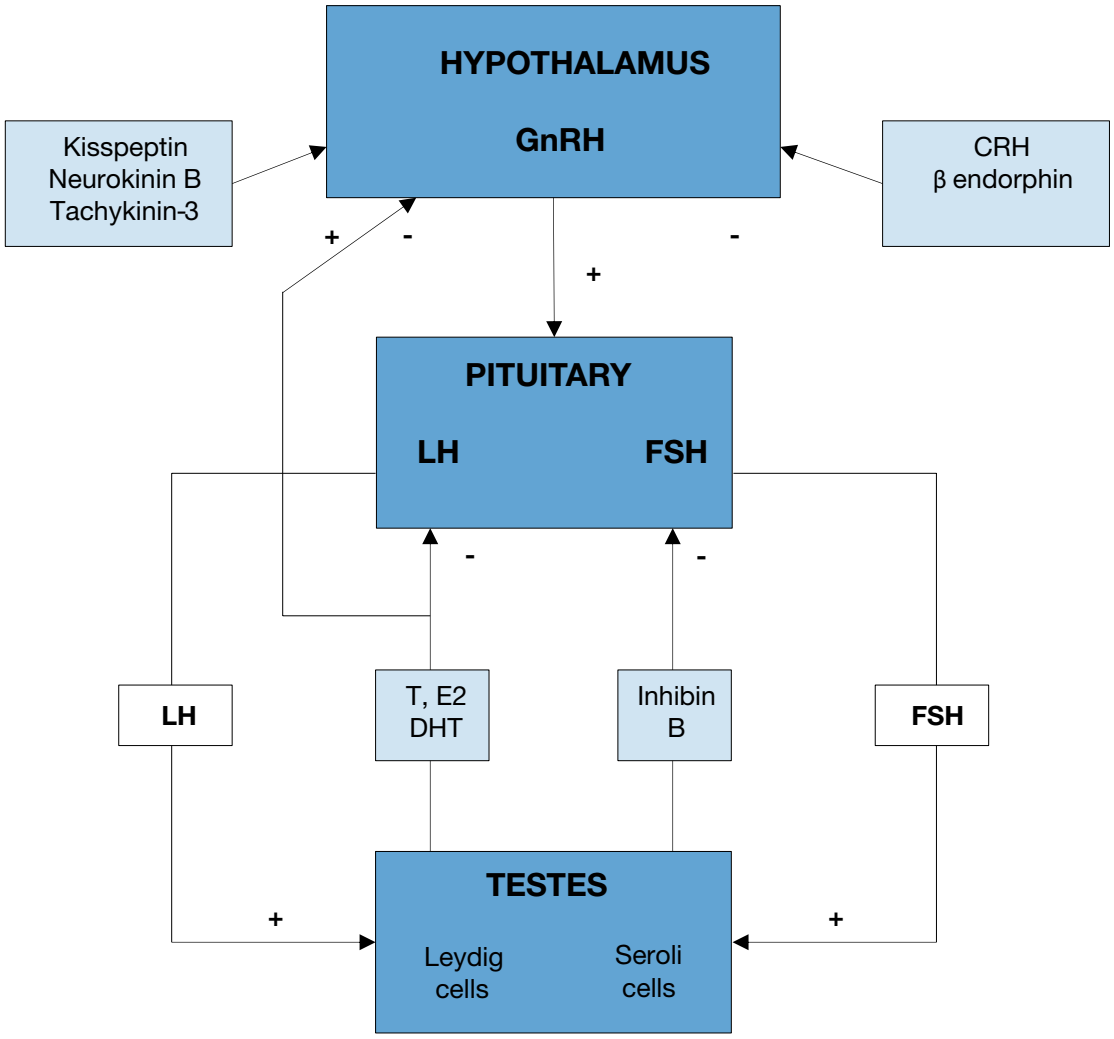
Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multifactorial and 30% of men with ED have co-existing testosterone deficiency. Some evidence has suggested that for patients with T2DM this has been demonstrated only to be the case in men with clearly reduced testosterone levels (< 8mmol/L [2.31 ng/mL]) [32]. From a pathophysiological point of view, it has been reported that this is because ED is predominantly due to vascular and neuropathic disease, therefore not likely to be the case in those men who do not have an established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

Randomised placebo-controlled trials of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, but not erectile function [24, 32]. The presence of multi-comorbidities in this group of patients may confound the response to testosterone alone.

3.2 Physiology of testosterone production

The pituitary gland regulates testis activity, through the secretion of luteinising hormone (LH), which regulates testosterone production in Leydig cells and follicle-stimulating hormone (FSH), which mainly controls sperm production in seminiferous tubules [33, 34]. The production and secretion of gonadotropins is stimulated by hypothalamic gonadotropin releasing hormone (GnRH) and inhibited by a negative feedback mediated by the central action of sex steroids and inhibin B (Figure 1) [33, 34]. Gonadotropin releasing hormone is secreted in a pulsatile manner and negatively controlled by the activity of other hypothalamic neurons, including corticotrophin releasing hormone (CRH) and β endorphin neurons [33, 34]. Conversely, kisspeptin-1 (Kiss-1) neurons, neurokinin-B or tachykinin-3 are involved in GnRH stimulation. Finally, leptin is also involved in the activation of Kiss-1 signaling [35]. About 25 mg of testosterone is present in the normal testes, and, on average, 5-10 mg of testosterone are secreted daily [33, 34]. The testis also produces lesser amounts of other androgens such as androstenedione and dehydroepiandrosterone (DHT). In addition, a small amount of extra-gonadal testosterone is derived from circulating weak adrenal androgen precursor dehydroepiandrosterone (DHEA), although its specific contribution to daily testosterone production is limited in men [36, 37]. In physiological terms, DHT formation accounts for about 6-8% of testosterone metabolism, and the ratio of plasma testosterone/DHT is approximately 1:20 [33, 34]. Finally, testosterone and its precursor, Δ4 androstenedione, can be aromatised through P450 aromatase to other bioactive metabolites, such as oestrone (E1) and 17-β-estradiol (E2), with a daily production of about 45 μg [33, 34]. Furthermore, Leydig cells, can also directly produce and release into the bloodstream a small amount of oestrogens, with a daily production rate of about 5-10 μg (up to 20% of circulating oestrogens) [38].

Figure 1: Physiology of testosterone production



GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; T = testosterone; E2 = 7-β-estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

*3.2.1 **Circulation and transport of testosterone***

In normal men 60% to 70% of circulating testosterone is bound to the high affinity sex hormone-binding globulin (SHBG), a protein produced by the liver, which prevents its bound testosterone sub-fraction from biological action. The remaining circulating testosterone binds lower affinity, high-capacity binding protein sites, (albumin, α-1 acid glycoprotein and corticosteroid binding protein), and only 1%-2% of testosterone remains non-protein bound [39]. There is a general agreement that testosterone bound to lower affinity proteins can easily dissociate in the capillary bed of many organs accounting for so-called 'bioavailable' testosterone [39]. It is important to recognise that several clinical conditions and aging itself can modify SHBG levels, thus altering circulating total testosterone levels (Table 1). Therefore, if not recognised, these factors could lead to an incorrect estimation of male androgen status. Therefore, when indicated (see Table 1) SHBG should be tested and free testosterone calculated.

Table 1: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	Drugs: anticonvulsant, oestrogens, thyroid hormone Hyperthyroidism Hepatic disease Aging Smoking AIDS/HIV
SHBG decrease	Drugs: GH, glucocorticoids, testosterone, anabolic androgenic steroids Hypothyroidism Obesity Acromegaly [40] Cushing Disease Insulin resistance (MetS/T2DM) o non-alcoholic fatty liver disease (NAFLD), Nephrotic syndrome

*3.2.2 **Androgen receptor (AR)***

Testosterone and DHT exert their biological action through the activation of a specific nuclear receptor. The AR gene is localised on the X chromosome (Xq11-12), encoded in eight exons [41]. Exon 1 includes two polymorphic trinucleotide repeat segments encoding polyglutamine (CAG) and polyglycine (GGN) tracts in the N-terminal transactivation domain of its protein. It has been established that the activity of the AR is inversely associated with the length of the CAG repeat chains [41]. However, the specific role of AR CAG repeat number in relation to hypogonadal symptoms or to clinical management of testosterone deficiency remains unclear [42, 43]. It has been shown in an RCT that a higher CAG repeat number is positively associated with a change in fasting insulin, triglyceride and diastolic blood pressure, demonstrating the more sensitive the receptor the greater the benefit [44].

3.3 Role of testosterone in male sexual and reproductive health

*3.3.1 **Sexual development and maturation***

Testosterone production in the foetal testis starts between the eighth and ninth week of gestation after the expression of the SRY (Sex-determining Region Y) gene, which regulates the organisation of the undifferentiated gonadal ridge into the testis [45]. During the first trimester, the testes drive the virilisation of internal and external genitalia through placental human chorionic gonadotropin (hCG) stimulated androgen secretion by Leydig cells. During foetal life, testosterone mainly controls the differentiation of internal genitalia and testis descent (regression of gubernaculums testis), whereas DHT is mainly involved in the development of the external male genitalia [46]. During puberty, the reactivation of the hypothalamus-pituitary-gonadal (HPG) axis allows the development of secondary sexual characteristics, spermatogenesis maturation and, along with the contribution of other hormonal axes, the completion of the adolescent growth spurt [5, 47]. Clinical models of aromatase deficiency and oestrogen receptor insensitivity have demonstrated that testosterone conversion to estradiol is essential for epiphyseal closure and growth arrest [48].

*3.3.2 **Sexual function***

Testosterone is involved in the regulation of all steps of the male sexual response. Sexual thoughts and motivations are universally accepted as the most testosterone-dependent aspects of male sexual behaviour [20]. The European Male Aging Study (EMAS), a population-based survey including more than 3,400 subjects aged 40-80 years from eight European countries, showed that sexual symptoms and, in particular, sexual desire impairment, ED and a decreased frequency of morning erections were the most specific symptoms associated with age-depended decline of testosterone [10]. Similar findings were reported in subjects consulting for sexual dysfunctions [49]. Accordingly, several brain areas, including the amygdala, medial preoptic area, paraventricular nucleus of the hypothalamus, and peri-aqueductal grey matter express the AR [49, 50]. Both experimental and clinical studies have documented that testosterone plays a crucial role in regulating penile function. In particular, testosterone controls the structural integrity necessary for penile erection as well as several enzymatic activities within the corpora cavernosa, including a positive action on nitric oxide (NO) formation and a negative influence on the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK) pathways [49, 51]. Testosterone is also involved in penile adrenergic response and cavernous smooth muscle cell turnover [49, 51]. Finally, although some authors have suggested a positive role of testosterone in regulating penile phosphodiesterase 5 (PDE5) expression and activity, other evidence showed a prevalent inhibiting role of oestrogens on this pathway [49, 52].

More limited evidence documented a possible role of testosterone in regulating ejaculatory process acting either at central and peripheral level. Androgen receptors are expressed in several central spinal and super-spinal areas involved in the control of ejaculatory reflex [53]. In addition, the male genital tract expresses NO-PDE5 as well as RhoA/ROCK pathways, which are modulated by testosterone [53].

3.4 Classification and causes of male hypogonadism

Male hypogonadism can be classified according to the origin of the underlying problem into primary, if a consequence of testicular dysfunction, or secondary if due to a pituitary or hypothalamic dysfunction (Table 2).

Primary hypogonadism is also called hypergonadotropic hypogonadism (HH), since the pituitary tries compensating the dysfunctional testis by increasing central stimulation. Conversely, in secondary hypogonadism the testis is inadequately stimulated by gonadotropins resulting in a HH, usually with inappropriately normal or reduced gonadotropin levels [5, 34]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated LH production, has also been reported [54]; the clinical significance of the latter condition is unclear [54, 55]. Finally, hypogonadism can also result from a group of several conditions leading to a reduced sensitivity/insensitivity to testosterone and its metabolites (Table 2) [5, 34]. This classification, based on the aetiology of hypogonadism, allows the clinician to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with an adequate treatment, whereas in primary hypogonadism only testosterone therapy can be considered, which will impair fertility due to suppression of the hypothalamic pituitary axis (HGP) (Table 2) [5, 34].

In 2017, Grossmann and Matsumoto suggested a new classification of adult male hypogonadism, distinguishing functional versus organic hypogonadism [56]. Accordingly, organic hypogonadism is characterised by any proven pathology affecting the HPG axis and should be treated with the conventional medications (i.e., gonadotropins or TRT); conversely, functional hypogonadism is based on the absence of any recognised organic alterations in the HPG axis and should be treated, first by resolving or improving the associated comorbidities. These Guidelines refer to the validated international classification of adult male hypogonadism.

Table 2: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*

Klinefelter syndrome	- Rare chromosomal abnormalities
	  - XX male syndrome
	  - 47 XYY syndrome
	  - 48 XXYY syndrome
	- 21 Trisomy (Down syndrome)
	- Noonan syndrome
	- Autosomal translocations[1]
	- Defects of testosterone biosynthesis
	- CAH (testicular adrenal rest tumours)
	- Disorders of sex development (gonadal dysgenesis)
	- LHR gene mutations
	- Myotonic dystrophy (including type I and II)
	- Uncorrected cryptorchidism (including INSL3 and LGR8 mutations)
	- Bilateral congenital anorchia
	- Sickle cell disease
	- Adreno-leukodystrophy

Acquired disorders	
Drug-induced	*Localised problems*
- Chemotherapy agents • Alkylating agents - Methotrexate • Testosterone synthesis inhibitors • Ketoconazole • Aminoglutethimide • Mitotane • Metyrapon	- Bilateral surgical castration or trauma - Testicular irradiation - Orchitis (including mumps orchitis) - Autoimmune testicular failure - Testicular Torsion - Alcohol/Cirrhosis • Environmental Toxins

Systemic diseases/conditions with hypothalamus/pituitary impact	

- Chronic systemic diseases*
- Chronic organ failure*
- Glucocorticoid excess (Cushing syndrome)*
- Aging*
- HIV
	- Malignancies
	  - Lymphoma
	  - Testis cancer
	- Spinal cord injury
	- Vasculitis
	- Infiltrative diseases (amyloidosis; leukaemia)

SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*

- Hemochromatosis*	- Combined hormone pituitary deficiency
	- Idiopathic hypogonadotropic hypogonadism (IHH) with variants:
	  - Normosmic IHH
	  - Kallmann syndrome
	  - Isolated LH β gene mutations
	  - Prader-Willi Syndrome

Acquired disorders	
Drug-induced	*Localised problems*

- Oestrogens
- Testosterone or androgenic anabolic steroids
- Progestogens (including cyproterone acetate)
- Hyperprolactinaemia-induced drugs
- Opiates
  - GnRH agonist or antagonist
  - Glucocorticoids
	- Traumatic brain injury
	- Pituitary neoplasm (micro/macro adenomas)
	- Hypothalamus tumours
	- Pituitary stalk diseases
	- Iatrogenic
	  - Surgical hypophisectomy
	  - Pituitary or cranial irradiation
	- Inflammatory and infectious diseases
	  - Lymphocytic hypophysitis
	  - Pituitary infections
	  - Granulomatous lesions
	  - Sarcoidosis
	  - Wegener's granulomatosis
	  - Other granulomatosis
	  - Encephalitis
	- Langerhans' histiocytosis
	- Hyperprolactinaemia as a consequence of localised problems (hypothalamus-pituitary mass)

Systemic diseases/conditions impacting the hypothalamus/pituitary	

- Chronic systemic diseases*
  - Metabolic diseases
  - HIV infection
  - Chronic organ failure
  - Chronic Inflammatory Arthritis
- Glucocorticoid excess (Cushing syndrome)*
- Eating disorders*
- Endurance exercise
- Acute and critical illness
- Aging*
	- Spinal cord injury
	- Transfusion-related iron overload (β-thalassemia)

ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
- Aromatase deficiency - Kennedy diseases (spinal and bulbar muscular atrophy)and other extensions of CAG repeats - Partial or complete androgen insensitivity - 5α reductase type II (5αR) deficiency	
Acquired disorders	
Drug-induced	*Localised problems*

- Drug-induced AR blockage
  - Steroidal antiandrogen
  - Cyproterone acetate
  - Spironolactone
  - Non-steroidal antiandrogen
  - Flutamide
  - Bicalutamide
  - Nilutamide
- Drug-induced 5α reductase (5αR) activity blockade
  - Finasteride
  - Dutasteride
- Drug-induced ER blockade
  - Clomiphene
  - Tamoxifen
  - Raloxifene
- Drug-induced aromatase activity blockade
  - Letrozole
  - Anastrazole
  - Exemestane
- Increased Sex Hormone Binding Protein (SHBG)
	- Celiac disease

** Conditions acting and central and peripheral levels resulting in either primary and secondary hypogonadism*
[1] Different autosomal translocations can cause rare cases of hypogonadism and infertility

3.5 Late-onset hypogonadism

Testosterone production declines as a function of age. The EMAS study reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (fT) [8]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood, in particular. Evidence has documented that a number of associated diseases and chronic co-morbidities can interfere with the HPG axis leading to the development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, thus significantly influencing the physiological age-dependent decline of testosterone. By combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), a population-based, observational study including 1,709 men aged 40-70 years, Mohr *et al.* [57] showed that associated comorbidities and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations. Similarly, data derived from the EMAS study confirm these findings [8, 55]. Based upon these data and other evidence, the concept of *functional and organic hypogonadism* has been recently introduced [56]. The diagnosis of functional hypogonadism is based on the exclusion of a classical (organic) aetiology. The main causes of functional hypogonadism are obesity, co-morbidities and aging with the first two of these accounting for the majority of this definition. Inflammatory cytokines released in states of chronic inflammation, and adipocytokines and estradiol in obesity, can suppress the HPG axis. The role of aging up to the age of 80 years seems relatively small [56]. Considering that suppression of HPG axis activity is functional, and potentially reversible by empiric measures, such as weight loss, the need for testosterone therapy has been questioned [56].

*3.5.1 **Diagnostic evaluation***

The phenotype of the hypogonadal patient appears independent of the aetiology causing the problem, but is more often affected by the age of onset of hypogonadism. When androgen deficiency is complete and develops during the foetal life, symptoms can be dramatic, spanning from an almost complete female phenotype (complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various

defects in virilisation and ambiguous genitalia (micropenis, hypospadias, cryptorchidism) [5, 34]. Delay in puberty with an overall eunochoidal phenotype (scant body hair, high-pitched voice, small testis, penis and prostate) is typical of defects manifesting in the pre- or peri-pubertal period due to milder central (isolated HH) or peripheral defects (such as in Klinefelter syndrome) [5, 34]. When hypogonadism occurs in adulthood, especially in the case of functional hypogonadism, symptoms can be often relatively mild, difficult to recognise and frequently confused with the aging process [5, 34] or with the comorbid chronic conditions. Several non-specific clinical features such as fatigue, weakness, and decreased energy, as well as sexual impairment may be clinical manifestations. The EMAS study showed that a triad of sexual symptoms, including low libido, reduced spontaneous erections and ED, are typically associated with a decrease in testosterone serum levels [10]. Conversely, psychological and physical symptoms were less informative [10].

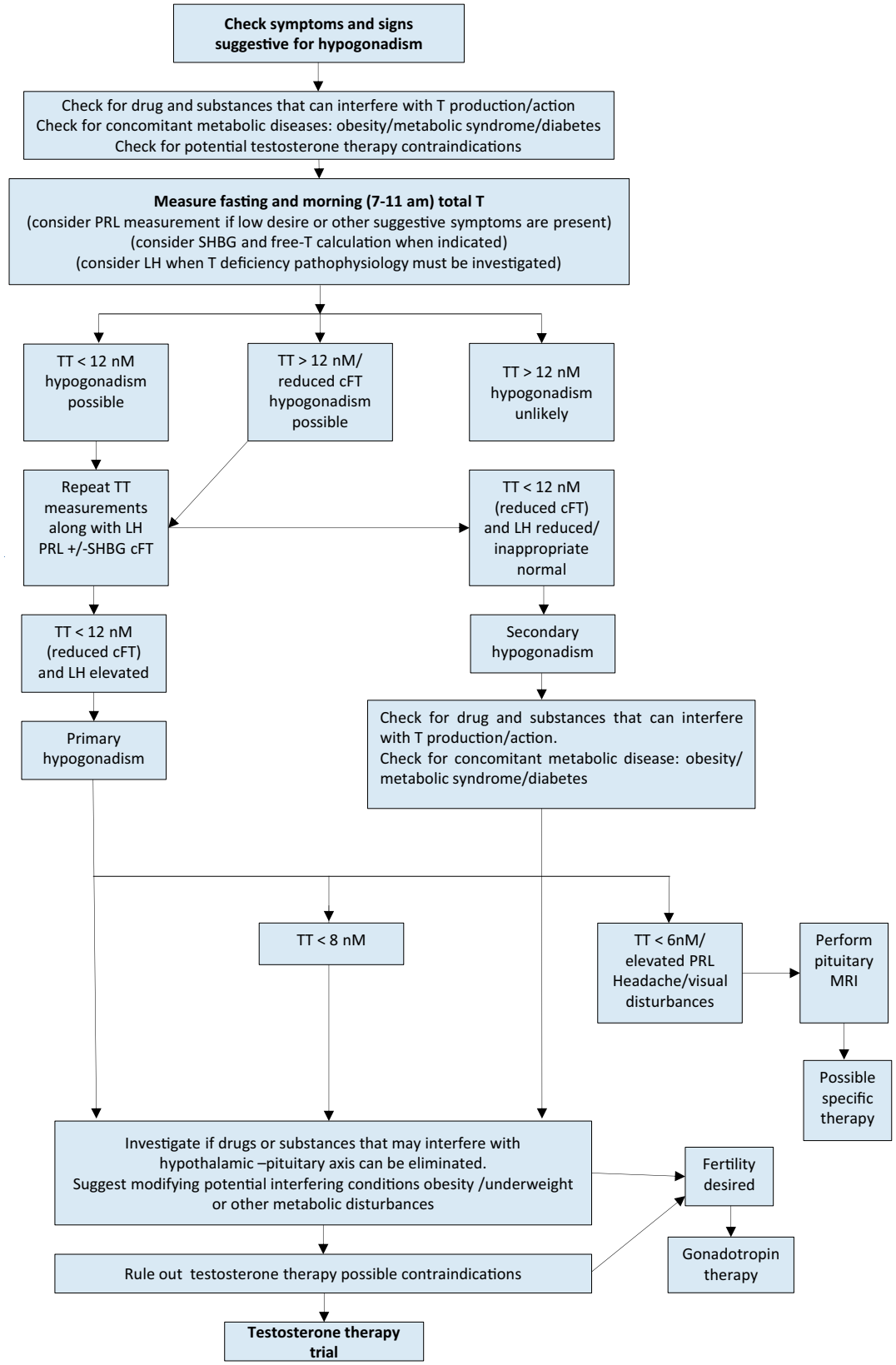
The mainstay of a LOH diagnosis includes the presence of signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay. Testosterone levels show a circadian variation, which persist in aging men [58, 59]. Likewise, testosterone levels are potentially influenced by food intake [60]; hence, serum total testosterone should be measured in fasting conditions and in the morning (between 7.00 and 11.00 hours). Moreover, a confirmatory measurement should always be undertaken in the case of a primary pathological value.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the standard and most accurate method for sex steroid evaluation; however, standardised automated platform immuno-assays for total testosterone assessment demonstrate a good correlation with LC-MS/MS [61]. Conversely, available immuno-assays are not able to provide an accurate estimation of fT; therefore, direct fT evaluation with these methods is not recommended and should be avoided [39]. Liquid chromatography-tandem mass spectrometry remains the standard method for fT determination. Alternatively, fT can be derived from specific mathematical calculations taking into account serum SHBG and albumin levels [62] (http://www.issam.ch/freetesto.htm).

Data derived from available meta-analyses have documented that testosterone therapy is ineffective when baseline levels are above 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are below 12 nmol/l, being higher in symptomatic patients with more severe forms of hypogonadism (T < 8 nmol/L). Hence, 12 nmol/L should be considered as a possible cut-off to start with testosterone therapy in the presence of hypogonadal symptoms [21, 63]. As reported above, in the presence of clinical conditions which may potentially interfere with SHBG levels, the evaluation of fT should be considered in order to better estimate of androgen levels (Figure 2). Unfortunately, despite its potential clinical value [64], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, some data indicate that fT levels below 225 pmol/L (< 6.5 ng/dl) are associated with hypogonadal symptoms [10, 49, 65, 66].

The determination of LH must be performed along with prolactin (PRL) when pathological total testosterone levels are detected, in order to correctly define the underlying conditions and exclude possible organic forms (Figure 2). Due to its negative influence on libido, PRL can be also be considered as first-line screening in patients with reduced sexual desire. In addition, pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluation, is required in the presence of specific symptoms such as visual disturbances, headache [67, 68] or when hyperprolactinaemia is confirmed. In addition, limited evidence suggests performing pituitary MRI also in the case of severe hypogonadism (< 6 nmol/L; 1.75 ng/mL) with inadequate gonadotropin levels (Figure 2) [67, 68].

Figure 2: Diagnostic evaluation of Late-Onset Hypogonadism



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = Magnetic resonance imaging.

History taking

Specific symptoms associated with LOH are shown in Table 3. Past history of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Likewise, chronic and systemic comorbid conditions must be comprehensively investigated in every patient. Possible use of drugs potentially interfering with the HPG axis should be ruled out (Table 2). Acute illnesses are associated with the development of functional hypogonadism and the determination of serum total testosterone levels should be avoided in these conditions. Several self-reported questionnaires or structural interviews have been developed for the screening of hypogonadism. Although these case-history tools have demonstrated clinical utility in supporting the biochemical diagnosis of hypogonadism, or in the assessment of testosterone therapy outcomes, their specificity remains relatively poor and they should not be used for a systematic screening of hypogonadal men [69].

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	**Physical symptoms**	**Psychological symptoms**
More specific	- Reduced libido - Erectile dysfunction - Decreased spontaneous/ morning erections	- Decreased vigorous activity - Difficulty walking >1 km - Decreased bending	- Low mood/mood deflection - Decreased motivation - Fatigue
Less specific	- Reduced frequency of sexual intercourse - Reduced frequency of masturbation - Delayed ejaculation	- Hot flushes - Decreased energy - Decreased physical strength/function/activity	- Concentration or mnemonic difficulties - Sleep disturbances

*3.5.2 **Physical examination***

Since obesity is frequently associated with hypogonadism (mostly functional), the determination of body mass index (BMI) and the measurement of waist circumference are strongly recommended in all individuals. Testicular and penile size, as well the presence of sexual secondary characteristics can provide useful information regarding overall androgen status. In addition, upper segment/lower segment ratio (n.v. > 0.92) and arm-span to height ratio (n.v. < 1.00) can be useful to identify a eunochoid body shape, especially in subjects with pre-pubertal hypogonadism or delayed puberty. Finally, digital rectal examination (DRE) should be performed in all subjects to exclude prostate abnormalities before testosterone therapy (any type) or to support the suspicion of hypogonadism [70].

*3.5.3 **Summary of evidence and recommendations for the diagnostic evaluation of LOH***

Summary of evidence
Sexual symptoms are the most specific symptoms associated with LOH.
The diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.
Functional hypogonadism is a consequence of comorbidities/concomitant drugs, which can impair testosterone production in adulthood. The diagnosis of functional hypogonadism is a diagnosis of exclusion, after ruling out organic causes of hypogonadism.

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (7.00 and 11.00 hours) and in the fasting state, with a reliable method.	Strong
Repeat total testosterone on at least two separate occasions when below 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut off for diagnosis of LOH.	Weak
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between primary hypogonadism and secondary hypogonadism forms.	Strong
Consider prolactin (PRL) measurement if low desire (or other suggestive signs/symptoms) and low or low-normal testosterone is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

*3.5.4 **Recommendations for screening men with LOH***

Recommendations	Strength rating
Screen for late onset hypogonadism (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

3.6 Treatment of LOH

*3.6.1 **Indications and contraindications for treatment of LOH***

Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy (Table 4).

Absolute contraindications are untreated breast and prostate cancer (PCa). Acute cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure and severe low urinary tract symptoms (International Prostate Symptom Score (IPSS) score > 19) represent other relative contraindications, as there is not sufficient information on the long-term effects of testosterone therapy in these patients [66]. In addition, a positive familial history for venous thromboembolism requires further analyses in order to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [71]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) level higher than 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation in order to avoid any potential cardio-vascular complications. Lower levels of baseline HTC (48-50%) should be carefully evaluated before testosterone therapy initiation, in order to avoid pathological increases during treatment, especially in high-risk men such as those with chronic obstructive pulmonary disease (COPD) or Obstructive Sleep Apnea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HTC > 48% represented a condition associated with an increased risk of coronary artery disease (CAD) and mortality and was associated with cardio-vascular disorders [72]. Finally, testosterone therapy suppresses gonadotropins and endogenous testosterone secretion as well as spermatogenesis. Hence, testosterone therapy is contraindicated in individuals who desire fertility [73]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with FSH and LH analogues, if fertility is desired [74].

Table 4: Main contraindications of testosterone therapy

Absolute contraindications	Locally advanced or metastatic prostate cancer (PCa) Male breast cancer Men with an active desire to have children Haematocrit ≥ 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score > 19 Baseline haematocrit 48-50% Familial history for venous thromboembolism

*3.6.2 **Testosterone therapy outcomes***

3.6.2.1 Sexual dysfunction

Sexual concerns are the main symptoms of the hypogonadal patient [5, 10, 75, 76]. A consistent body of evidence shows that testosterone therapy in hypogonadal men (total testosterone < 12 nmol/L) may have a beneficial effect on several aspects of sexual life; in contrast, there is no evidence of benefits in using testosterone for treating sexual dysfunction in eugonadal men [51, 63, 77, 78]. The beneficial effects on sexual function seems to be more related to testosterone level normalisation rather than the specific testosterone formulations used [78, 79].

A recent meta-analysis of only placebo controlled RCTs using the International Index of Erectile Function (IIEF) [80] as a possible tool for outcome evaluation, showed that testosterone therapy significantly improves erectile function (as measured by IIEF-Erectile Function domain score) and that patients with more severe hypogonadism (i.e., total testosterone < 8 nmol/L) are more likely to achieve a better improvement than patients with milder hypogonadism (i.e., total testosterone < 12 nmol/L). Similar results were observed for sexual desire; however, the presence of metabolic comorbidities (such as diabetes and obesity) decreased the magnitude of these improvements. In particular, testosterone therapy alone resulted in a clinically effective outcome only in patients with milder ED [63]. Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [63]. Men with comorbidities such as diabetes usually show modest improvements in terms of sexual function after testosterone therapy and may potentially require concomitant phosphodiesterase type 5 inhibitors (PDE5Is) to improve effectiveness [5, 78]. However, the specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is not completely clear [51]. Similarly, information related to the combined use of testosterone therapy with other ED pharmacotherapies is lacking [5, 78].

The Sexual Function Trial of the Testosterone Trials (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in ten of twelve measures of sexual activities in older (≥ 65 years old) hypogonadal men particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [81]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and E2 levels, it was not possible to demonstrate a threshold level [82]. Furthermore, a study of 220 men with MetS with or without T2DM also found that sexual function did improve in those men who reported sexual problems with improvement in IIEF scores with specific increases in libido and sexual satisfaction [24].

3.6.2.2 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage fat mass and a lesser lean mass compared to testosterone replete men [83]. The major effect of low testosterone is to increase visceral adiposity but also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. As detailed above, a number of published data has suggested that testosterone therapy reduces percentage body fat and increases lean mass [84]. Moreover, testosterone therapy also has been also found to decrease waist circumference, body weight and BMI, with these effects more predominant after twelve months of treatment [84-86]. However, it should be recognised that these results are mainly derived from registry and observational trials which have important limitations due to the risk of selection bias for the non-random assignment of testosterone exposure. Accordingly, data derived from RCTs showed only an improvement of fat mass and lean mass of the same amount without any modifications in body weight [21].

3.6.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [87, 88]. However, the specific relationship between hypogonadism and the incidence of

depression is still unclear [88]. Only a few placebo-controlled RCTs have investigated the role of testosterone therapy in improving depressive symptoms. Data derived from TTrials showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [81]. However, the final effect was small in magnitude. In line with this data, the largest meta-analysis of available studies, including 1,890 hypogonadal (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [89]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond in regard to symptoms of sexual dysfunction compared to men without depression [29].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [79, 90].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrials evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment in order to assess possible improvement of several aspects of cognitive function. However, the final results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [81].

3.6.2.4 Bone

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [91]. The possible association between mild hypogonadism and osteopenia/osteoporosis is weak, whereas severe hypogonadism (total testosterone < 3.5 nM) is frequently associated with bone loss and osteoporosis, independent of patient age [91]. Two independent meta-analyses showed a positive effect of testosterone therapy on bone mass density (BMD), with the highest effect at the lumber level [92, 93]. Similarly, data derived from TTrials confirmed that testosterone therapy increased BMD in hypogonadal aging men, particularly at the lumbar level [81]. However, available data is insufficient to determine the effect of testosterone therapy alone on the risk of bone fractures [91]. In addition, the use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures is not established. Therefore, anti-resorptive therapy alone must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-reabsorptive treatment with testosterone therapy should be offered only in conjunction with hypogonadal related symptoms.

3.6.2.5 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well-established. Accordingly, androgenic-anabolic steroids (AAS) have been using as performance-enhancing agents for increasing physical performance in several competitive sport [94]. To this aim, testosterone therapy in hypogonadal men has been showed to both increase muscle mass and to reduce fat mass, with limited effects on final weight [21]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. Findings from the National Health and Nutrition Examination Survey 1999-2004 [95] were unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low normal testosterone than those in the lowest tertile. Data from TTrials indicated that testosterone therapy did not substantially increase the fraction of men whose distance walked in six minutes increased > 50 m or the absolute increase in the distance walked by the 387 subjects enrolled in the physical function trial [81]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [81]. Similar data were derived from the Vitality Trial [81].

3.6.2.6 Summary of evidence and recommendations for testosterone therapy outcome

Summary of evidence
Testosterone therapy can improve milder forms of ED and libido in hypogonadal men.
Testosterone therapy can improve other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.
Testosterone therapy can similarly increase lean mass, and reduce fat mass, and improves insulin resistance.
Testosterone therapy may improve weight, waist circumference and lipid profile, but findings are not unique.
Testosterone therapy can improve milder depressive symptoms in hypogonadal men.
Testosterone therapy can improve bone mineral density, but information related to fracture risk is lacking.

Recommendations	Strength rating
The use of testosterone therapy T in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in symptomatic hypogonadal patients with milder ED.	Strong
Use the combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak
Use conventional medical therapies for treating severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy for improving cognition vitality and physical strength in aging men.	Strong

*3.6.3 **Choice of treatment***

3.6.3.1 Lifestyle factors

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [96]. Therefore, weight loss and lifestyle changes should be the first approach for all overweight and obese men with hypogonadism. A previous meta-analysis documented that a low calorie diet is able to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [97]. This was confirmed in a recent updated meta-analysis showing that the increase in testosterone was significantly associated with weight reduction [98]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [98]. However, it should be recognised that the increase in testosterone levels observed after a low calorie diet and physical activity is rather modest (1-2 nmol) [97, 98]. In addition, it should be recognised that from 60% to 86% of weight lost is regained after three years and 75% to 121% after five years [99]. A greater testosterone increase can be achieved through bariatric surgery, which results in an average increase of about 10 nmol/L depending on the degree of weight loss [98]. Lifestyle changes represent a relevant and essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, in obese men, testosterone therapy-treated men benefited most from symptomatic relief of their symptoms associated with testosterone deficiency whereas those not treated did not [74]. Accordingly limited evidence suggests that the combination of life-style interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [83]. In particular, a large placebo-controlled RCT aimed to determine whether testosterone treatment combined with lifestyle intervention or lifestyle intervention alone might reduce T2DM incidence and improve glucose tolerance at two years is ongoing [100]. The results of this RCT will better clarify this point.

3.6.3.2 Medical preparations

Several testosterone formulations are available (Table 5). Direct comparisons among different testosterone products are still lacking. Candidates for testosterone therapy should be adequately informed about the possible risks and benefits of all available testosterone preparations. The final choice should be based on the clinical situation, testosterone formulations availability and patient needs and expectations [101].

3.6.3.2.1 Oral formulations

The esterification of testosterone with a long-chain fatty acid (testosterone undecanoate; TU) enables testosterone to be absorbed by the intestine through the lymphatic system, by-passing liver metabolism. This formulation has been available in oleic acid since the 1970s, and it has been recently reformulated in a mixture of castor oil and propylene glycol laureate (TU caps), to allow the drug to be maintained at room temperature without any degradation of the product [102]. The main limitation is related to the poor bioavailability, which is strongly dependent on the dietary fat content [102]. Recently, the US Food and Drug Administration (FDA) approved a new formulation of oral TU incorporating a liquid-filled hard capsule drug delivery system and containing a higher amount (225 mg) of the compound, which improves oral availability (https://www.fda.gov/media/110187/download). In an open label study of approximately four months duration (NCT02722278), 145 (87%) of 166 hypogonadal men enrolled who received the TU caps formulation had mean total testosterone concentration within the normal eugonadal range at the end of treatment (https://www.fda.gov/media/110187/download). However, the TU caps compound is not available in Europe.

Mesterolone is a 5α-DHT derivate available for oral administration. Along with DHT, it cannot be converted to oestrogens and can be used for a limited period and specific indications, such as the presence of painful gynecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [102].

3.6.3.2.2 Parenteral formulations

Injectable testosterone preparations can be classified according to their half-lives (Table 5). Testosterone propionate is a short-term ester formulation requiring multiple fractionated doses (usually 50 mg, every two to three days), thus representing a major limitation for its use [102]. Cypionate and enanthate-T esters are short-term formulations, requiring administration every two to four weeks. A formulation containing mixed testosterone esters (TU, isocaproate, phenyl propionate, propionate - Sustanon®) which allows some benefit of a smoother release of testosterone into the circulation is available in some countries. The use of these older formulations is associated with wide fluctuations in plasma testosterone concentrations, often reported as unpleasant by patients and potentially resulting in side effects, such as polycythemia [102, 103]. A longer lasting TU injectable formulation is widely available [102]; this formulation has been demonstrated to have a very good safety/benefit profile allowing the maintenance of normal stable testosterone levels with a dosing regimen of 1,000 mg initially every twelve weeks, following a six-week loading dose, but can be adjusted to a frequency of ten to fourteen weeks dependent on the trough (pre-injection level) after three to five injections to maintain levels in the therapeutic range (usually >12nmo/L and less than 18nmol/L at that time point [102, 104].

3.6.3.2.3 Transdermal testosterone preparations

Among the available transdermal formulations, testosterone gels represent the most frequently used preparations. The gel is quickly absorbed by the stratum corneum, creating a reservoir within the subcutaneous tissues from where testosterone is continuously delivered for 24 hours, after a single daily application. These formulations have been shown to normalise serum testosterone levels with an excellent safety profile [102]. In addition, the introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential side effects. Adverse local skin side effects are limited when compared to testosterone patches, but they potentially allow transference of testosterone during close contact with the skin's surface. The risk can be reduced by wearing clothing or by applying the gel on skin surfaces not usually touched (e.g., the inner thigh surface) [102]. Moreover, in order to reduce the total amount of gel applied and residual quantities remaining on the skin, new formulations of testosterone gel have been introduced with a testosterone concentration of 1.62-2% [102]. Another transdermal testosterone formulation includes a topical, alcohol-based testosterone (2%) solution, which must be applied to the underarm once daily, using a metered dose applicator [102]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken between 2-4 hours after gel application to use the peak level of testosterone absorbed as a reference for adequate therapeutic levels. Levels of testosterone after application can vary and a repeat measurement may be indicated especially as sometimes inadvertently the skin over the site of the vene-puncture can be contaminated by the gel leading to falsely elevated results.

In some European countries, DHT is available as a hydroalcoholic 2.5% gel. It is rapidly absorbed, reaching a steady state in 2-3 days. Similar to what reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynecomastia and microphallus [102].

3.6.3.2.4 Transmucosal formulations

3.6.3.2.4.1 Transbuccal Testosterone preparations

A testosterone buccal system is still available in several countries. It consists on a sustained-release muco-adhesive buccal-testosterone-tablet requiring twice-daily application to the upper gums. The tablet does not dissolve completely in the mouth and must be removed after twelve hours. This formulation has been proven to restore testosterone levels within the physiological range with minimal or transient local problems, including gum edema, blistering and gingivitis [102].

3.6.3.2.4.2 Transnasal testosterone preparations

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires administration two or three times a day using a specific metered-dose pump. The application is rapid, non-invasive, convenient, and avoids secondary transference observed with other topical products [102].

3.6.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in the USA, UK and Australia, represents the longest available testosterone formulation lasting from four to seven months. However, the procedure is invasive and may be unattractive to patients [102].

3.6.3.2.6 Anti-oestrogens

Anti-oestrogens, including selective oestrogen receptor (ER) modulators (SERMs) and aromatase inhibitors (AI) have been suggested as "off-label" treatments to restore testosterone levels and fertility in men with functional secondary hypogonadism or idiopathic infertility. Essentially, they work by preventing down-regulation of the

HPG axis by oestrogens and, for this reason are particularly useful in men with obesity and metabolic disorders [98]. In the latter case, the hypothesis is that the excess of adipose tissue leads to increased aromatase activity and oestrogens levels resulting in impairment of HPG [96]. Due to their putative mechanism of action, they require an intact HPG axis and cannot work in primary hypogonadism or secondary hypogonadism due to organic damage of the HPG axis. Both SERMs, which bind ERs with an agonist or antagonist effect depending upon the target tissue, and AIs, which prevent androgens from being converted into oestrogens by aromatase, have been used in clinical practice [102]. The evidence published so far is poor; all these products are off-label treatments and SERMs, due to their agonistic effect on venous vessels, could predispose men to the development of venous thromboembolic disease [102]. In this context patients should be warned of the potential increased risk of venous thromboembolic disorders although data is lacking. Long-term use of these agents can lead to reduced bone density and the development of osteoporosis potentially increasing fracture risk.

3.6.3.2.7 Gonadotropins

Considering the aforementioned limitations regarding the use of anti-oestrogens, gonadotropin therapy should be considered the standard treatment in men with secondary hypogonadism who desire paternity (Table 5) [102]. The treatment is based on the use of human chorionic gonadotropin (hCG), purified from the urine of pregnant women. The most expensive recombinant hCG (rhCG) and LH (rhLH) formulations do not offer clinical advantages [102]. According to a meta-analysis of the available evidence, the use of hCG should be administered with FSH as the combined therapy results in better outcomes. Similar to hCG, the use of recombinant FSH (rFSH) does not seem not to offer any advantages compared to urinary-derived preparations [105]. More details on the use of gonadotropins is provided in section 9.

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	T 1/2	Standard dosage	Advantages	Disadvantages
GONADOTROPINS					
Human chorionic gonadotrophin (HCG)					
Extractive	HCG purified from the urine of pregnant women	NA	1,000 - 2,000 IU 3 times/ week	Low cost	Multiple weekly administration
Recombinant	Human recombinant HCG	NA	No data in men	NA	
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data in men	NA	
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from the urine of pregnant women	NA	75-150 IU 3 times/week	High cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week	High cost	Multiple weekly administration
TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate	17-α-hydroxylester	4 hours	120-240 mg 2-3 times daily	- Reduction of liver involvement - Oral convenience - Modifiable dosage	- Unpredictable absorption depending of meal fat content - Has to be taken with meals
Mesterolone	1α-methyl-4, 5α-dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynecomastia	- Not aromatisable

Parental					
Testosterone enanthate	17-α-hydroxylester	4-5 days	250 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionathe	17-α-hydroxylester	8 days	200 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone propionate	17-α-hydroxylester	20 hours	100 mg every 2 days	- Low cost - Very short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone ester mixture Propionate (30mg) Phenylpropionate (60 mg) Isocaproate (60 mg) Decanoate (100 mg)	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone undecanoate in castor oil	17-α-hydroxylester	34 days	1000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at injection site - Long-acting preparation not allowing rapid drug withdrawal in case of side-effects
Surgical implants	Native testosterone	--	4-6 200 mg implants lasting up to 6 months	- Long duration and constant serum testosterone level	- Placement is invasive - Risk of extrusion and site infections
TRANSDERMAL					
Testosterone patches	Native testosterone	10 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Skin irritation - Daily administration
Testosterone gel 1-2%	Native testosterone	6 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/ day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynecomastia	- Possible transfer during intimate contact - Daily administration - Not aromatisable

TRANSMUCOSAL					
Testosterone buccal system	Native testosterone	12 hours	60 mg 3 times daily	Steady-state testosterone level without fluctuation	- Possible oral irritation - Twice-daily dosing - Unpleasant taste
Testosterone nasal	Native testosterone	6 hours	33 mg 3 times daily	Steady-state testosterone level without fluctuation	- Nasal irritation - Multiple daily administration

NA = not applicable.

3.6.3.3 Summary of evidence and recommendations for LOH choice of treatment

Summary of evidence
Weight loss obtained through a low calorie diet and physical activity result in a small improvement in testosterone levels.
Testosterone gels and long-acting injectable TU represent testosterone preparations with the best safety profile.
Gonadotropin treatment can be used to restore fertility in men with secondary hypogonadism.

NA = not applicable.

Recommendations	**Strength rating**
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinaemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs which can impair testosterone production; treat comorbidities before starting testosterone therapy.	Weak
Fully inform the patient about expected benefits and side effects of any treatment option. Select the testosterone preparation in a joint decision process, only with a fully informed patient.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse side effects.	Weak

3.7 Safety and follow up in hypogonadism management

*3.7.1 **Hypogonadism and fertility issues***

The aim of the pharmacological management of hypogonadism is to increase testosterone levels. The first choice is to administer exogenous testosterone. However, while exogenous testosterone provides benefits to the clinical symptoms of hypogonadism, it also inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [106]. Therefore testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [73]. When secondary hypogonadism is present, gonadotropin therapy can maintain normal testosterone levels and restore sperm production [5].

*3.7.2 **Male breast cancer***

In vitro and *in vivo* studies have clearly documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to E2 through different mechanisms and pathways [107]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [107]. No information is available on the role of testosterone therapy in patients successfully-treated for male breast cancer; therefore, treated and active male breast cancer should be recognised as absolute contraindications for testosterone therapy.

3.7.3 Lower urinary tract symptoms/benign prostatic hyperplasia

Based on the assumption that prostate growth is dependent on the presence of androgens, historically testosterone therapy has raised some concerns regarding the possibility of aggravating lower urinary tract symptoms (LUTS) in patients affected by benign prostatic hyperplasia (BPH) [70, 108]. However, pre-clinical and clinical data has indicated that low rather than higher androgen levels may decrease bladder capacity, alter tissue histology and decrease the ratio of smooth muscle to connective tissue, impairing urinary dynamics [70, 108].

A trial of 60 patients undergoing testosterone therapy for six months showed no significant differences in post-voidal residual urine and prostate volume, while storage symptoms as measured by the IPSS significantly improved, despite an increase in PSA level. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS [109]. A long-term study of 428 men undergoing testosterone therapy for eight years demonstrated significant improvements in IPSS score, no changes in Q_{max} and residual urine volume, but also a significant increase in prostate volume [110]. Similarly data from the Registry of Hypogonadism in Men (RHYME), including 999 subjects with a follow-up of three years, did not document any difference in prostate-specific antigen (PSA) levels, total IPSS score in men undergoing testosterone therapy, compared to those untreated [111]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from fifteen centres [112]. Accordingly, available meta-analyses did not find significant changes in LUTS compared to placebo [113-119]. On the basis of the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS; instead there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS score >19), as these patients are usually excluded from RCTs, therefore limiting the long-term safety data of testosterone therapy in these subjects [70].

*3.7.4 **Prostate cancer (PCa)***

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [120]. On the other hand, analytical studies aimed at investigating the relationship between low levels of testosterone and the risk of PCa have found that men with very low levels of fT have a reduced risk of developing low-to-intermediate grade PCa, but have a non-significantly increased chance of developing high grade disease [120]. This peculiar pattern was also reported in previous trials such as the Health Professionals Follow-up Study, the PCPT and by the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [121].

The most recent meta-analysis, including 27 placebo-controlled, RCTs found no evidence of increased PSA levels following testosterone therapy for one year. When considering eleven studies reporting on the occurrence of PCa, the meta-analysis found no evidence of an increased risk of PCa. However, a one-year follow-up may be considered too short a time to draw conclusions on PCa occurrence. Furthermore, the analysis was also restricted to studies with longer than one-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [114]. Furthermore, at five-year median follow-up in three independent registry studies with more than 1,000 patients undergoing testosterone therapy, PCa occurrence remained at all times well below the reported incidence rate in the general population [122]. Similar results were reported by a more recent large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [123]. In addition, the same study, also showed that the risk of PCa was decreased for those subjects in the highest tertile of testosterone therapy cumulative dose exposure compared with controls [123].

With regards to PCa survivors, safety in terms of the risk of recurrence and progression has not yet been established. Limited data are available in the literature, with most case series not providing sufficient data to draw definitive conclusions (e.g. insufficient follow-up length, small sample sizes, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [124]. More recently, a meta-analysis derived from thirteen studies including 608 patients, of which 109 had a history of high-risk PCa, with a follow-up ranging from one to 189.3 months [125] suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is very poor, limiting data interpretation [125]. Similar considerations can be derived from another meta-analysis including a larger number of studies (n=21) [126]. It is important to recognise that the vast majority of studies analysed, included low-risk patients with Gleason score < 8 [125].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. On the other hand, while it is obviously necessary to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of androgen administration in PCa survivors [126], without disease recurrence should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. Specifically, patients should be fully counselled that the long-term effects of testosterone therapy in this setting are still unknown and requires further investigation. If the presence of an occult PCa is not detected before initiation of testosterone therapy, treatment may unmask the cancer detected by an early rise in PSA over six to nine months of therapy. Due to the lack of strong evidence-based data on safety, the possible use of testosterone therapy in symptomatic hypogonadal men previously treated for PCa should be adequately discussed with the patients and limited to low-risk subjects.

*3.7.5 **Cardiovascular Disease***

Evidence suggests that hypogonadal men have an increased risk of CVD [127, 128]. Whether or not LOH is a cause or consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism

is associated with CV risk factors which include central obesity, insulin resistance and hyperglycaemia, dyslipidaemia (elevated total cholesterol, LDL-cholesterol, triglycerides and low HDL-cholesterol), pro-thrombotic tendency and a chronic inflammatory state [129]. Atherosclerosis itself is a chronic inflammatory disease, which releases pro-inflammatory cytokines into the circulation which are known to suppress testosterone release from the HPG axis. Evidence from RCTs using testosterone therapy in men with MetS and/or T2DM have demonstrated some benefit in CV risk including a reduction in central adiposity, insulin resistance, total and LDL-cholesterol and suppression of circulating cytokines [14, 23-25, 29, 129]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for indications outside the specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [12, 130-133]. These studies are supported by a meta-analysis which concluded that hypogonadism is a risk factor for cardiovascular mortality [134] and morbidity [118]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [128]. Longitudinal population studies have reported that men with testosterone in the upper quartile of the normal range have a reduced number of CV events compared to the combined data from the lower three quartiles [130]. Androgen deprivation therapy for PCa is linked to an increased risk of CV events and sudden death [135]. Conversely, two long-term epidemiological studies reported reduced cardiovascular events in men with high normal serum testosterone levels [136, 137]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation of a male with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt an individual assessment of their CV risk profile. Individual risk factors (e.g. lifestyle, diet, exercise, smoking, hypertension, diabetes, dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients treated with androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but they should be appropriately counseled by clinicians active in prescribing testosterone therapy [75]. If appropriate, they could be referred to cardiologist for risk stratification and treatment of co-existent comorbidities.

There are no RCTs that provide a clear answer, on whether testosterone therapy affects cardiovascular outcomes. The Ttrial (n=790) a study in older men [138], the TIMES2 (n=220) [24] and the BLAST studies in men with MetS and T2DM and the pre-frail and frail study in elderly men - all of one-year duration - did not reveal any increase in Major Adverse Cardiovascular Events (MACE) [24, 27, 138, 139]. In this context, MACE is defined as the composite of cardiovascular death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. Randomised controlled trials between three and twelve months in men with known heart disease treated with testosterone have not found an increase in MACE events but did report improvement in cardiac ischaemia, angina and functional exercise capacity [140-142]. The European Medicines Agency (EMA) has stated 'The Co-ordination Group for Mutual recognition and Decentralisation Procedures-Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.' [143].

As a whole, as for MACE, current available data from interventional studies suggest that there is no increased risk with testosterone therapy with up to three-years of therapy [144-147]. The weight of the currently available published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients where the testosterone levels have been normalised. However, these findings could be considered sufficiently reliable for a three-year course of testosterone therapy, after which no available study may exclude further or long-term CV events [148, 149].

3.7.5.1 Cardiac Failure

Testosterone treatment is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to an exacerbation of the condition. Some studies including one of twelve month's duration have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [141, 150, 151]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed up carefully with clinical assessment and both testosterone and haematocrit measurements on a regular basis. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [152].

3.7.6 ***Erythrocytosis***

An elevated haematocrit is the most common side effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action, which enhances the delivery of oxygen to testosterone sensitive tissues (e.g. striated, smooth and cardiac muscle). Any elevation above the normal range for haematocrit usually becomes evident between three and twelve months after testosterone therapy initiation. However, polycythaemia can also occur after any subsequent increase in testosterone dose, switching mode of formulation from topical to parenteral administration and if there is the development of a comorbidity, which can be linked to an increase in haematocrit (e.g. respiratory or haematological diseases).

There is no evidence that an increase of haematocrit up to and including 54% causes any adverse effects on health. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [72, 153-155]. Any relationship is complex as these studies were based on subjects with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies including men with only testosterone-induced erythrocytosis.

Three large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [156, 157]. However, one study showed that an increased risk was observed peaking at six months after initiation of testosterone therapy, then declining over the subsequent period [158]. No study reported whether or not there was monitoring of the haematocrit, testosterone and/or E2 levels. High endogenous testosterone or E2 levels have not been associated with a greater risk of venous thromboembolism [159]. In one study venous thromboembolism was reported in 42 cases and 40 of these had a diagnosis of an underlying disorder of thrombophilia (including Factor V Leiden deficiency, prothrombin mutations, homocysteinuria) [160]. In an RCT of testosterone therapy in men with chronic stable angina there was no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [161]. A meta-analysis of RCTs of testosterone therapy reported that cases of venous thromboembolism were frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [71].

With testosterone therapy an elevated haematocrit is more likely to occur if the baseline level is toward the upper limit of normal prior to initiation of therapy. Added risks for a raised haematocrit on testosterone therapy include factors, such as smoking or respiratory conditions at baseline. Higher haematocrit values are more common on parenteral rather than topical formulations. In men with pre-existing CVD extra caution is advised with a definitive diagnosis of hypogonadism before initiating testosterone therapy and monitoring of testosterone as well as the haematocrit over treatment.

An elevated haematocrit in the absence of any co-morbidities or acute cardiovascular or venous thromboembolism can be managed by a reduction in testosterone dose, change in formulation or if the elevated haematocrit is very high by venesection (500 mL) and repeated if necessary, with usually no need to stop the testosterone therapy.

3.7.7 ***Obstructive Sleep Apnoea***

There is also no evidence that testosterone therapy can result in the onset or worsening of sleep apnoea. It has been demonstrated that combined therapy with Continuous Positive Airway Pressure (CPAP) with the addition of testosterone gel was more effective than CPAP alone in the treatment of obstructive sleep apnoea [162]. In one RCT, testosterone therapy in men with severe sleep apnoea reported a reduction in oxygen saturation index and nocturnal hypoxaemia after seven weeks of therapy compared to placebo, but this change was not evident after eighteen weeks' treatment and there was no association with baseline testosterone levels [163].

3.7.8 ***Follow up***

Testosterone replacement therapy in hypogonadal men has proven to be effective in alleviating symptoms and signs in a specific time-dependent manner. The TTrials clearly showed that testosterone therapy may result in improvement of sexual symptoms as early as three months after testosterone therapy initiation [81]. Similar results have been derived from available meta-analyses [51, 71]. Hence, the first evaluation should be planned after three months of treatment. Further evaluation may be scheduled at six months or twelve months, according to patient characteristics, as well as results of biochemical testing (see below). Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

Trials were designed to maintain the serum testosterone concentration within the normal range for young men (280-873 ng/dL or 9.6-30 nmol/L [81]. This approach resulted in a good benefit/risk ratio. Accordingly, a similar approach could be considered during follow-up. The correct timing for testosterone levels evaluation can vary according to the type of testosterone preparation used (Table 5). Testosterone is involved in the regulation of

erythropoiesis [103] and prostate growth [70], hence evaluation of PSA and haematocrit should be mandatory before and during testosterone therapy. However, it is important to recognise that the risk of PCa in men aged < 40 years in very low. Similarly, the risk of dying for PCa in men older than 70 years has not been considered high enough to warrant monitoring in the general population [164]. Hence, the screening for PCa through the determination of PSA and DRE in men younger than 40 older than 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annually glyco-metabolic profile evaluation may be a reasonable consideration, particularly in the management of functional hypogonadism. Moreover, since testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [91], dual energy X-ray absorptiometry (DEXA) bone scan may be also considered at baseline and 18-24 months following testosterone therapy, particularly in those subjects with more severe hypogonadism [91].

Digital rectal examination may detect prostate abnormalities, which can be present even in men with normal PSA values. Hence DRE is mandatory in all men at baseline and during testosterone therapy justify. The decision to stop testosterone therapy or to perform prostate biopsy due to PSA increase or prostate abnormalities should be based on local PCa guidelines. There is a large consensus that any increase of haematocrit > 54% over testosterone therapy requires testosterone therapy withdrawal and phlebotomy in order to avoid potential side effects including venous-thromboembolism and CV events especially in high-risk subjects. In patients with lower risk the situation can be alternatively managed by reducing testosterone dose and by switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled in regard to testosterone therapy in order to avoid/ prevent a condition of thrombophilia-hypofibrinolysis [71]. Finally, caution should be used in men with pre-existing CVD or at higher risk of CVD

Table 6: The clinical and biochemical parameters to be checked during testosterone therapy

Parameters	**1st year of treatment**	**After the first year of treatment**			
	Baseline	**3 months**	**6/12 months**	**Annually**	**18-24 months**
Clinical					
Symptoms	X	X	X	X	
Body Mass Index					
Waist circumference	X	X	X	X	
Digital rectal examination	X	X	X	X	
Blood pressure	X	X	X	X	
Biochemistry					
PSA (ng/ml)	X	X	X	X	
Haematocrit (%)	X	X	X	X	
Testosterone	X	X	X	X	
Lipid and glycemic profile	X		X	X	
Instrumental					
DEXA	X				X

*3.7.9 **Summary of evidence and recommendations on risk factors in testosterone treatment***

Summary of evidence
Testosterone therapy is contraindicated in men with secondary hypogonadism who desire fertility.
Testosterone therapy is contraindicated in men with active prostate or breast cancer.
Testosterone therapy does not increase the risk of prostate cancer, but long-term prospective follow-up data is required to validate this statement.
The effect of testosterone therapy in men with severe lower urinary tract symptoms is limited, as these patients are usually excluded from RCTs.
There is no substantive evidence that testosterone therapy, when replaced to normal levels results in the development of major adverse cardiovascular events.
There is no evidence of a relationship between testosterone therapy and mild, moderate or CPAP- treated severe sleep apnoea.

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., Gleason score < 8; pathological stage T1-2; pre-operative PSA < 10 ng/mL) and should start after at least one year follow-up with a PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before commencing testosterone therapy.	Strong
Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit more than 54% should require testosterone therapy withdrawal and phlebotomy. Reintroduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

4. EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH

4.1 Erectile dysfunction

Epidemiological data have shown a high prevalence and incidence of ED worldwide [165]. Among others, the Massachusetts Male Aging Study (MMAS) [166] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [167]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [168] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [169]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [170]. Differences between these studies can be explained by differences in methodology, in the ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 7.

4.2 Premature ejaculation

As evidenced by the highly discrepant prevalence rates reported in Table 8 [171], the method of recruitment for study participation, method of data collection and operational criteria can all greatly affect reported prevalence rates of premature ejaculation (PE). The major problem in assessing the prevalence of PE is the lack of a universally recognised definition at the time the surveys were conducted [172]. Vague definitions without specific operational criteria, different manners of sampling, and non-standardised data acquisition have led to tremendous heterogeneity in estimated prevalence [172-176]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS) study, which determines adult sexual behavior in the United States [177]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20-30% based on the relatively low number of men who present seeking medical help for PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [178]. Two separate observational, cross-sectional surveys from different continents found the overall prevalence of the complaint of PE to be

19.8 and 25.80%, respectively [179, 180]. Further stratifying these complaints into the classifications defined by Waldinger *et al.* [181], lifelong PE was seen at rates of 2.3 and 3.18%, while the rates of acquired PE were 3.9 and 4.48%, variable PE were 8.5 and 11.38% and subjective PE were 5.1 and 6.4% [179, 180]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. Treatment seeking behaviour may contribute to errors in the previously reported rates of PE, as it is possible that men with lifelong PE come to terms with their problem and not seek treatment. The additional psychological burden of a new change in ejaculatory latency in acquired PE on the other hand may prompt more frequent treatment seeking behaviours [182]. Thus, it is likely that a disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE exists [183, 184]. This disparity could be a further barrier to understanding the true incidence of each sub-type of PE. An approximately 5% prevalence of acquired PE and lifelong PE in general populations is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of less than two minutes [185].

4.3 Other ejaculatory disorders

4.3.1 ***Delayed ejaculation***

Due to its rarity and uncertain definitions, the epidemiology of delayed ejaculation (DE) is not clear [186]. However, several well-designed epidemiologic studies revealed that its prevalence is around 3% among sexually active men [177, 187]. According to data from the NHSLS, 7.78% of a national probability sample of 1,246 men between the ages of 18 and 59 years reported "inability achieving climax or ejaculation" [177]. In a similar study where a stratified national probability sample survey completed over six months among 11,161 men and women aged 16-44 years in Britain, 0.7% of men reported the inability to reach orgasm. In an international survey of sexual problems among 13,618 men aged 40-80 years from 29 countries, 1.1 to 2.8% of men reported that they frequently experience the inability to reach orgasm [188]. Another study conducted in the United States, where a national probability sample of 1,455 men aged 57 to 85 years was recruited, 20% of men reported the inability to climax and 73% of them reported that they were bothered by this problem. [189]. Considering the findings of these epidemiologic studies and their clinical experiences, some urologists and sex therapists postulated that the prevalence of DE may be higher among older men [190-192]. Similar to the general population, the prevalence of men with the complaint of DE is also small among patients who seek treatment for their sexual problems. An Indian study that evaluated the data on 1,000 consecutive patients with sexual disorders who attended a psychosexual clinic demonstrated that the prevalence of DE was 0.6% and it was observed more frequently in elderly diabetics [193]. Nazareth *et al.* [194] evaluated the prevalence of International Classification of Diseases 10th edition (ICD-10) diagnosed sexual dysfunctions among 447 men attending 13 general practices in London, and the authors found that 2.5% of the men reported inhibited orgasm during intercourse.

4.3.2 ***Anejaculation and Anorgasmia***

Establishing the exact prevalence of anejaculation and anorgasmia is very difficult since many men cannot distinguish between ejaculation and orgasm. The rarity of these clinical conditions further hampers the attempts to conduct epidemiological studies. In a report from the USA, 8% of men reported unsuccessfully achieving orgasm during the past year [177].

According to Kinsey *et al.* [195], 0.14% of the general population have anejaculation. The most common causes of anejaculation were reported as spinal cord injury, diabetes mellitus and multiple sclerosis. Especially in most cases of spinal cord injury, medical assistance is the only way to ejaculate. While masturbation leads to the lowest rates of ejaculation, higher response rates can be obtained with penile vibratory stimulation or acetylcholine esterase inhibitors followed by masturbation in patients with spinal cord injury [196].

4.3.3 ***Retrograde ejaculation***

Similar to anejaculation, it is very difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3% to 2% of patients attending fertility clinics [197], diabetes may increase these rates by leading autonomic neuropathy. Autonomic neuropathy results in ED and ejaculatory dysfunctions ranging from DE to RE and anejaculation, depending on the degree of sympathetic autonomic neuropathy involved [198]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [199]. In a more recent controlled trial, RE was observed in 34.6% of diabetic men [200]. Retrograde ejaculation was also reported in studies of patients who had undergone transurethral resection of prostate (TURP) or open prostatectomy due to disrupted bladder neck integrity. In a study that investigated the effect of prostatectomy on QoL it was found that of 5,276 men after TURP, 68% reported postsurgical RE [201]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [202, 203].

*4.3.4 **Painful ejaculation***

Painful ejaculation is a common, but poorly understood clinical phenomenon, which is associated with sexual dysfunction. Several studies demonstrated its prevalence to range between 1 and 10% in the general population [204-206]; however, it may increase to 30-75% among men who suffer from chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS) [207-211]. It should be noted that the design of the majority of these papers is not scientifically sound and the condition is probably under-reported due to the lack of an evidence-based definition and well-defined prognostic criteria.

*4.3.5 **Haemospermia***

The exact incidence and prevalence of haemospermia are difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptom represents approximately 1-1.5 % of all urological referrals and occurs in all age groups with a mean age of 37 years [212, 213]. In a PCa screening study of 26,126 men, ~ 50 years or older than 40 with a history of PCa or of black ethnicity, haemospermia was found in 0.5% on entry to the trial [214].

4.4 Low sexual desire

The global prevalence of low sexual desire in men ranged from 3-28% [188, 215, 216]. Overall, low solitary versus low dyadic sexual desire, have been reported in 68% and 14% of men, respectively [217]. Also, low sexual desire has been observed as a common complaint in gay men, with its prevalence ranging from 19% to 57% [218, 219]. Despite its relationship with age, low sexual desire has been reported even among young men (i.e., 18-29 years old), with prevalence rates ranging from 6% to 19% [177, 220, 221].

Table 7: The prevalence rates of erectile dysfunction [165]

Date	Authors	Population	Response rate	Age (years)	Measurement technique	Principal findings	Correlates
1993	Solstad *et al.* [222, 223]	439 men; random population sample (Denmark)	81%	51	Interview and self-administered questionnaire	Overall, 4% of men had ED as assessed by questionnaire Interviews identified a higher frequency of sexual dysfunction	Not reported
1994	Feldman *et al.* [166] **MMAS*	1,290 men; random population sample (United States)	40%	40-70	Self-administered questionnaire	Overall, 52% of men had ED 17.2% of men had minimal ED 25.2% of men had moderate ED 9.6% of men had complete ED	Age
1995	Panser *et al.* [224]	2,155 men; random population sample (United States)	55%	40-79	Self-administered questionnaire	1% ED in men aged 40-49 years 6% ED in men aged 50-59 years 22% ED in men aged 60-69 years 44% ED in men aged 70-79 years	
1996	Helgason *et al.* [225]	319 men; random population sample (Sweden)	73%	50-80	Self-administered questionnaire	3% ED in men aged 50-59 years 24% ED in men aged 60-69 years 49% ED in men aged 70-80 years	Age, Prostate cancer, Diabetes, Myocardial infarction, Diuretic use, Warfarin use, H2 receptor blocker use

1996	MacFarlane *et al.* [226]	1,734 men; random population sample (France)	86%	50-80	Self-administered questionnaire	20% ED in men aged 50-59 years 33% ED in men aged 60-69 years 38% ED in men aged 70-80 years	Age
1996	Fugl-Meyer [215]	1,288 men; random population sample men (Sweden)	52%	18-74	Structured interview	Overall, 5% of men had ED 3% ED in men aged 18-24 years 2% ED in men aged 25-34 years 2% ED in men aged 35-49 years 7% ED in men aged 50-65 years 24% ED in men aged 66-74 years	Age
1999	Laumann *et al.* [177] **NHSLS*	1,244 men; random population sample (United States)	70%	18-59	Structured interview	Overall, 10% of men had ED (moderate plus severe) 7% ED in men aged 18-29 years 9% ED in men aged 30-39 years 11% ED in men aged 40-49 years 18% ED in men aged 50-59 years	Age, Race, Emotional stress, Urinary symptoms, Poor health, Low income
1999	Pinnock *et al.* [227]	427 men; random population sample (Australia)	69.8%	> 40	Self-administered questionnaire	6% ED in men aged 40-49 years 12% ED in men aged 50-59 years 41% ED in men aged 60-69 years 63% ED in men aged 70-79 years 81% ED in men aged 80+ years	Age, Hyper-cholesterolemia,
2000	Braun *et al.* [167] (COLOGNE Study)	8,000 men	56%	30-80	The self-administered questionnaire by mail (Cologne ED Questionnaire)	The prevalence of ED was 19.2%	Age, Hypertension, Diabetes, Pelvic surgery, LUTS
2001	Moreira *et al.* [228]	1,170 men; attending public places (heavy bias toward younger men) (Brazil)	91%	>18	Self-administered questionnaire	Overall, 14.7% of men had ED (moderate plus severe); 9.4% ED in men aged 18-39 years 15.5% ED in men aged 40-49 years 22.1% ED in men aged 50-59 years 37% ED in men aged 60-69 years 39.6% ED in men aged >70 years	Age, Education, Racial origin, Diabetes, Hypertension, Depression

2001	Meuleman *et al.* [229]	1,233 men; random population sample (the Netherlands)	70%	40-79	Self-administered questionnaire	Overall, 13% of men had ED 6% ED in men aged 40-49 years 9% ED in men aged 50-59 years 22% ED in men aged 60-69 years 38% ED in men aged 70-79 years	Age
2001	Blanker *et al.* [205, 230]	1,688 men; random population sample (the Netherlands)	50%	50-75	Self-administered questionnaire	3% ED in men aged 50-54 years 5% ED in men aged 55-59 years 11% ED in men aged 60-64 years 19% ED in men aged 65-69 years 26% ED in men aged 70-78 years	Age, Smoking, Obesity, LUTS, COPD, Treatment for CV disease
2001	Martin-Morales *et al.* [231]	2,476 men; random population sample (Spain)	75%	25-70	Self-administered questionnaire and single question	Overall, 12.1% of men had ED (single question) and 18.9% for questionnaire According to single question: 3.9% ED in men aged 25-39 years 6.3% ED in men aged 40-49 years 15.9% ED in men aged 50-59 years 32.2% ED in men aged 60-70 years IIEF identified more mild ED, and single question identified more moderate and severe ED	Age, Hypertension, Diabetes, Cardiac disease, Pulmonary disease, Circulatory disease, Rheumatic disease, High cholesterol, Prostatic disease, Allergy, Medication "for nerves", Sleeping tablets, Heavy smoking, Alcohol abuse
2002	Moreira *et al.* [232]	602 men; random population sample (Brazil)	92%	40-70	Interview	Overall, 14.4% of men had ED (moderate or severe) 9.9% ED in men aged 40-49 years 11.8% ED in men aged 50-59 years 31.7% ED in men aged 60-69 years	Age, Marital status, Diabetes, Depression, IPSS, Decreased physical activity

2002	Moreira *et al.* [233]	342 men; random population sample (Brazil)	47.6%	40-70	Self-administered questionnaire	Overall, 12.0% of men had ED (moderate or severe) 3.5% ED in men aged 40-49 years 16.7% ED in men aged 50-59 years 39.6% ED in men aged 60-69 years	Age, Diabetes, Hypertension, Heavy smoking
2002	Morillo *et al.* [234]	1,963 men; random population sample (Columbia, Venezuela and Ecuador)	82%	> 40	Standardised questionnaire	Overall, 19.8% of men had ED (moderate or severe)	Age, Diabetes, Hypertension, BPH
2003	Richters *et al.* [235]	8,517 men; random population sample (Australia)	69.4%	16-59		Overall, 9.5% of men had ED 4.3% ED in men aged 16-19 years 4.5% ED in men aged 20-29 years 5.1% ED in men aged 30-39 years 12.5% ED in men aged 40-49 years 19.2% ED in men aged 50-59 years	Age
2003	Rosen *et al.* [236]	12,815 men; random population sample (multinational: United States, United Kingdom, France, Germany, the Netherlands, Italy, Spain)	36.8%	50-80	Self-administered questionnaire (IIEF and DAN-PSS)	According to DAN-PSS: Overall, 48.9% of men had ED 30.8% ED in men aged 50-59 years 55.1% ED in men aged 60-69 years 76% ED in men aged 70-80 years	Age, LUTS, Diabetes, Hypertension, Cardiac disease, Hyperlipidemia, Tobacco use
2004	Rosen *et al.* [237] **MALES*	27,839 men random population sample (multinational: United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil)	US: 45%; UK: 48%; Germany: 45%; France: 48%; Italy: 53%; Spain: 50%; Mexico: 55% and Brazil: 51%.	20-75	Random digit dialing and interviewed via computer-assisted telephone interviewing. A standardised questionnaire	The overall prevalence of ED in the MALES sample was 16%	Age, High blood pressure, Heart trouble or angina, High cholesterol, Diabetes, Depression or anxiety

2004	Shiri *et al.* [238]	2,198 men; stratified birth cohort (Finland)	70%	50,60, and 70 at first survey 55, 65, and 75 at second survey	Self-administered questionnaire at two separate time points, 5 years apart	48% of men had minimal ED 15.2% of men had moderate ED 13.2% of men had complete ED	Age, Diabetes, Hypertension, Heart disease, Cerebrovascular disease, Smoking
2005	Laumann *et al.* [188] **GSSAB*	13,750 men; random population sample (world)	19%	40-80	Telephone survey (random dialed digit)	Overall: In Northern Europe, 13.3% had ED In Southern Europe, 12.9% had ED In non-European West, 20.6% had ED In Central/South America, 13.7% had ED In Middle East, 14.1% had ED In East Asia, 13.3% had ED In Southeast Asia, 28.1% had ED	Age
2005	Moreira *et al.* [239]	750 men; random population sample (Spain)	23%	40-80	Telephone survey (random digit dialing)	Overall, 12.7% had ED	Age
2005	Moreira *et al.* [240]	750 men; random population sample (Germany)	17.4%	40-80	Telephone survey (random digit dialing)	Overall, 7.9% had ED	Age
2005	Moreira Junior *et al.* [241]	471 men; random population sample (Brazil)	18%	40-80	Telephone survey (random digit dialing)	Overall, 13.1% of men had ED	Age, Depression
2006	Brock *et al.* [242]	500 men; random population sample (Canada)	9.7%	40-80	Telephone survey (random digit dialing)	Overall, 16% of men had ED	Age, Depression, Diabetes
2007	De Almeida Claro *et al.* [243]	2,000 men; random population study (Brazil)	Not reported	>20	Standardised interview with self-reported questionnaire (IIEF)	Overall, 1.7% of men had ED 0.2% ED in men aged 20-30 years 0.22% ED in men aged 31-40 years 1.0% ED in men aged 41-50 years 2.8% ED in men aged 51-60 years 7.0% ED in men aged > 61 years	Age

2007	Ahn *et al.* [244]	1,570 men; geographically stratified random population study	Not reported	40-79	Self-administered questionnaire (IIEF-5)	Overall, 13.4% had self-reported ED ED prevalence as defined by IIEF-5 score less than 17 was 32.4% According to single question: 4.2% ED in men aged 40-49 years 13.0% ED in men aged 50-59 years 30.1% ED in men aged 60-69 years 41.1% ED in men aged 70-79 years	Age, Single status, Low income, Diabetes, Hypertension, Hyperlipidemia, Heart disease, Musculoskeletal disorders, Alcohol, Depression, Coffee intake
2008	Moreira *et al.* [245]	750 men; random population sample (Australia)	16.9%	40-80	Telephone survey (random digit dialing)	Overall, 32% of men had ED	Age
2008	Chew *et al.* [246]	1,580 men; random population sample (Australia)	37.3%	>20	Postal survey Self-administered questionnaire (IIEF-5)	15.7% ED in men aged 20-29 years 8.7% ED in men aged 30-39 years 12.9% ED in men aged 40-49 years 31.6% ED in men aged 50-59 years 52.4% ED in men aged 60-69 years 69.4% ED in men aged 70-79 years 68.2% ED in men aged > 80 years	Age, Marital status
2008	Teles *et al.* [247]	3,067 men; random population sample (Portugal)	81.3%	40-69	Self-administered questionnaire, including IIEF	Overall, 48.1% of men had ED 29% ED in men aged 40-49 years 50% ED in men aged 50-59 years 74% ED in men aged 60-69 years	Age, Diabetes, Cardiac insufficiency, Psychiatric illness
2008	Moreira *et al.* [248]	750 men; random population sample (United Kingdom)	17%	40-80	Telephone survey (random digit dialing)	Overall, 17.8% of men had ED	Age
2009	Laumann *et al.* [249]	742 men; random population sample (United States)	9%	40-80	Telephone survey (random digit dialing)	Overall, 22.5% of men had ED	Age, Depression
2009	Buvat *et al.* [250]	750 men; random population sample (France)	23.8%	40-80	Telephone survey (random digit dialing)	Overall, 15% of men had ED	Age

2010	Corona *et al.* [251]	3,369 men; random population study (Europe: Italy, Belgium, United Kingdom, Spain, Poland, Hungary, Estonia)	40%	40-80	Self-administered questionnaire	Overall, 30% of men had ED 6% ED in men aged 40-49 years 19% ED in men aged 50-59 years 38% ED in men aged 60-69 years 64% ED in men 70 and over	Age, Depression, LUTS, Cardiovascular disease, Diabetes, Obesity
2016	Oyelade *et al.* [252]	241 men; random sampling cross-sectional population based survey (Nigeria)	99%	30-80	Self-administered questionnaire (IIEF-5)	The general prevalence of ED in this study was 58.9%	Age, Hypertension, Use of anti-hypertensive drugs, Diabetes mellitus, Heart disease
2017	Cayan *et al.* [253]	2,760 men; random population study (Turkey)	Non-reported	≥ 40	Self-administered questionnaire (IIEF-5)	The prevalence of ED was calculated as 33% among all males of ≥ 40 years of age. ED prevalence rates were 17% for 40-49 years, 35.5% for 50-59 years, 68.8% for 60-69 years, and 82.9% for ≥ 70 years	Age, Diabetes, Hypertension, Atherosclerosis, Dyslipidemia, LUTS, Educational status, Monthly income
2017	Quilter *et al.* [254]	Randomly selected age-stratified population-based sample of 2,000 men (New Zealand)	30%	40-70	Self-reported erectile function (IIEF-5) and a single-question self-assessment tool.	Prevalence of ED was 42% (22% mild, 10% mild to moderate, 6% moderate, and 4% severe)	Age, Anxiety or depression

** Four baseline study estimating the prevalence of Erectile Dysfunction:*
MMAS = the Massachusetts Male Aging Study; NHSLS = the National Health of Social Life Survey; MALES = the multi-national men's attitudes to life events and sexuality; GSSAB = Global Study of Sexual Attitudes and Behaviours.
BPH = Benign Prostate Hyperplasia; COPD = Chronic Obstructive Pulmonary Disease; ED = Erectile Dysfunction; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = Lower urinary tract symptoms.

Table 8: The prevalence rates of premature ejaculation [171]

Date	Authors	Method of Data Collection	Method of Recruitment	Operational Criteria	Prevalence Rate	Number of Men
1998	Dunn *et al.* [255]	Mail	General practice registers - random stratification	Having difficulty with ejaculating prematurely	14% (past 3 mo)	617
					31% (lifetime)	618
1999	Laumann *et al.* (NHSLS) [177]	Interview	NA	Climaxing/ ejaculating too rapidly during the past 12 months	31%	1,410
2002	Fugl-Meyer and Fugl-Meyer [256]	Interview	Population register	NA	9%	1,475
2004	Rowland *et al.* [257]	Mailed questionnaire	Internet panel	DSM IV	16.3%	1,158
2004	Nolazco *et al.* [258]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3%	2,456
2005	Laumann *et al.* [188]	Telephone-personal interview/Mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75% (4.26% frequently)	13,618
2005	Basile Fasolo *et al.* [259]	Clinician-based	Invitation to outpatient clinic	DSM IV	21.2%	12,558
2005	Stulhofer *et al.* [260]	Interview	Stratified sampling	Often ejaculating in less than 2 minutes	9.5%	601
2007	Porst *et al.* (PEPA) [178]	Web-based survey Self-report	Internet panel	Control over ejaculation, Distress	22.7%	12,133
2008	Shindel *et al.* [261]	Questionnaire	Male partners of infertile couples under evaluation	Self-report premature ejaculation	50%	73
2009	Brock *et al.* [262]	telephone interview	Web-based survey	DSM III	16%	3,816
				Control	26%	
				Distress	27%	
2010	Traeen and Stigum [221]	Mailed questionnaire + internet	Web interview + Randomisation		27%	11,746+1,671
2010	Son *et al.* [263]	Questionnaire	Internet panel (younger than 60)	DSM IV	18.3%	600
2010	Amidu *et al.* [264]	Questionnaire	NA	NA	64.7%	255
2010	Liang *et al.* [265]	NA	NA	ISSM	15.3%	1,127
2010	Park *et al.* [266]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5%	2,037
2010	Vakalopoulos *et al.* [267]	One-on-one survey	Population based cohort	EED	58.43%	522
				ISSM Lifelong PE	17.7%	
2010	Hirshfeld *et al.* [218]	Web-based survey	Online advertisement in the United States and Canada	Climaxing/ ejaculating too rapidly during the past 12 months	34%	7,001
2011	Christensen *et al.* [268]	Interview + questionnaire	Population register (random)	NA	7%	5,552
2011	Serefoglu *et al.* [179]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0%	2,593

2011	Son *et al.* [269]	Questionnaire	Internet panel	Estimated IELT ≤ 5 mins, inability to control ejaculation, distress	10.5%	334
2011	Tang and Khoo [270]	Interview	Primary care setting	PEDT ≥ 9	40.6%	207
2012	Mialon *et al.* [271]	Mailed questionnaire	Convenience sampling (18-25 years old)	Control over ejaculation Distress	11.4%	2,507
2012	Shaeer and Shaeer [272]	Web-based survey	Online advertisement in Arabic countries	Ejaculate before the person wishes to ejaculate at least sometimes	83.7%	804
2012	Shindel *et al.* [273]	Web-based survey	Online advertisement targeted to MSM + distribution of invitation to organisations catering to MSM	PEDT ≥ 9	8-12%	1,769
2012	McMahon *et al.* [274]	Computer assisted interviewing, online, or in-person self-completed	NA	PEDT ≥ 11	16%	4,997
				Self-Reported (always/nearly-always)	13%	
2012	Lotti *et al.* [275]	Interview	Men seeking medical care for infertility	PEDT ≥ 9	15.6%	244
2013	Zhang *et al.* [276]	Interview	Random stratified sample of married men aged 30-60	Self-reported premature ejaculation	4.7%	728
2013	Lee *et al.* [277]	Interview	Stratified random sampling	PEDT ≥ 11	11.3%	2,081
				Self-Reported	19.5%	
				IELT<1 min	3%	1,035
2013	Gao *et al.* [180]	Interview	Random stratified sample of monogamous heterosexual men in China	Self-reported premature ejaculation	25.8%	3,016
2013	Hwang *et al.* [278]	Survey of married couples	Married heterosexual couples in Korea	Estimated IELT < 2 minutes	21.7%	290
				PEDT > 11	12.1%	
2013	Vansintejan *et al.* [279]	Web Based survey	Online and flyer advertisements to Belgian men who have sex with men (Only HIV+ men in this study)	IPE score < 50% of total possible	4%	72
2013	Shaeer *et al.* [280]	Web Based survey	Targeting English-speaking males above the age of 18, living most of their lives in the USA, regardless of personal interests and web browsing preferences	ISSM definition [175]	6.3%	1133
				PEDT	49.6%	
				Unfiltered self-reported	77.6%	
				Filtered self-reported	14.4%	

2016	Karabakan [281]	Interview (heavy bias toward younger men)	Targeting police academy students aged 24-30 who applied for routine urological examination	PEDT > 10	9.2%	1000
2017	Gao *et al.* [282]	Field survey with face-to-face interviews	Comprising men aged 20-68 years in five cities in the Anhui province	Self-estimated IELT	Lifelong PE 10.98% Acquired PE 21.39%	1239

DMS = Diagnostic and Statistical Manual of Mental Disorders; NA = not applicable; ISSM = International Society for Sexual Medicine; PEDT = Premature Ejaculation Diagnostic Tool; IELT = intravaginal ejaculatory latency time; IPE = Index of Premature Ejaculation; mo = months.

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Penile erection is a complex physiological process, which involves integration of both neural and vascular events, along with an adequate endocrine milieu. It involves arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [283]. Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [284]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [166, 285-287].

There is increasing evidence that the presence of ED increases the risk of future CV events including MI, cerebrovascular events, and all-cause mortality, with a trend towards an increased risk of cardiovascular mortality [288]. Therefore, ED can be an early manifestation of coronary artery and peripheral vascular disease and should not be regarded only as a QoL issue, but also as a potential warning sign of CVD [289-291]. A cost analysis showed that screening men presenting with ED for CVD represents a cost-effective intervention for secondary prevention of both CVD and ED, resulting in substantial cost savings relative to identification of CVD at the time of presentation [292].

Erectile dysfunction is commonly classified into three groups based on aetiology. These include organic, psychogenic and mixed ED. However, this classification should be used with caution as most cases are actually of mixed aetiology. It has therefore been suggested to use the terms "primary organic" or "primary psychogenic".

5.2 Risk factors

Erectile dysfunction is associated with unmodifiable and modifiable common risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, BMI/obesity, MetS, hyperhomocysteinemia, lack of exercise, and smoking (a positive dose-response association between quantity and duration of smoking has been demonstrated) [286, 290, 293-300]. Furthermore, an association between ED status and pharmaco-therapeutic agents for CVD (e.g., thiazide diuretics and β-blockers, except nebivolol, exert detrimental effects on erectile function, whereas newer drugs i.e., angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor-blockers and calcium-channel-blockers have neutral or even beneficial effects) [290, 301, 302], atrial fibrillation [303], hyperthyroidism [20], vitamin D deficiency [304, 305], hyperuricemia [306], and depression [307] have also been reported as risk factors. Available data do not confirm a clear association between ED and hypothyroidism and hyperprolactinaemia [20].

A number of studies have shown that lifestyle modification [308], including physical activity [309], weight loss [310] and pharmacotherapy [302, 311, 312] for CVD risk factors may be of help in improving sexual function in men with ED. Meta-analytic data reveals a positive effect of lipid-lowering therapy with statins on erectile function [313, 314]. However, it should be emphasised that further controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in the prevention and treatment of ED [308].

Further epidemiological data have also highlighted other potential risk factors associated with ED including sleep disorders [315], obstructive sleep apnoea [316], psoriasis [317-319], gouty arthritis [320] and ankylosing spondylitis [321], non-alcoholic fatty liver disease [322], other chronic liver disorders [323], chronic periodontitis [324], open-angle glaucoma [325], inflammatory bowel disease [326], chronic fatigue syndrome [327] and allergic rhinitis [328].

Erectile dysfunction is also frequently associated with other urological conditions and procedures (Table 9). Epidemiological studies have also demonstrated consistent evidence for an association between LUTS/BPH and sexual dysfunction, regardless of age, other comorbidities and lifestyle factors [329]. The Multinational Survey on the Aging Male study, performed in the USA, France, Germany, Italy, Netherlands, Spain, and the UK, systematically investigated the relationship between LUTS and sexual dysfunction in over 12,000 men aged 50-80 years. In the 83% of men who were reported to be sexually active, the overall prevalence of LUTS was 90%, with the overall prevalence of ED 49%, with a reported complete absence of erections in 10% of patients. Moreover, the overall prevalence of ejaculatory disorders was 46% [236]. Regardless of the technique used, surgery for BPH-LUTS had no significant impact on erectile function. In fact, even an improvement was found depending on the degree of improvement of urinary symptoms [330, 331]. An association between ED and CP/CPPS [332], and bladder pain syndrome/interstitial cystitis has been confirmed, mostly in younger men [333]. Furthermore, a relevant interplay and association between ED and PE has also been demonstrated (section 6.2) [334]. An increased risk of ED is reported following transrectal ultrasound (TRUS)-guided prostate biopsy [335] and after open urethroplasty, especially for correction of posterior strictures [336].

Table 9: Urological conditions associated with ED

Urological Condition	Association with ED
LUTS/BPH [329]	Depending on the severity of LUTS and patients' age/population characteristics: Odds ratio (OR) of ED among men with LUTS/BPH ranges from 1.52 to 28.7 and prevalence ranges from 58% to 80%
Surgery for BPH/LUTS (TUR-P, laser, open, laparoscopic, etc.) [330]	Overall, absence of significant variations in terms of erectile function scores after surgery
Chronic Prostatitis/Chronic Pelvic Pain Syndrome [332]	Prevalence of ED among patients with CP/CPPS 29% [24%-33%, 95%CI], Range: 11% - 56% among studies
Bladder Pain Syndrome/Interstitial Cystitis [333]	OR of BPS/IC among patients with ED. Overall: OR (adjusted) = 1.75 [1.12 - 2.71, 95%CI] Age ≥ 60: OR (adjusted) = 1.07 [0.41 - 2.81, 95%CI] Age 40-59: OR (adjusted) = 1.44 [1.02 - 2.12, 95%CI] Age 18-39: OR (adjusted) = 10.40 [2.93 - 36.94, 95%CI]
Premature Ejaculation [334]	OR of ED among patients with PE = 3.68 [2.61 - 5.68, 95%CI]
Urethroplasty surgery for posterior urethral strictures [336]	OR of ED after posterior urethroplasty = 2.51 [1.82 - 3.45, 95%CI]

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 10) [283]. In most cases, numerous pathophysiology pathways can co-exist and may all negatively impact on erectile function.

The proposed ED etiological and pathophysiological division should not be considered prescriptive. In most cases, ED is associated with more than one pathophysiological factor and very often, if not always, will have a psychological component. Likewise, organic components can negatively impact on erectile function with different pathophysiological effects. Therefore, Table 10 must be considered for diagnostic classifications only (along with associated risk factors for each subcategory).

Table 10: Pathophysiology of ED

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g. hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases

Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure; chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, urethroplasty, etc.)
Anatomical or structural
Hypospadias; epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)
Hormonal
Diabetes mellitus; Metabolic Syndrome;
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiology pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, etc.)
Psoriasis; gouty arthritis; ankylosing spondylitis; non-alcoholic fatty liver; chronic periodontitis; open-angle glaucoma; inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy, etc.)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake, etc.)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5α-reductase inhibitors.

*A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as an anti-erectogenic drug. The analysis only assessed the short-term risk. [337].

*5.3.1 **Pelvic surgery and prostate cancer treatment***

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [338] or radical cystectomy [339] and colorectal surgery [340]), may have a negative impact on erectile function and overall sexual health. The most relevant causal factor is a lesion (any) occurring to the neurovascular bundles that control the complex mechanism of the cavernous erectile response, whose preservation (either partial or complete) during surgery eventually configures the so-called nerve-sparing (NS) approach. Thereof, surgery resulting in damage of the neurovascular bundles, will result in ED, although NS approaches have been adopted over the last a few decades. This approach is applicable to all types of surgery that are potentially harmful to erectile function, although to date, only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [341-343]. However, even non-surgical treatments of PCa (i.e., radiotherapy; brachytherapy) can be associated with an impairment of erectile function. The concept of an active surveillance (AS) strategy for the treatment of PCa was developed to avoid over-treatment of non-significant localised low-risk diseases, while limiting potential functional side-effects (including ED). However, it is interesting that data suggest that even AS may have a detrimental impact on erectile function (and sexual well-being as a whole) [344-346].

To date the most robust data on patient-reported outcome measures (PROMS) including erectile function, comparing treatments for clinically localised PCa come from the Prostate Testing for Cancer and Treatment (ProtecT) trial where 1,643 patients were randomised to active treatment (either RP or RT) and active monitoring (AM) and were followed-up for six years [347]. Sexual function, including erectile function, and the effect of sexual function on QoL outcomes were assessed with the Expanded Prostate Cancer Index Composite with 26 items (EPIC-26) instrument [348, 349]. At baseline, 67% of men reported erections firm enough for sexual intercourses this fell to 52% in the AM group, 22% in the RT group, and to 12% in the RP group, at six-month assessment. Interestingly, the worst trend over time was recorded in the RP group (with 21% erections firm enough for intercourse after three years versus 17% after six years). In the RT group, the percentage of men reporting erections firm enough for intercourse increased between six and twelve months, with a subsequent further decrease to 27% at six-year assessment. The percentage declined over time on a yearly basis in the AM group, with 41% of men reporting erections firm enough for intercourse at three-year and 30% at six-year evaluation [347].

Radical prostatectomy (either open, laparoscopic or robot-assisted) is a widely performed procedure with a curative intent for patients presenting with clinically localised intermediate- or high-risk PCa and a life expectancy of more than ten years based on health status and comorbidities [350, 351]. This procedure may lead to treatment-specific sequelae affecting health-related QoL. Men undergoing RP (any technique) should be adequately informed before the operation that there is a significant risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie's-like disease, and changes in penile length [343]. These outcomes have become increasingly important with the more frequent diagnosis of PCa in both younger and older men [352-354]. Overall, research has shown that 25-75% of men experience post-RP ED [355], even though these findings suffer from methodological flaws, in particular, the heterogeneity of reporting and assessment of ED in the studies [341, 356]. Conversely, the rate of unassisted post-operative erectile function recovery is in the range of between 20 and 25% in most studies; these rates do not appear to have substantially improved or changed over the past seventeen years, despite the growing attention to post-surgical rehabilitation protocols and the refinement of surgical techniques [356-358].

Overall, patient age, baseline erectile function and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [342, 353, 355, 359]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [352, 353]. Overall, the recovery time following surgery is of major clinical importance in terms of post-operative recovery of erectile function. Available data confirms that post-operative erectile function recovery can occur up to 48 months after RP [360]. Likewise, it has been suggested that post-operative therapy (any type) should be commenced as close as possible to the surgical procedure [352, 355], although evidence suggests that the number of patients reporting return of spontaneous erectile function has not actually increased.

In terms of the effects of surgical interventions (e.g., robot-assisted RP [RARP] versus other types of surgery), the data is still conflicting. An early systematic review showed a significant advantage in favour of RARP in comparison with open retropubic RP in terms of twelve-month potency rates [361], without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the probability of erectile function recovery is about twice as high for RARP compared with open RP [362]. More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen Swedish centres comparing RARP versus open retropubic RP, showed a small improvement with respect to erectile function after RARP [363]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at twelve weeks [364]. As a whole, more controlled prospective well-designed studies, with longer term follow-up, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [365]. Furthermore, to overcome the problem of heterogeneity in the assessment of erectile function, for which there is variability in terms of the PROMS used (IIEF, IIEF-5, EPIC 26, Sexual Health Inventory for Men, etc.) to measure potency or erectile function; the criteria used to define restoration of erectile function should be re-evaluated utilising objective and validated thresholds (e.g., normalisation of scores or return to baseline erectile function) [341].

Erectile dysfunction is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED is 34% at 1 year and 57% at 5.5 years, respectively [366, 367]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at 60 months [368].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including whole gland and focal (lesion-targeted) treatments, in order to ablate tumours selectively whilst limiting sexual toxicity by sparing the neurovascular bundles. These include high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy, and focal radiation therapy (RT) by brachytherapy or CyberKnife®. Overall, all these approaches have been shown to have a less negative impact on erectile function, although all these approaches lack robust mid- and long-term oncological outcomes and prospective randomised controlled studies are needed to compare functional and oncological outcomes between the treatment modalities [369, 370].

*5.3.2 **Summary of evidence on the epidemiology/aetiology/pathophysiology of ED***

Summary of evidence	**LE**
Erectile dysfunction is common worldwide.	2b
Erectile dysfunction shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in BMI) can improve erectile function.	1b
Erectile dysfunction is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
Erectile dysfunction is common after RP, irrespective of the surgical technique used.	2b
Erectile dysfunction is common after external radiotherapy and brachytherapy.	2b
Erectile dysfunction is less common after cryotherapy and high-intensity focused US.	2b

5.4 Diagnostic evaluation (basic work-up)

*5.4.1 **Medical and sexual history***

The first step in evaluating ED is always a detailed medical and sexual history of patients and when available their partners [371]. It is important to establish a relaxed atmosphere during history-taking; this will make it easier to ask questions about erectile function and other aspects of the patient's sexual history; and to explain the diagnosis and therapeutic approach to the patient and their partner. Figure 3 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

The sexual history must include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [372, 373]. Validated psychometric questionnaires, such as the IIEF [80] or its short version the SHIM [80], help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interview have been demonstrated to allow the identification and quantification of the different underlining factors impacting upon erectile function [374].

Psychometric analyses also support the use of the Erectile Hardness Score for the assessment of penile rigidity in practice and in clinical trials research [375]. In cases of depressive mood, clinicians may use the Beck Depressive Inventory [376], which is one of the most recognised self-reported measures in the field, takes approximately ten minutes to complete, and assigns the patient to a specific level of depression (varying from "normal mood" to "extreme depression").

Patients should always be screened for symptoms of possible hypogonadism (testosterone deficiency), including decreased energy, libido, and fatigue; potential cognitive impairment may be also observed in association with hypogonadism (see sections 3.5 and 3.6), as well as for LUTS. In this regard, although LUTS/BPH in itself does not represent a contraindication to treat a patient for LOH, screening for LUTS severity is clinically relevant [7].

*5.4.2 **Physical examination***

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [377, 378]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive for hypogonadism (i.e., small testes, alterations in secondary sexual characteristics etc.).

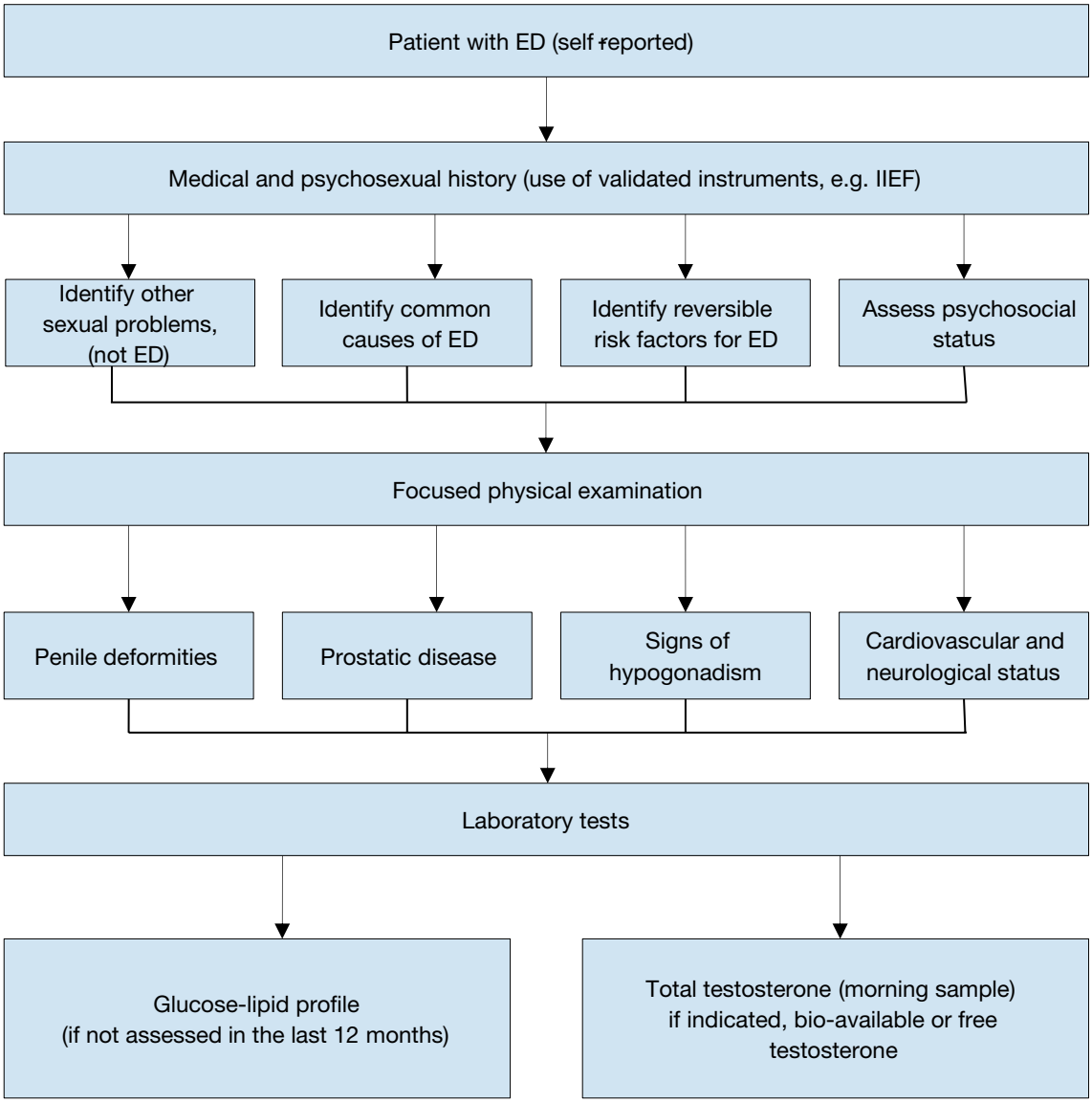
Overall, assessing previous or concomitant penile abnormalities (e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity) during the medical history and the physical examination is mandatory.

Blood pressure and heart rate should be measured if they have not been assessed in the previous three to six months. Likewise either a BMI calculation or waist circumference measurement should be undertaken to assess patients for comorbid conditions (e.g. MetS).

*5.4.3 **Laboratory testing***

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients should undergo a fasting blood glucose or HbA1c and lipid profile if they have not been assessed in the previous twelve months. Hormonal tests should include an early morning total testosterone in a fasting state. The bio-available or calculated-free testosterone values may be sometimes needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism (see sections 3.5 and 3.6) [20, 51, 294, 379, 380]. Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., PSA) [381]; prolactin, and LH [382]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, clinical and biochemical evaluation presents an opportunity to identify comorbid conditions [378].

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

*5.4.4 **Cardiovascular system and sexual activity: the patient at risk***

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular/metabolic risk factors and sexual dysfunction in both men and women [383]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with

diabetes [384, 385]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease and stroke. All of these cause mortality and the increase is probably independent of conventional cardiovascular risk factors [289, 290, 386, 387]. Longitudinal data from an observational population-based study of 965 men without CVD showed that younger men (especially those < 50 years) with transient and persistent ED have an increased Framingham CVD risk [388].

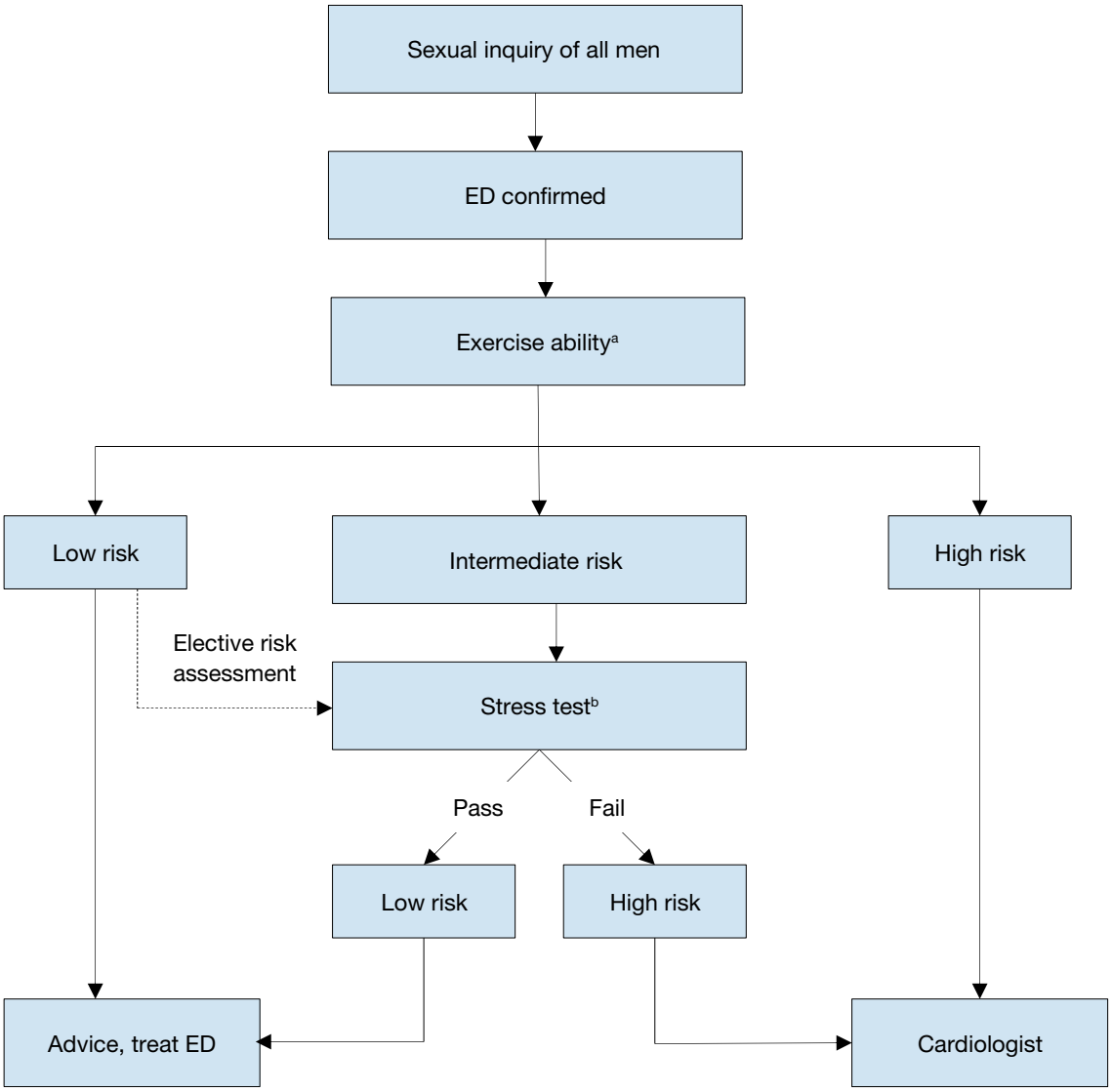
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [389]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [389-391]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 11), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [312].

Table 11: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [389, 391]

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 4: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [389]



[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.*

[b] *Sexual activity is equivalent to four minutes of the Bruce treadmill protocol.*

5.4.4.1 Low-risk category

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as, ≥ 6 metabolic equivalents of energy expenditure in the resting state without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

5.4.4.2 Intermediate- or indeterminate-risk category

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

5.4.4.3 High-risk category

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk

individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

5.5 Diagnostic Evaluation (advanced work-up)

Most patients with ED can be managed based on the basis of medical and sexual history; conversely, some patients may need specific diagnostic tests (Tables 12 and 13).

*5.5.1 **Nocturnal penile tumescence and rigidity test***

The nocturnal penile tumescence and rigidity (NPTR) test applies nocturnal monitoring devices that measure the number of erectile episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erection(s). The NPTR assessment should be performed on at least two separate nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ten or more minutes [392]. Nocturnal penile tumescence and rigidity monitoring is an attractive approach for objectively differentiating between organic and psychogenic ED (patients with psychogenic ED usually have normal findings in the NPTR test). However, many potential confounding factors (e.g., situational) may limit its routine use for diagnostic purposes [393].

*5.5.2 **Intracavernous injection test***

The intracavernous injection test gives limited information about the vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within ten minutes after the intracavernous injection and lasts for 30 minutes [394]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

*5.5.3 **Dynamic duplex ultrasound of the penis***

Dynamic duplex ultrasound (US) of the penis is a second-level diagnostic test specifically aimed to study the haemodynamic pathophysiology of erectile function. Therefore in clinical practice it is usually applied in those conditions where a potential vasculogenic aetiology of ED (e.g., diabetes mellitus; renal transplantation; multiple concomitant CV risk factors and/or overt peripheral vascular disease; poor responders to oral therapy, etc.) is suspected. A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal [395, 396]. Recent data have suggested that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave (LI-SWT) treatment and for diagnosing vasculogenic ED [397]. Further vascular investigation is unnecessary if a duplex US examination is normal.

*5.5.4 **Arteriography and dynamic infusion cavernosometry or cavernosography***

Pudendal arteriography should be performed only in patients who are being considered for penile revascularisation [398]. Recent studies have advocated the use of computerised tomography (CT) angiography as a diagnostic procedure prior to penile artery angioplasty for patients with ED and isolated penile artery stenosis [399]. Nowadays, dynamic infusion cavernosometry or cavernosography are infrequently used diagnostics tools aimed at diagnosing venogenic ED.

*5.5.5 **Psychiatric and psychosocial assessment***

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist. In younger patients (< 40 years) with long-term primary ED [170], psychiatric assessment may be helpful before any clinical assessment is carried out.

Mental health issues are frequently comorbid with ED; this is most evident for depression and anxiety related disorders, but may also include transitory states of altered mood (i.e., dysfunctional affective states resulting from a specific life stressor) [307, 400]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected with the partner during sex, have been related to erectile difficulties and dysfunction [400-402]. On the other hand, feeling emotionally supported, and motivated toward intimacy are protective factors in men with ED [403]. Additionally, the cognitive factors underpinning organic and non-organic ED must also be assessed. Cognitive factors include men's dysfunctional thinking styles and expectations about sexuality and sexual performance. These expectations result from the sexuality norms and stereotypes, shared by a given culture. Expectations emphasising high sexual performance in men, result in sexual performance anxiety, acting as a maintenance factor of ED [404]. Unrealistic expectations about male sexual performance may further align with internal causal attributions regarding the loss of erection (i.e., men attribute the loss of erection to themselves [sense of personal inadequacy]), thereby worsening ED [405]. Likewise, poor self-esteem and cognitive distraction from erotic cues, are expected to negatively impact ED [406, 407].

Psychosexual assessment in ED cases include a clinical interview considering all the previous topics; clinicians are expected to collect information on the individual's psychopathology symptoms, life stressors, relationship dynamics, cognitive style, and cognitive distraction sources [406]. Also, self-reported measures are frequently used within the psychological context. These may include measurement scales such as the Brief Symptom Inventory [408] for measuring psychopathology symptoms, the Sexual Dysfunctional Beliefs Questionnaire [409] or the Sexual Modes Questionnaire [410] for measuring dysfunctional cognitive styles in men.

Figure 5: Psychiatric and psychosocial assessment

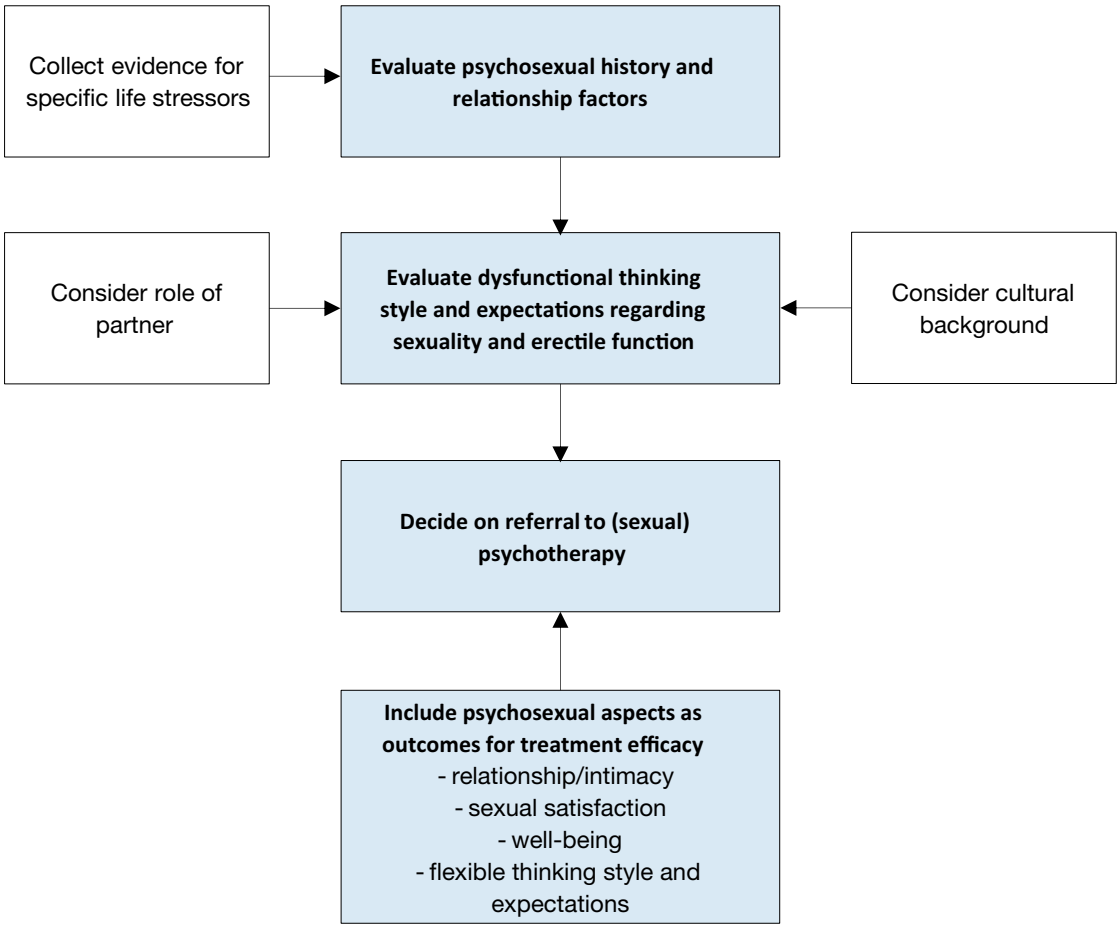


Table 12: Indications for specific diagnostic tests for ED

Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

Table 13: Specific diagnostic tests for ED

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies - Intracavernous vasoactive drug injection - Penile dynamic duplex ultrasonography - Penile dynamic infusion cavernosometry and cavernosography - Internal pudendal arteriography
Specialised endocrinological studies
Specialised psychodiagnostic evaluation

*5.5.6 **Recommendations for the diagnostic evaluation of ED***

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting for erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 11.	Strong

5.6 Treatment of erectile dysfunction

*5.6.1 **Patient education - consultation and referrals***

Educational intervention is often the first approach to sexual complaints, and consists of informing patients about the psychological and physiological processes involved in the individual's sexual response, in ways he can understand. This first level approach was shown to favour sexual satisfaction in ED men [411]. Accordingly, consultation with the patient should include firstly a discussion of the expectations and needs of both the patient and their sexual partner. It should also review both the patient and partner's understanding of ED and the results of diagnostic tests, and provide a rational for the selection of treatment options [412]. Patient and partner education is an essential part of ED management [412, 413], and may prevent misleading information that may be at the core of dysfunctional psychological processes underpinning ED.

*5.6.2 **Treatment options***

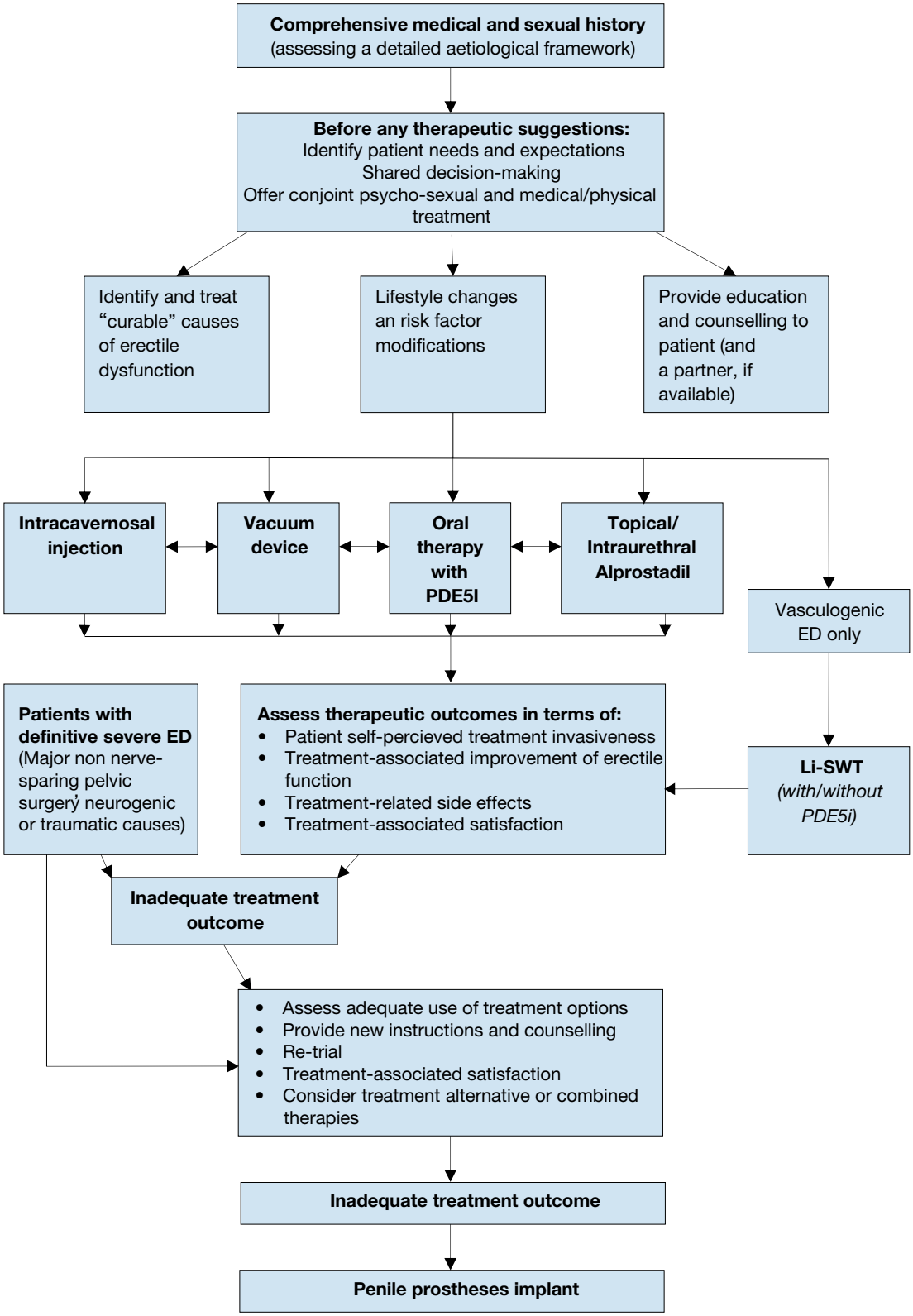
Based on the currently available evidence and the consensus of the panel, a novel comprehensive therapeutic and decision-making algorithm (Figure 6) for treating ED, which takes into account both the level of invasiveness of each therapy and the efficacy of the therapy itself, is presented. This newly-developed treatment algorithm has been extensively discussed within the guidelines panel as an alternative to the traditional three-level concept in order to better tailor a personalised therapy to individual patients, according to invasiveness, tolerability, effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [308]. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (such as, endocrine disorders and metabolic disorders - e.g., diabetes - some cardiovascular problems - e.g., hypertension) which should always be well-controlled as the first step of any ED treatment [414]. Major clinical potential benefits of lifestyle changes may be achieved in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [308, 415].

As a rule, ED can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism) [51, 382], which potentially can be cured with specific treatments. Most men with ED

will be treated with therapeutic options that are not cause specific. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety, and cost, as well as patient preference [412]. In this context, physician-patient (partner, if available) dialogue is essential throughout the management of ED.

Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.

5.6.2.1 Oral pharmacotherapy

Four potent selective PDE5Is have been approved by the EMA for the treatment of ED [416]. Phosphodiesterase type 5 catalyses the hydrolysis of the second messenger cyclic guanosine monophosphate (cGMP) in the cavernous tissue; cGMP is involved in intra-cellular signal pathways of cavernous smooth muscle. Indeed, the accumulation of cGMP sets in motion a cascade of events at the intracellular level, which induces a loss of contractile tone of the vessels at the penile level by lowering cytosolic Ca^{2+}. Nitric oxide (NO) has an essential role in promoting the formation of cGMP and other pathways leading to corporeal smooth muscle relaxation and erection of the penis [414, 417]. This is associated with increased arterial blood flow, eventually leading to compression of the sub-tunical venous plexus followed by penile erection [418]. Since they are not initiators of erection, PDE5Is require sexual stimulation to facilitate an erection. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [414].

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [419]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects [419]. Sildenafil is effective 30-60 minutes after administration [419]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to twelve hours [420]. The pharmacokinetic profile for sildenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited [421, 422]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% in a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [423]. Sildenafil significantly improved patient scores for IIEF, Sexual Encounter Profile (SEP)2, SEP3, and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established, irrespective of age [424]. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at a dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about two hours [425]. Efficacy is maintained for up to 36 hours [425] and is not affected by food [426]. Usually, it is administered in on-demand doses of 10 and 20 mg or a daily dose of 5 mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and side-effects [425, 427]. Pharmacokinetic data for tadalafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after twelve weeks of treatment in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group [425]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [425].

Efficacy has been confirmed in post-marketing studies [416, 428]. The efficacy of tadalafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established [429], in addition to the evidence of a net clinical advantage in the short-term on ejaculatory and orgasmic functions in ED patients [430]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in patients with concomitant ED and LUTS [431]. Recent data also confirms that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH to treatment with tadalafil 5 mg once daily, with symptom improvement after twelve weeks [432].

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [433], with up to one out of three patients achieving satisfactory erections within 15 minutes of ingestion [434]. Its effect is reduced by a heavy, fatty meal. Doses of 5, 10 and 20 mg have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects [435]. Pharmacokinetic data for vardenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use [435]. After twelve weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [435, 436]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction.

Efficacy has been confirmed in post-marketing studies [435, 436]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. More recently, an ODT form of vardenafil has been released [436]. Orodispersable tablet formulations offer improved convenience over film-coated formulations and may be

preferred by patients. Absorption is unrelated to food intake and they exhibit better bio-availability compared to film-coated tablets [437]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [437-439].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [440]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes, ideally allowing for the drug to be used for ED while minimising adverse effects (although head-to-head comparison studies are not yet available) [441]. Doses of 50 mg, 100 mg, and 200 mg have been approved for on-demand treatment of ED [440]. The recommended starting dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity and the dosage may be adapted according to efficacy and tolerability [440, 442, 443]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo [440, 442]. Data from sexual attempts made within fifteen minutes of dosing showed successful attempts in 64%, 67%, and 71% of cases, with avanafil 50, 100, and 200 mg, respectively. Dosage adjustments are not warranted based on renal function, hepatic function, age or gender [442]. Pharmacokinetic data for avanafil is presented in Table 14 [440, 442]. Adverse events are generally mild in nature (Table 15) [440, 442]. Pairwise meta-analytic data from available studies suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ, with an evident dose-response relationship [440, 444]. Administration with food may delay the onset of effect compared with administration in a fasting state but avanafil can be taken with or without food [445]. The efficacy of avanafil in many groups of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established. As for dosing, 36.4% (28 of 77) of sexual attempts (SEP3) at fifteen minutes or less were successful with avanafil versus 4.5% (2 of 44) after placebo ($p < 0.01$) [446]. A recent meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil treatments [445].

Choice or preference between the different PDE5Is

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for the most-widely available PDE5Is (i.e., sildenafil, tadalafil, vardenafil, and avanafil). Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it. A meta-analysis demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to udenafil 100 mg if the treatment is not sufficient (however, udenafil 100 mg is not EMA or FDA approved and is not available in Europe) [428]. In addition, results of another clinical trial revealed that tadalafil 5 mg once daily may improve the erectile function outcomes among men who had a partial response to on-demand PDE5I therapy [447].

Continuous use of PDE5Is

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structural alterations due to age, diabetes, or surgical damage [448-452]. No data exists in humans. In humans, it has been clinically demonstrated that treatment with tadalafil 5 mg once-daily in men complaining of ED of various severities was well tolerated and effective [453]. In 2007, tadalafil 2.5 and 5 mg were approved by the EMA for daily treatment of ED. According to the EMA, a once-daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg, taken once a day at approximately the same time. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be linked. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [453, 454]. A recently published integrated analysis showed that no clinical populations of patients with ED seemed to benefit overwhelmingly from tadalafil once daily over on-demand dosing regimen and vice versa [455]. Furthermore, a recent RCT showed that there is no clinical benefit on endothelial dysfunction measured by flow-mediated dilation deriving from daily tadalafil when compared to placebo [456]. Although some authors reported improved erectile function when long-term tadalafil 5 mg once daily is combined with sildenafil as needed [457], more safety analyses are required to give a formal recommendation on such a therapy.

Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics. C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration time curve.*

Table 15: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasalcongestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormalvision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Safety issues for PDE5Is

- **Cardiovascular safety**

Clinical trial results for the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina [416, 458]. Chronic or on-demand use is well tolerated with a similar safety profile. The prescription of all PDE5Is in patients with CVD or in those with high CV risk should be based on the recommendations of the 3rd Princeton Consensus Panel [389].

- **Contraindication for the concomitant use of organic nitrates**

Absolute contraindication to PDE5Is is represented by patients who are using any form of organic nitrate (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors (e.g., other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as “poppers” which are used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, four hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than twelve hours if avanafil is used (half-life, 6-17 hours) [459-462].

- **Use caution with antihypertensive drugs**

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor [389]. In general, the adverse event profile of a PDE5I is not worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents [463].

- **Interaction with Nicorandil**

In vitro studies in animals suggest that the potassium channel opener nicorandil may potentiate the vasorelaxation induced by isoproterenol in isolated rat aorta by increasing cyclic GMP levels [464]. This may be due to the nitric oxide donating properties of nicorandil. Therefore the concurrent use of nicorandil and PDE5Is is also contraindicated.

α-Blocker interactions

All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α-blocker (especially doxazosin). Hypotension is more likely to occur within four hours following treatment with an α-blocker. A starting dose of 25 mg is recommended [421].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on their α-blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [433, 435, 436].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [425, 465].
- Avanafil labelling currently reports that patients should be stable on α-blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α-blocker therapy should be initiated at the lowest dose.

In the everyday clinical practice, a patient presenting for ED should be stable on one medication (every α-blocker except for doxazosin which should be avoided whenever possible) before starting a PDE5Is.

Dosage adjustment

Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g. ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

Management of non-responders to PDE5Is

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. Data suggest that an adequate trial involves at least six attempts with a particular drug [466]. The management of non-responders depends upon identifying the underlying cause [467]. Check that the patient has been using a licensed medication. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

Check that the medication has been properly prescribed and correctly used. The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The most common causes of incorrect drug use are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Oral PDE5Is take different times to reach maximal plasma concentrations [420, 422, 437, 444, 468-470]. Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 minutes of oral ingestion [422, 437, 468-470], most patients require a longer delay between taking the medication [435, 444, 471, 472]. Absorption of both sildenafil and vardenafil can be delayed by a heavy, fatty meal [473]. Absorption of tadalafil is less affected, and food has negligible effects on its bioavailability [468]. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [440, 441, 444].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about four hours, suggesting that the normal window of efficacy is six to eight hours following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is six to seventeen hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is much longer at ~36 hours. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I [467, 474-477]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I [467, 474, 475].

Recent data suggested that response to sildenafil treatment was also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [478-480].

Clinical strategies in patients correctly using a PDE5Is

Overall, treatment goals should be individualised to restore sexual satisfaction for the patient and/or couple and improve QoL based on the patient's expressed needs and desires [481]. In this context, data suggests that almost half of patients abandon first-generation PDE5Is within one year, with no single specific factor playing a major role in PDE5Is dropout rates [482].

Uncontrolled trials have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [51, 414, 483]. Therefore, in the real-life setting most patients with ED will first be prescribed a PDE5I, which is usually effective; however, if diagnostic criteria suggestive for testosterone deficiency are present, testosterone replacement therapy may be a more appropriate treatment even in ED patients [5, 51].

Modification of other risk factors may also be beneficial as previously discussed. Limited data suggest that some patients might respond better to one PDE5I than to another [484] and although these differences might be explained by variations in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. However it is important to emphasise that the very few randomised studies show any difference in clinical outcomes with different drugs and intake patterns both in patients with classic ED [485] and in special populations such as diabetics [486].

Moreover, in patients with severe ED, it has been suggested to combine tadalafil daily dosing with a short acting PDE5I (such as sildenafil), without any significant increase in terms of side-effects [457]; robust prospective data from RCTs to support combination treatments with any oral preparations are still lacking and should therefore be used with caution. If drug treatment fails, then patients can be offered an alternative therapy such as intracavernous injection therapy or use of a vacuum erection device (VED). Likewise, limited data suggest the combination of a PDE5I with alprostadil as intracavernosal, intraurethral or topical application in patients who have previously failed therapy with either drug [487]. Review findings indicated that with all three formulations the combination therapy resulted in an improved outcome compared with either of the drugs as monotherapy, even for patients with post-prostatectomy ED. Treatment-emergent side-effects of the combined treatment did not result in treatment discontinuation [487].

5.6.2.2 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered per urethra with two different formulations. The first compound is the topical route using a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300 µg) via the urethral meatus [488, 489]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [490]. Side-effects include penile erythema, penile burning and pain that usually resolves within two hours of application. Systemic side effects are very rare. Topical alprostadil (VITAROSTM) at the dose of 300 µg is currently approved and it is available in some European countries. Recently a randomised cross-over clinical trial showed that, compared to the standard administration route, the direct delivery of the drug within the urethral meatus is able to increase the level of treatment efficacy and confidence among patients, without increasing the incidence of side-effects [491].

The second method of delivery is by the intra-urethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil be initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regard to adverse events. In case of unsatisfactory clinical response the dose can be increased to 1000 µg [492-494]. The application of a constriction ring at the root of the penis may improve efficacy [493, 494].

Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than intracavernous pharmacotherapy [495], with a ~30% of adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

5.6.2.3 Shockwave therapy

The use of l LI-SWT has been increasingly proposed as a treatment for vasculogenic ED over the last decade, being the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [397, 496-503].

Overall, several single-arm trials have shown benefit of LI-SWT on patient-reported erectile function scores, but data from prospective randomised trials are conflicting, and many questions remain to be answered especially because of the variation in shockwave generators (electrohydraulic, electromagnetic, piezoelectric, electropneumatic), type of shockwaves delivered (focused, linear, semi-focused, unfocused), set-up parameters (energy flux density and number of pulses per session) and treatment protocols (duration of treatment course, number of sessions per week, total number of shockwaves pulses delivered, penile sites of application) [504]. As a whole, most of the studies suggest that LI-SWT can significantly increase the IIEF and Erection Hardness Score in patients with mild vasculogenic ED, rather than improve penile hemodynamic parameters [504, 505]. Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are PDE5Is non-responders [501, 506] or inadequate responders [507], reducing the immediate need for more invasive treatments. However, prospective RCTs and longer-term follow-up data would provide the clinician with more confidence regarding the use and efficacy of LI-SWT for ED. Further clarity is also needed in defining treatment protocols that can result in greater clinical benefits [508, 509].
Overall, according to the available data and the novel treatment decision algorithm, patients with vasculogenic ED may be treated with LI-SWT, although they should be fully counselled before treatment.

5.6.2.4 Psychosexual counselling and therapy

For patients with a recognised psychological problems [510], psychosexual therapy may be given either alone or with another therapeutic approach in order to improve couple's sexual satisfaction and partner's sexual function [511]. Psychosexual therapy requires ongoing follow-up and has had variable results [512]. Despite this psychological treatments including different modalities (e.g., sexual skills training, marital therapy, psychosexual education) [411], Cognitive and Behaviour Therapy (CBT), including group or couple format, has been recommended [406]. Cognitive and behaviour therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. Some of its techniques include identifying triggers preceding erectile difficulties, cognitive restructuring of dysfunctional thinking styles, learning coping skills aimed at dealing with erectile difficulties and emotional symptoms, and relapse prevention. The CBT approach combined with the medical treatment for ED has received empirical support and is considered an optimal procedure [406].

5.6.2.5 Hormonal treatment

The advice of an endocrinologist should be sought for managing patients with hormonal abnormalities or endocrinopathies [382]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g., a functional pituitary tumour resulting in hyperprolactinaemia) [382, 513]. When clinically indicated [514], testosterone replacement therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, erectile function and dissatisfaction derived from intercourse and overall sexual life (see section 3.6 for a comprehensive discussion of testosterone replacement therapy).

5.6.2.6 Vacuum erection devises

Vacuum erection devices (VED) provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [515, 516]. Most men who discontinue use of VEDs do so within three months. Long-term use of VEDs decreases to 50-64% after two years [517]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [516]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy [518, 519]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidities requiring non-invasive, drug-free management of ED [515, 516, 520].

5.6.2.7 Intracavernous injections therapy

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [477, 521]. According to invasiveness, tolerability, effectiveness and patients' expectations (Figure 6), patients may be offered intracavernous injections. The success rate is high (85%) [495, 522].

5.6.2.7.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [477, 523]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (of note 40 µg dose may be offered off label in some European countries). The erection appears after five to fifteen minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training

program is required for the patient to learn the injection technique. In men with limited manual dexterity, the technique may be taught to their partners. The use of an automatic pen that avoids a view of the needle may be useful to resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections, respectively [477, 521]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively-prolonged undesired erections (5%), priapism (1%), and fibrosis (2%) [477, 521, 524]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [477, 521, 525]. Cavernosal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic side-effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been described for intracavernous pharmacotherapy [477, 521, 526, 527], with most drop-outs occurring within the first two to three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year [528]. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection program [529-531].

5.6.2.8 Combination therapy

Table 16 details the available intracavernous injection therapies (compounds and characteristics). Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side-effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy due to its high incidence of side-effects as monotherapy. Papaverine is currently not licensed for the treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide, usually combined with the main drugs [532, 533]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, Trimix: Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg) (also known as bimix), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg) (also known as trimix), have been widely used with improved efficacy rates, although they have never been licensed for ED [534, 535]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- Invicorp: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp™), currently licensed in Scandinavia, is a combination of two active components with complementary modes of action. Clinical studies showed that the combination is an effective treatment for intracavernous injections in > 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernous therapies, is associated with a very low incidence of penile pain and a virtually negligible risk of priapism [536].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [537]. However, combination therapy is associated with an increased incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

Table 16: Intracavernous injection therapy - compounds and characteristics

Name	Substance	Dosage	Efficacy	Adverse Events	Comment
Caverject™ or Edex/Viridal™	Alprostadil	5-40 µg/mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	Papaverine	20 - 80 mg	< 55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy
Phentolamine	Phentolamine	0.5 mg/mL	Very poor efficacy as monotherapy	Systemic hypotension, reflextachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg /mL + 0.5 mg/mL	~ 90%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Trimix	Papaverine + Phentolamine + Alprostadil	30 mg/mL + 1 mg /mL + 10 µg/ mL	~ 92%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Invicorp™	Vasoactive intestinal peptide (VIP) + Phentolamine	25 µg + 1-2mg	~ 80%	Similar as Alprostadil without pain	Easily available

There are currently several potential novel treatment modalities for ED, from innovative vasoactive agents and trophic factors to stem cell therapy and gene therapy. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies in order to achieve an adequate evidence base and clinically-reliable grade of recommendation [538-543].

5.6.2.8.1 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function and to allow patients to resume sexual activity. There is also some evidence in animal studies that this may avoid cavernous fibrosis and maintain penile length. Overall, a number of trials have shown improvements in erectile function after RP in patients receiving drug compounds (any therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment seems to impact on the natural recovery time for potency [544], although there is a lack of data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacological assisted erections [343, 545, 546]. In prospective studies, there is no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of erectile function in men following NSRP [546]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 4.

Historically, also the management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. In this context, it must be emphasised that post-RP, ED patients are poor responders to PDE5Is. Since their launch on the market, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [343, 352, 353]. A number of clinical parameters have been identified as potential predictors of PDE5Is in men undergoing RP. As detailed, patient age, baseline erectile function, and quality of NS technique are key factors in preserving post-RP erectile function [352, 353, 361, 547].

Analysing results in further detail, the response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [352, 548]. Early use of high-dose sildenafil after RP is associated with preservation of smooth muscle within the corpora cavernosa [549]. A single study demonstrated that daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [550]. Conversely, a recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal penile rigidity score in addition to the IIEF-erectile function showed no

therapeutic benefit for nightly sildenafil when compared to on-demand dosing in recovery of erectile function post-prostatectomy [551].

A large multicentre trial in Europe and the USA investigated the effects of tadalafil in patients with ED following bilateral NSRP. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil versus 26% with placebo [552]. Moreover, a randomised, double-blind, double-placebo trial in men < 68 years of age and with normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [546]. Tadalafil was most effective for drug-assisted erectile function in men with ED following NSRP and data suggested a potential role for tadalafil once daily (provided early after surgery) in contributing to the recovery of post-operative erectile function and maintaining penile length [546]. Conversely, unassisted or spontantaeous recovery of erectile function was not improved after cessation of active therapy for nine months [546]. However, tadalafil once daily improved QoL post-operatively, both at double-blind treatment and open label treatment period [553].

Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study [554]. Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [555]. A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP [545]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand [545].

A double-blind, placebo-controlled, parallel-group study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for twelve weeks showed significantly greater increases in SEP question 2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil versus placebo ($p < 0.01$) [391].

A recent Cochrane database systematic review analysed data from eight RCTs [556]. It showed that scheduled PDE5I may have little or no effect on short-term (up to twelve months) self-reported potency when compared to placebo or no treatment. In this study, daily PDE5I made little to no difference in short-term and long-term erectile function (short term: RR 1.00, 95% CI 0.65 to 1.55; long term: RR 0.74, 95% CI 0.48 to 1.14; both very low quality evidence). The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported potency and erectile function compared to on-demand use. Therefore, daily PDE5Is appeared to result in little to no difference in both short-term and long-term (greater than twelve months) self-reported potency when compared to scheduled use. Finally, at short-term follow-up, daily PDE5I may result in little or no effect on self-reported potency when compared to scheduled intra-urethral application of PGE1.

Historically, the treatment options for post-RP ED have included intracavernous injections [557], urethral micro-suppository [352, 558], vacuum device therapy [343, 352, 559, 560], and penile implants [352, 561, 562]. Intracavernous injections and penile implants had been suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not usable for post-operative patients [342, 343, 563]. A recent meta-analysis showed that the early use of vacuum device therapy appears to have excellent therapeutic effect on post-RP patients and no serious side-effects, therefore it should be considered as a therapeutic alternative to discuss with the patient [564].

5.6.2.9 Vascular surgery

5.6.2.9.1 Surgery for post-traumatic arteriogenic ED

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [519, 565]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography.

5.6.2.9.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [565].

5.6.2.9.3 Penile prostheses

The surgical implantation of a penile prosthesis may be considered in patients who (i) are not suitable for different pharmacotherapies or prefer a definitive therapy; and, (ii) do not respond to pharmacological therapies (Figure 6) [566]. The two currently available classes of penile implants include inflatable (2- and 3-piece) and semi-rigid devices (malleable, mechanical, soft flexible) [352, 561, 567-569]. Patients may prefer the 3-piece inflatable devices due to the more "natural" erections obtained, although there are no prospective RCTs comparing satisfaction rates with both types of implants. The two-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements (e.g., previous abdominal surgery). Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient [352, 561, 567, 568]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [568, 570]. They may also be an option in men with limited manual dexterity.

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic [567, 568, 570, 571]. The peno-scrotal approach has been suggested to provide an excellent exposure; afford proximal crural exposure; avoid dorsal nerve injury; and permit direct visualisation of pump placement. However, with this approach, the reservoir is either placed blindly into the retropubic space, which can result in visceral injury in patients with a history of major pelvic surgery (mainly radical cystectomy) or a separate incision in the abdomen is placed under direct vision. A recent systematic review comparing the satisfaction and complication rates of the different surgical approaches showed that there is no specific advantage between the two, but rather it is recommended that the surgeon has knowledge of both techniques and is capable of tailoring the incision strategy for complex cases [572]. Revision surgery is associated with poorer outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED with appropriate counselling [352, 561, 567, 573-581]. In patients with favourable oncologic prognosis after RP for PCa, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established and definitive role to address both problems [352, 561, 582-584]. Structured psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [585].

5.6.2.9.4 Penile prostheses implantation: complications

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used 3-piece prosthesis (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after five years of follow-up [561, 586, 587]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and in high volume centres, although the definition of a high volume centre still needs clarity [588-591]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [561, 588, 592-595]. Methods that decrease infections include using coated prostheses and strictly adhering to surgical techniques that avoid prolonged wound exposure and skin contact minimisation (i.e. no-touch technique). Techniques that might prevent penile prostheses infection but lack definitive evidence include the use of prolonged post-operative antibiotics (> 24 hours), shaving with clippers, and prepping with chlorhexidine-alcohol [596]. Furthermore, identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine prior to surgery has been shown to reduce the incidence of surgical site infection after surgery from 4.4% to 0.9% in a placebo-controlled randomised trial [597]. On the whole, growing evidence suggests that the risk of penile prosthesis infection has reduced over the last few decades with device improvement and surgical expertise [598].

Higher-risk populations include patients undergoing revision surgery, those with impaired host defences (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [561, 567, 589, 599-601]. A recent large database-study showed that diabetes mellitus is a risk factor for penile prostheses infection, highlighting the need for an optimal patient selection other than raising the question of whether lowering this risk by optimising glycaemic control before surgery [602]. Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients [603].

Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [589, 600, 604, 605]. A final recommendation on how to proceed after removal in this setting cannot be given. The majority of revisions are secondary to mechanical

failure and combined erosion or infection [594, 596]. Ninety-three percent of cases are successfully revised, providing functioning penile prosthesis [588, 589, 604, 606, 607].

Besides infection and mechanical failure, impending erosion involving the distal lateral corpora, urethra, glans or other structures can occur in 1-6% of cases after surgery [608]. Similarly glans ischaemia and necrosis have been reported in about 1.5% of patients [609]. Risk factors for these serious complications are higher in those patients with significant vascular impairment, such as patients with diabetes, or who have undergone concomitant lengthening procedures.

5.6.2.9.4.1 Conclusions penile prostheses implantation

Penile implants are an effective solution for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates [610]. There are also currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another.

Table 17: Penile prostheses models available on the market

Semi-rigid prostheses	**Inflatable prostheses**	
	Two-piece	Three-piece
AMS Tactra™ [Boston Scientific]	AMS Ambicor™ [Boston Scientific]	Titan ™ [Coloplast]
Genesis ™ [Coloplast]		Titan OTR NB ™ (Narrow base) [Coloplast]
		Titan Zero Degree ™
Tube ™ [Promedon]		AMS 700 CX ™ [Boston Scientific]
ZSI 100 ™ [Zephyr]		AMS 700 LGX ™ [Boston Scientific]
Virilis II ™ [Subrini]		AMS 700 CXR ™ [Boston Scientific]
		ZSI 475 ™ [Zephyr]

5.6.3 *Recommendations for the treatment of ED*

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to PDE5Is.	Weak
Use Cognitive Behaviour Therapy as psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than ED, including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to or at the same time as initiating erectile dysfunction (ED) treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapeutic options.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak
Use topical/intraurethral alprostadil as an alternative therapy to intracavernous injections in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices as a first-line therapy in well-informed patients with infrequent sexual intercourse and comorbidities requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/ pelvic surgery and other curative treatments for prostate cancer.	Weak

5.6.4 *Follow-up*

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

6. DISORDERS OF EJACULATION

6.1 Introduction

Ejaculation is a complex physiological process which is composed of emission and expulsion and is mediated by interwoven neurological and hormonal pathways [611]. Any interference with those pathways may cause a wide range of ejaculatory disorders (Table 18).

Table 18: Spectrum of ejaculation disorders

Premature ejaculation
Retarded or delayed ejaculation
Anejaculation
Painful ejaculation
Retrograde ejaculation
Anorgasmia
Haemospermia

6.2 Premature ejaculation

*6.2.1 **Epidemiology***

Historically, the main problem in assessing the prevalence of premature ejaculation (PE) has been the lack of a universally recognised definition at the time the surveys were conducted [172]. In this context, the highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLS) study [177]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that PE prevalence was as high as 20-30% based on the relatively low number of men who presented for treatment of PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question, asking if ejaculation occurred too early. The Internet-based survey PEPA [the PE Prevalence and Attitudes] revealed a 22.7% prevalence of PE (24.0% in the United States, 20.3% in Germany, and 20% in Italy), which did not vary significantly with age among men over 24 years of age [178]. According to the four PE subtypes proposed by Waldinger *et al.* [181], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (variable PE) and, 5.1% (premature-like ED or subjective PE) [179]. A prevalence of approximately 5% of acquired PE and lifelong PE in the general population is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency time of less than two minutes [185].

*6.2.2 **Pathophysiology and risk factors***

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety [612-616], penile hypersensitivity [617-623] and 5-hydroxytryptamine (HT) receptor dysfunction [624-629]. The classification of PE into four subtypes [181] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [630-632]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a very complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [633]. On the other hand, acquired PE may occur due to either psychological problems - such as sexual performance anxiety, psychological or relationship problems - and/or comorbid medical conditions, including ED, prostatitis and hyperthyroidism [634-636].

A significant proportion of men with ED also experience PE [188, 334]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the NHSLS, the prevalence of PE is not affected by age [177], unlike ED, which increases with age. Conversely, other data depicted an increased prevalence with ageing [637]; for instance, Verze *et al.* reported that PE prevalence based on the Premature Ejaculation Diagnostic Tool (PEDT) score (≥ 11) [638] proportionally increased with age [639]. Premature ejaculation is not affected by marital or income status [177, 639]. However, PE is more common in Black men, Hispanic men, and men from regions where the Islamic background is particularly common [176, 640] and may be higher in men with a lower educational level [177, 188]. Other risk factors may include a genetic predisposition [629, 641-644], poor overall health status and obesity [177], prostate inflammation [323, 645-648], low prolactin levels [649], higher testosterone levels [650], vitamin D and B12 deficiency [651, 652], diabetes [653, 654], metabolic syndrome [654, 655], lack of physical activity [656], emotional problems and stress [177, 657, 658], depressive symptoms [658], and traumatic sexual experiences [177, 188]. In the only published study on risk modification/prevention strategies [659], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients.

*6.2.3 **Impact of premature ejaculation on quality of life***

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse [257, 660, 661]. However, the negative impact of PE extends beyond sexual dysfunction. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [257, 662, 663]. Moreover, PE may impact on the partner's sexual functioning

and their satisfaction with the sexual relationship decreases with increasing severity of the patients' condition [664-666]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors (GSSAB) survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [188], with men more likely to seek treatment for ED than for PE [188]. In the PEPA survey, only 9% of men with self-reported PE consulted a doctor [178]. The main reasons for not discussing PE with their physician are embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [667, 668]. Physicians need to encourage their patients to talk about PE.

*6.2.4 **Classification***

There is still little consensus about the definition and classification of PE [669]. It is now universally accepted that "premature ejaculation" is a broad term that includes a number of concepts belonging to the common category of PE. The most recent definition comes from the International Classification of Diseases 11th Revision, where PE was renamed as Early Ejaculation [670]: *"Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress."*

This definition includes five categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, unspecified.

In the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), PE is defined as a sexual disorder with:

- consistent ejaculation within one minute or less of vaginal penetration;
- over a period of at least six months;
- experienced 75%-100% of the time;
- the condition results in clinically significant distress, sexual frustration, dissatisfaction, or tension between partners;
- this condition is not better accounted for by another non-sexual mental disorder, medication or illicit substance use, or medical condition [671].

The EAU Guidelines have adopted the definition of PE which has been developed by the International Society for Sexual Medicine (ISSM) as the first evidence-based definition [672]. According to this definition, PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

- Ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE).
- The inability to delay ejaculation on all or nearly all vaginal penetrations.
- Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Two more PE syndromes have been proposed [631]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may help in overcoming the limitations of each individual definition and it may support a more flexible view of PE for patient stratification, diagnosis and treatment [673].

6.2.5 Diagnostic evaluation

Diagnosis of PE is based on the patient's medical and sexual history [185, 674, 675]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [334, 676]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [677]. There are several overlapping definitions of PE, with four shared factors (Table 19), resulting in a multi-dimensional diagnosis [678].

Table 19: Common factors in different definitions of PE

Time to ejaculation assessed by IELT
Perceived control
Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction

6.2.5.1 Intravaginal ejaculatory latency time

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [679, 680], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [681, 682]. Moreover, some men may experience PE in their non-coital sexual activities (e.g. during masturbation, oral sex or anal intercourse) thus measuring IELT will not be suitable for their assessment. IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [683]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation) [684]. In everyday clinical practice, self-estimated IELT is sufficient [173]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [685]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) scale on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all, to 4 = extremely). However, self-estimated IELT may be over-estimated by approximately one minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [686].

On the other hand, measurement of IELT with a calibrated stopwatch is mandatory in clinical trials. For any drug treatment study of PE, Waldinger *et al.* suggested using geometric mean IELT instead of using arithmetic mean IELT as the distributed IELT data are skewed. Otherwise, any treatment-related ejaculation delay may be overestimated if the arithmetic mean IELT is used instead of the geometric mean IELT [687].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): A five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [688]. A total score > 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of < 8 indicates a low likelihood of PE.

- Arabic Index of Premature Ejaculation (AIPE): A seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction of the patient and partner, anxiety or depression [689]. A cut-off score of 30 (range of scores 7-35) discriminated PE diagnosis best. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Although it is widely used, some studies reported a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. Only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [274]. On the contrary, a recent study has shown that the PEDT was highly valid in screening the presence of evidence-based-defined lifelong PE and acquired PE [62]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [690].

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [682], Index of Premature Ejaculation (IPE) [691] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [692]. Currently, their role is optional in everyday clinical practice.

6.2.5.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a focused examination of the urological, endocrine and neurological systems to identify underlying medical conditions

associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [674].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

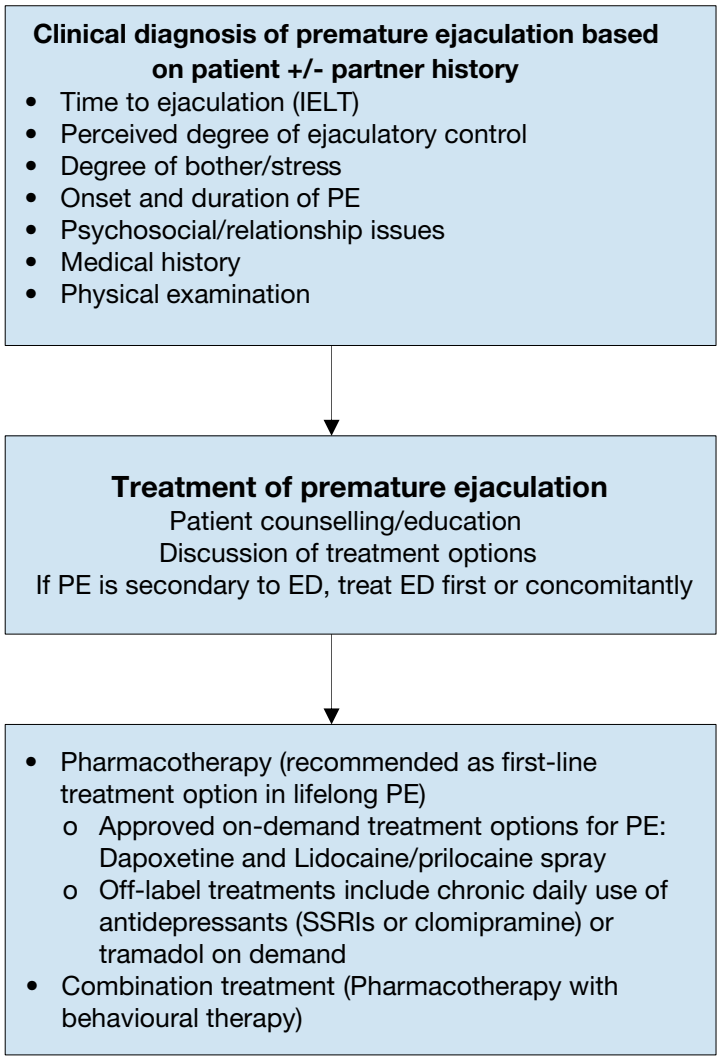
Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction (ED).	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

*6.2.6 **Disease management***

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient's expectations thoroughly. Pharmacotherapy must be considered as the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety, hyperthyroidism) must be the initial goal for patients with acquired PE [185]. Various behavioural techniques may be beneficial in treating variable and subjective PE [693]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [694, 695]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [696].

In lifelong PE, behavioural techniques are not recommended alone, and pharmacotherapy must be considered as the basis of treatment [185]. Dapoxetine (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA [697]. Moreover, the metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formula to be officially approved for the on-demand treatment of lifelong PE by the EMA in the European Union [698]. All other medications used in PE are off-label indications [699]. Daily or on-demand use of selective serotonin re-uptake inhibitors (SSRIs) and clomipramine, and on-demand topical anaesthetic agents have consistently shown efficacy in PE [700-703]. Long-term outcomes of pharmacological treatments are unknown. An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided, and a treatment algorithm is presented (Figure 7).

Figure 7: Management of premature ejaculation*



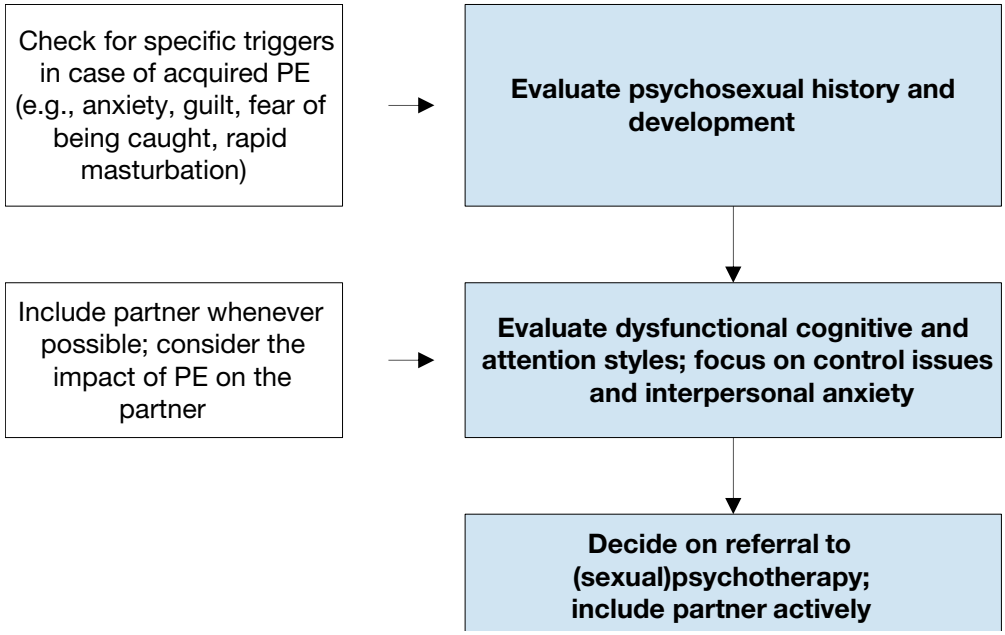
* Adapted from Lue *et al.* 2004 [704].
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Only a few studies have addressed the psychological factors underpinning PE. Men with PE were shown to present dysfunctional responsibility attribution patterns regarding their sexual experience. These men blamed themselves for their dysfunctional sexual response, even when the negative sexual outcome was unrelated to early ejaculation; additionally, they took less credit for any positive sexual experience they might have [705, 706]. In addition to this style of internalised blame, men with PE were found to focus on bodily sensations and partners' reactions during sex, in order to monitor potential signs of threat to their sexual performance. This monitoring process denotes a dysfunctional cognitive and attention style that contributes to the maintenance of PE [407]. Premature ejaculation has been further related to increased levels of anxiety, including social anxiety [407, 684]. Yet, it is not known whether anxiety is a precursor or a consequence of PE [613]. Furthermore, the negative impact of PE on the couple has been consistently mentioned. Female partners of men with PE present with an increased likelihood of sexual dysfunction [707]; the intimate sphere, as well as the overall relationship quality, was compromised by PE [696]. An important trigger for seeking help in PE is partner dissatisfaction and the negative impact of PE on the general QoL of the couple [708]. Accordingly, psychosexual interventions, whether these are behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem solving within the couple [693]. Is worth noting, however, that psychosexual interventions alone regarding PE lack empirical support. Behavioural therapy may be most effective when used to 'add value' to medical interventions. A combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised

trial [694]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

Figure 8: Key aspects for psychosexual evaluation



6.2.6.1.1 Recommendation for the assessment and treatment (psychosexual approach) of PE

Recommendations for assessment	**Strength rating**
Consider sexual history and psychosexual development.	Strong
Consider anxiety, interpersonal anxiety; focus on control issues.	Strong
Include partner if available; check for the impact of PE on the partner.	Strong
Recommendations for treatment (psychosexual approach)	
Use behavioural, cognitive and/or couple therapy approaches.	Weak

6.2.6.2 Pharmacotherapy

6.2.6.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE [699]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [709]. Dapoxetine has been investigated in 6,081 subjects to date [710]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA. Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with a baseline average IELT of < 0.5 minutes [697, 711, 712].

In RCTs, dapoxetine, 30 mg or 60 mg one to two hours before intercourse, was effective on IELT and increased ejaculatory control, decreased distress, and increased satisfaction [713]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [697, 714, 715]. Treatment-related side-effects were dose-dependent and included nausea, diarrhoea, headache, and dizziness. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [173]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [716, 717]. Moreover, dapoxetine is found to be safer compared with formal anti-depressant compounds which are used for the treatment of PE [718].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [719]. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine and dose-titration must be considered [720]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope has been proven manageable with adequate risk minimisation measures [721]. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [722].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I in order to extend the time until ejaculation and minimise the risk of ED due to dapoxetine treatment. Phase 1 studies of dapoxetine have confirmed that it does not have any pharmacokinetic interactions with PDE5I (i.e. tadalafil 20 mg and sildenafil 100 mg) [723]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [724]. A recent RCT including PE patients without ED, demonstrated that combination of dapoxetine with sildenafil can significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse effects [725]. Efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [726].

6.2.6.2.2 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [727, 728] under excitatory or inhibitory influences from the brain and the periphery [653]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT_{1B} and 5-HT_{2C} receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT_{1A} receptors precipitates ejaculation [729].

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore are widely used 'off-label' for PE since the 1990s [730]. For depression, SSRIs must be given for one to two weeks to be effective in PE [729]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT_{1A} and 5-HT_{1B} receptors [731]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar efficacy, whereas paroxetine exerts the strongest ejaculation delay [679, 732, 733].

Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [734, 735]. In a recent RCT, on-demand use of clomipramine 15 mg, two to six hours before sexual intercourse was found to be associated with IELT fold change and significant improvements in PRO measures in the treatment group as compared to the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19, $p < 0.05$). [736, 737]. The most commonly reported TEAEs were nausea in 15.7% of men and dizziness in 4.9% [736, 737].

Several SRs and meta-analyses of drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [679, 700-703]. Based on these meta-analyses, SSRIs may increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [738, 739].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks as receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after six to twelve months [734]. Common TEAEs of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; TEAEs are usually mild and gradually improve after two to three weeks of treatment [711, 734]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of the risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged eighteen years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be associated with a SSRI withdrawal syndrome [173]. Moreover, PE patients who are trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [740-743].

6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [744].
Several trials [620, 745, 746] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Meta-analyses confirmed the efficacy and safety of these agents for the treatment of PE [747, 748].

6.2.6.2.3.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine/prilocaine cream increased the IELT from one minute in the placebo group to 6.7 minutes in the treatment group [749]. In another randomised, double blind, placebo-controlled trial, lidocaine/prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes, while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [750]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. Moreover, these anaesthetic creams/gels may be transferred to the partner and result in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream on their penises. Alternatively, the penis can be washed clean of any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples who are wanting to achieve pregnancy should not use topical lidocaine/prilocain containing substances [751].

6.2.6.2.3.2 Lidocaine-prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) which has been officially approved by the EMA for the treatment of males with lifelong PE [752]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [753], without absorption through the penile shaft skin [754].

To date, one phase 2 proof-of-concept [754] and two phase 3 RCTs [755, 756] have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and the Index of Ejaculatory Control (IEC) of patients with primary PE, along with an improvement in scores assessing treatment satisfaction (IPE) [755, 756]. Based on these data, according to the patient information leaflet [757], the recommended dose of lidocaine/prilocaine spray is one dose (namely three sprays) to be applied on the glans penis at least five minutes before sexual intercourse [758]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over three months, with a month by month improvement through the course of the treatment in long term studies [759]. A low incidence of local TEAEs in both patients and partners have been reported, including genital hypoaesthesia (4.5% and 1.% in males and females partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [757, 760].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [761]. This mechanism of action distinguishes tramadol from other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of five to seven hours.

A large, randomised, double-blind, placebo-controlled, multicentre twelve-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [762]. A bioequivalence study had previously been performed demonstrating equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < two minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. However, in May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [763]. The tolerability during the twelve-week study period in men with PE was acceptable. Several other studies also reported that tramadol exhibits a significant dose-related efficacy and side-effects over placebo for the treatment of PE [764]. Moreover, the efficacy and safety of tramadol have been confirmed in SRs and meta-analyses [765-767].

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

There is one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo in men with PE [768]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation. Another RCT demonstrated that once-daily use of 5 mg tadalafil for six weeks is effective in improving PROs and is well tolerated by patients with PE [769].

Several open-label studies showed that PDE5Is combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction versus paroxetine alone [770];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly versus sertraline alone [771];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [772];
- Sildenafil combined with dapoxetine (30 mg.) improved IELT, satisfaction scores and PEDT vs. dapoxetine, paroxetine or sildenafil monotherapy [725];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction versus paroxetine and tadalafil alone [773];
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction versus behavioural therapy alone [774].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [775, 776]. However, some meta-analyses demonstrated that the combined use of SSRIs and PDE5Is may be more effective as compared with SSRIs or PDE5Is monotherapy [702, 777-781].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research for other treatment options. Considering the abundant α1a-adrenergic receptors in seminal vesicles and the prostate, and the role of sympathetic system in the ejaculation physiology, the efficacy of selective α-blockers in the treatment of PE has been assessed [782-784]. A recent study demonstrated that wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [785]. The efficacy of acupuncture was compared to dapoxetine for the treatment of PE and although acupuncture showed a significant ejaculation-delaying effect, this was less effective as compared with that of dapoxetine [786].

Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE has initially been proposed by Korean researchers in 2004 [787], and since then has gained popularity mainly in Asian countries [788, 789]. In a randomised controlled cross-over study, hyaluronic acid glans injection were found to be a safe treatment with a modest but significant increase in IELT [790]. However, these procedures may result in serious complications and more safety studies must be conducted before recommending this treatment to PE patients [791].

Considering the importance of central oxytocin receptors in ejaculation reflex, several researchers assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [792]. Epelsiban [793] and cligosiban [794-796] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [796].

*6.2.7 **Summary of evidence on the epidemiology/aetiology/pathophysiology of PE***

Summary of evidence	**LE**
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and the eutectic lidocaine/prilocaine spray (a topical desensitising agent) that are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a

*6.2.8 **Recommendations for the treatment of PE***

Recommendations	**Strength rating**
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Stong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

6.3 Retarded or Delayed Ejaculation

*6.3.1 **Definition and classification***

The American Psychiatric Association defines DE as requiring one of two symptoms as follows: marked delay, infrequency, or absence of ejaculation on 75-100% of occasions, that persists for at least six months, and which causes personal distress [671]. Delayed ejaculation is a medical and/or psychological condition that is not associated with other types of psychiatric diagnosis. This definition is paramount to understanding the psychologic implications and treatment strategies for DE.

*6.3.2 **Pathophysiology and risk factors***

The causes of DE can be psychological, organic (e.g. incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g. selective serotonin re-uptake inhibitors (SSRIs), antihypertensive drugs, or antipsychotics) (Table 20) [797, 798]. Although low testosterone levels has been considered as a risk factor in the past [53, 650], more contemporary studies did not confirm any association between ejaculation times and serum testosterone levels [799, 800].

Table 20: Etiological Causes of Delayed Ejaculation and Anejaculation [801]

Ageing Male	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Mullerian duct cyst Wolfian duct abnormalities Prune Belly Syndrome Imperforate Anus Genetic abnormalities
Anatomic causes	Transurethral resection of prostate Bladder neck incision Circumcision Ejaculatory duct obstruction (can be congenital or acquired)
Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/Inflammation	Urethritis Genitourinary tuberculosis Schistosomiasis Prostatitis Orchitis
Endocrine	Hypogonadism Hypothyroidism Prolactin disorders
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers Selective serotonin reuptake Inhibitors
Psychological	Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

*6.3.3 **Investigation and treatment***

Patients should have a full medical and sexual history performed along with a detailed physical examination when evaluating for DE. It is not uncommon for clinicians to feel uncomfortable with the level of sexual

information that is warranted in obtaining a full sexual history. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; the quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); the partners' assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history taking [802]. Investigation by a sexual therapist is often required to help get a complete psychological evaluation. It is incumbent on the clinician to diagnose medical pathologies that cause or contribute to DE, such as assessing the hormonal milieu, anatomy, and overall medical condition. Good communication between the sexual therapist and medical practitioner is vital to successful diagnosis and treatment of DE.

6.3.3.1 Psychological aspects and intervention

There is scarce literature on the psychological aspects relating to DE, as well as on empirical evidence regarding psychological treatment efficacy. Findings on psychological aspects revealed that men with DE showed a strong need for controlling their sexual experiences. Delayed ejaculation was associated with difficulties surrendering to sexual pleasure during sex, i.e., the sense of *letting go* [803], which denotes a psychological underlying mechanism influencing the reaching of orgasm [804]. As for psychological treatments, these may include, but are not limited to: increased genital-specific stimulation; sexual education; role-playing on his own and in front of his partner; retraining masturbatory practices; anxiety reduction on ejaculation and performance; and, re-calibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality) [802]. A basic understanding of the sexual cycle for their respective partners can assist men and women in managing expectations and in evaluating their own sexual practices. Masturbation techniques that are either solo or partnered can be considered practice for the "real performance" which can eventually result in greater psychosexual arousal and orgasm for both parties [192]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be quite supportive if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. Techniques geared towards reduction of anxiety are important skills that can help overcome the performance anxiety as this can often interrupt the natural erectile through orgasmic progression. Referral to a sexual therapist, psychiatrist or psychologist is appropriate and often warranted.

6.3.3.2 Pharmacotherapy

Pharmacologic agents have been used to treat DE with varied success. Unfortunately, there is no FDA or EMA approved medications to treat DE, as most of the cited research is based on case-cohort studies that have not been randomised, blinded, or placebo-controlled. Many drugs have been used as both primary treatments and/or as antidotes to other medications that can cause DE. A recent survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion, and oxytocin for treatments [805]. However, this survey measured the anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [801].

6.4 Anejaculation

*6.4.1 **Definition and classification***

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [806]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [807].

*6.4.2 **Pathophysiology and risk factors***

Generally, anejaculation shares the similar aetiologic factors with DE and retrograde ejaculation (see Table 20).

*6.4.3 **Investigation and treatment***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not very effective. In all these cases, and in men who have a spinal cord injury, vibro-stimulation (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, vibro-stimulation evokes the ejaculation reflex [808], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an *in-vitro* fertilisation program whenever fathering is desired. If vibro-stimulation has failed, electro-ejaculation can be the therapy of choice [809]. When electro-ejaculation fails or cannot be carried out, other sperm retrieval techniques may be used [810]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [811], respectively.

6.5 Painful Ejaculation

*6.5.1 **Definition and classification***

Painful ejaculation is a condition where a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [812].

*6.5.2 **Pathophysiology and risk factors***

Many medical conditions can result in painful ejaculations, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [813], sexual neurasthenia [814], sexually transmitted diseases [812, 815], inflammation of the prostate [210, 816], PCa [817, 818], BPH [208], prostate surgery [819, 820], pelvic radiation [821], herniorrhaphy [822] and antidepressants [823-825], among others. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculations [826, 827]. Psychological issues may also be the cause of painful ejaculations, especially if the patient does not experience this problem during masturbation [828].

*6.5.3 **Investigation and treatment***

Treatment of painful ejaculation must be tailored according to the underlying cause, if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [823, 824, 829] or the prescription of appropriate medical treatment (antibiotics, α-blockers, anti-inflammatory agents) may ameliorate painful ejaculations. Behavioural therapies, myorelaxants, antidepressant pelvic floor exercises, anticonvulsant drugs and/or opioids may be administered if no underlying cause can be identified [830, 831].

6.5.3.1 Surgical intervention

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct and neurolysis of the pudendal nerve have been suggested [832, 833]. However, there is no strong evidence supporting that surgical therapy improves painful ejaculations and therefore must be used with caution.

6.6 Retrograde ejaculation

*6.6.1 **Definition and classification***

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation, as a result of semen passing backwards through the bladder neck into the bladder. Patients may experience a normal, or decreased, orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence [812].

*6.6.2 **Pathophysiology and risk factors***

The process of ejaculation requires complex coordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [834]. Upon ejaculation, sperm are rapidly conveyed along the vas deferens and into the urethra via the ejaculatory ducts. From there, the semen progresses in an antegrade fashion, in part maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, coordinated by a centrally mediated reflex [834]. Closure of the bladder neck and seminal emission are initiated via the sympathetic nervous system from the lumbar sympathetic ganglia and subsequently hypogastric nerve. Prostatic and seminal vesicle secretion, as well as contraction of the bulbocavernosal, ischiocavernosal and pelvic floor are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [834].

Any factor, which disrupts this reflex and inhibits the bladder neck (internal vesical sphincter) contraction may lead to retrograde passage of semen into the bladder. These can be broadly categorised as pharmacological, neurogenic, anatomic and endocrinal causes of retrograde ejaculation (Table 21).

Table 21: Aetiology of retrograde ejaculation [797]

Neurogenic	Spinal cord injury Cauda equina lesions Multiple Sclerosis Autonomic neuropathy Retroperitoneal lymphadenectomy Sympathectomy or aortoiliac surgery Prostate, colorectal and anal surgery Parkinson´s disease Diabetes mellitus Psychological/behavioural
Urethral	Ectopic ureterocele Urethral stricture Urethral valves or verumontaneum hyperplasia Congenital dopamine beta-hydroxylase deficiency
Pharmacological	Antihypertensives, thiazide diuretics Alpha-1-adrenoceptor antagonists Antipsychotics and antidepressants
Endocrine	Hypothyroidism Hypogonadism Hyperprolactinaemia
Bladder neck incompetence	Congenital defects/dysfunction of hemitrigone Bladder neck resection (transurethral resection of the prostate) Prostatectomy

*6.6.3 **Disease management***

Medical and surgical strategies exist for the treatment of retrograde ejaculation. In recent years the reliance on medical treatment as first-line management has become common practice.

6.6.3.1 Pharmacological

Sympathomimetics stimulate the release of noradrenaline as well as activating α- and β-adrenergic receptors, resulting in closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [835]. Unfortunately, as time progresses their effect diminishes [836]. Many of the studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size with some represented by case reports.

A double-blind controlled study randomised patients to one of four α-adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine, and pseudoephedrine) with or without histamine. The patients suffered from the failure of ejaculation following retroperitoneal lymphadenectomy. They found that four days of treatment prior to ejaculation was most effective and that all the adrenergic agonists restored antegrade ejaculation [835]. In a SR, the efficacy of this group of medications was found to be 28% [197]. The side-effects of sympathomimetics include dryness of mucous membranes and hypertension.

The use of antimuscarinics has been described, including brompheniramine maleate and imipramine, as well as in combination with sympathomimetics. The calculated efficacy of antimuscarinics or antimuscarinics in combination with sympathomimetics are 22% versus 39%, respectively [197]. Combination therapy appears to be more effective although statistical analysis is not yet possible due to the small sample sizes.

6.6.3.2 Management of infertility

Infertility has been the major concern of patients with retrograde ejaculation. Beyond the use of standard sperm retrieval techniques, such as testicular sperm extraction (TESE), three different methods of sperm acquisition have been identified for the management of infertility in the patient suffering from retrograde ejaculation. These include; i) centrifugation and resuspension of post-ejaculatory urine specimens; ii) the Hotchkiss (or modified Hotchkiss) technique; and, iii) ejaculation on a full bladder.

1. *Centrifugation and resuspension.* In order to improve the ambient conditions for the sperm, the patient is asked to either increase their fluid intake or to take sodium bicarbonate to dilute or alkalise

the urine respectively. Afterwards, a post-orgasmic urine sample is collected by either introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids employed are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's, phosphate-buffered medium and the patients urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A SR of the literature in couples with the male partner suffering from retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [197].

2. *Hotchkiss method*. The Hotchkiss method involves emptying the bladder prior to ejaculation using a catheter and then washing out and instilling a small quantity of Lactated Ringers to improve the ambient conditions of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [837]. Modified Hotchkiss methods involve a variance in the instillation medium. Pregnancy rates per cycle were 24% per cycle (0-100%) [197].
3. *Ejaculation on a full bladder*. Few papers have described results from this technique [838, 839]. The patient is encouraged to ejaculate on a full bladder and semen is suspended in Baker's Buffer. The pregnancy rate in the two studies which included only five patients in total was 60% [197].

6.7 Anorgasmia

*6.7.1 **Definition and classification***

Anorgasmia is the perceived absence of orgasm and can give rise to anejaculation. Regardless of the presence of ejaculation, anorgasmia can be a lifelong (primary) or acquired (secondary) disorder [840].

*6.7.2 **Pathophysiology and risk factors***

Primary anorgasmia is defined as starting from the men's first sexual intercourse and lasts throughout his life, while for secondary anorgasmia patients should have a normal period before the problem starts [841]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered the risk factors for anorgasmia. There are only a few studies available that describe anorgasmia alone and generally it has been considered as a symptom linked to ejaculatory disorders especially with DE and therefore they are believed to share the same risk factors. However, psychological factors are considered to be responsible for 90% of anorgasmia problems [842]. Causes of delayed orgasm and anorgasmia are shown in Table 22 [841].

Table 22: Causes of delayed orgasm and anorgasmia [841]

Endocrine	Testosterone deficiency Hypothyroidism
Medications	Antidepressants Antipsychotics Opioids
Psychosexual Causes	
Hyperstimulation	
Penile sensation loss	

*6.7.3 **Disease management***

The psychological/behavioural strategies for anorgasmia are similar for DE. The patient and his partner should be examined physically and psychosexually in detail including determining the onset of anorgasmia, medication and disease history, questioning penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and thyroid-stimulating hormone (TSH) levels. Patients who have loss of penile sensitivity require further investigations [841].

6.7.3.1 Psychological/behavioural strategies

Lifestyle changes can be recommended to affected individuals including: changing masturbation style; taking steps to improve intimacy; and, decreasing alcohol consumption. Several psychotherapy techniques or their combinations have been offered, including alterations in arousal methods, reduction of sexual anxiety, role-playing an exaggerated orgasm and increased genital stimulation [804, 843]. However, it is very difficult to determine the success rates from the literature.

6.7.3.2 Pharmacotherapy

Several drugs have been reported to reverse anorgasmia, including cyproheptadine, yohimbine, buspirone, amantadine and oxytocin [844-849]. However, these reports are generally from case-cohort studies and drugs

have limited efficacy and significant adverse effect profiles. Therefore current evidence is not strong enough to recommend drugs to treat anorgasmia.

6.7.3.3 Management of infertility

If patients fail the treatment methods mentioned above, penile vibratory stimulation, electro-ejaculation or TESE are the choice of options for sperm retrieval in anorgasmia cases [841].

6.8 Haemospermia

6.8.1 Definition and classification

Haemospermia is defined as the appearance of blood in the ejaculate. Although it is often regarded as a symptom of minor significance, blood in the ejaculate causes great anxiety in many men and may be indicative of underlying pathology [213].

6.8.2 Pathophysiology and risk factors

Several reasons of haemospermia have been acknowledged and can be classified into the following sub-categories; idiopathic, congenital malformations, inflammatory conditions, obstruction, malignancies, vascular abnormalities, iatrogenic/trauma and systemic causes (Table 23) [850].

Table 23: Pathology associated with haemospermia [850]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condylomata of urethra and meatus, urinary tract infections
Obstruction	Prostatic, SV and ejaculatory duct calculi, post inflammatory, seminal vesicle diverticula/cyst, urethral stricture, utricle cyst, BPH
Tumours	Prostate, bladder, SV, urethra, testis, epididymis, melanoma
Vascular	Prostatic varices, prostatic telangiectasia, haemangioma, posterior urethral veins, excessive sex or masturbation
Trauma/ iatrogenic	Perineum, testicle, instrumentation, post hemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, hemophilia, purpura, scurvy, bleeding disorders, chronic liver disease, renovascular disease, leukaemia, lymphoma, cirrhosis, amyloidosis
Idiopathic	-

The risk of any malignancy in patients presenting with haemospermia is approximately 3.5% (0-13.1) [851]. In an observational study of 300 consecutive patients over a 30-month period, 81% had no cause of their haemospermia identified. In those patients for whom a cause was identified, the diagnosis varied dependent upon the age of presentation. When the patients were divided into those under and those over 40 years of age, urinary tract infections were more common among younger patients compared to older patients (15% versus 10.3%). In the older group (> 40 years old), stones (2.2% versus 1.4%) and malignancy (6.2% versus 1.4%) were more common when compared with the younger cohort [60]. In the over 40 group, thirteen patients had PCa and one had a low-grade urethral carcinoma. In the under 40 group, one patient had testicular cancer [212].

6.8.3 Investigations

As with other clinical conditions, a systematic clinical history and assessment to help identify the reason of haemospermia is undertaken. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [213].

The basic examination of haemospermia should start with a thorough symptom-specific and systemic clinical history. The first step is to understand if the patient has true haemospermia. Pseudo-haemospermia may occur as a consequence of haematuria or even suction of a partner's blood into the urethra during copulation [812, 852, 853]. A sexual history should be taken to identify those whose haemospermia may be as a consequence of a sexually transmitted disease. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic disease such as hypertension, liver disease and coagulopathies should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bony pain. Examination of the patient should also include measurement of

the blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [854, 855].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, however, there is no consensus n this regard [850-852]. A urinalysis should be performed along with sending the urine for culture and sensitivities as well as microscopy. If tuberculosis or schistosomiasis is the suspected cause, the semen or prostatic secretions should be sent for analysis. A full sexually-transmitted disease screen including first void urine as well as serum and genitourinary samples should be taken and tested for *Chlamydia, Ureaplasma* and *Herpes*. Using this strategy, it may be possible to find an infectious agent among patients who would have been labelled as idiopathic haemospermia [856].

A serum PSA should be taken in men over the age of 40 years who have been appropriately counselled [214]. Blood work including a full blood count, liver function tests, and a clotting screen should be taken to identify systemic diseases. The question of whether further investigation is warranted depends on clinician judgment, patient age and an assessment of risk factors [850]. Digital rectal examination should also be performed and the meatus re-examined after DRE for the presence of bloody discharge [857]. Detection of a palpable nodule in the prostate is of importance as an association between haemospermia and PCa has been postulated although not completely proven.

Magnetic Resonance Imaging is being increasingly used as a definitive means to investigate haemospermia. The multiplanar ability of MRI to accurately represent structural changes in the prostate, seminal vesicles, ampulla of vas deferens, and ejaculatory duct has enabled the modality to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [858]. The addition of an endorectal coil can improve the diagnostic accuracy for identifying the site and case of haemorrhage [859].

The use of cystoscopy has been included in the majority of suggested investigation protocols in patients with high-risk features (patients who are refractory to conservative treatments and patients with persistent haemospermia). It can provide invaluable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia such as although not limited to; polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [860, 861].

With the advancement of optics, the ability to create ureteroscopes of diameters small enough to allow insertion into the ejaculatory duct and seminal vesicles has been made possible [862]. In a prospective study of 106 patients with prolonged haemospermia patients underwent both transrectal US and seminal vesiculoscopy. With both modalities combined, diagnoses were made in 87.7% of patients. When compared, head-to-head, the diagnostic yield for TRUS versus seminal vesiculoscopy was 45.3% versus 74.5%, respectively ($p < 0.001$) [863].

Melanospermia that is a consequence of malignant melanoma involving the genitourinary tract is a very rare condition and has also been described in two case reports [864, 865]. Chromatography of the semen sample can be used to distinguish the two by identifying the presence of melanin if needed.

6.8.4 ***Disease management***

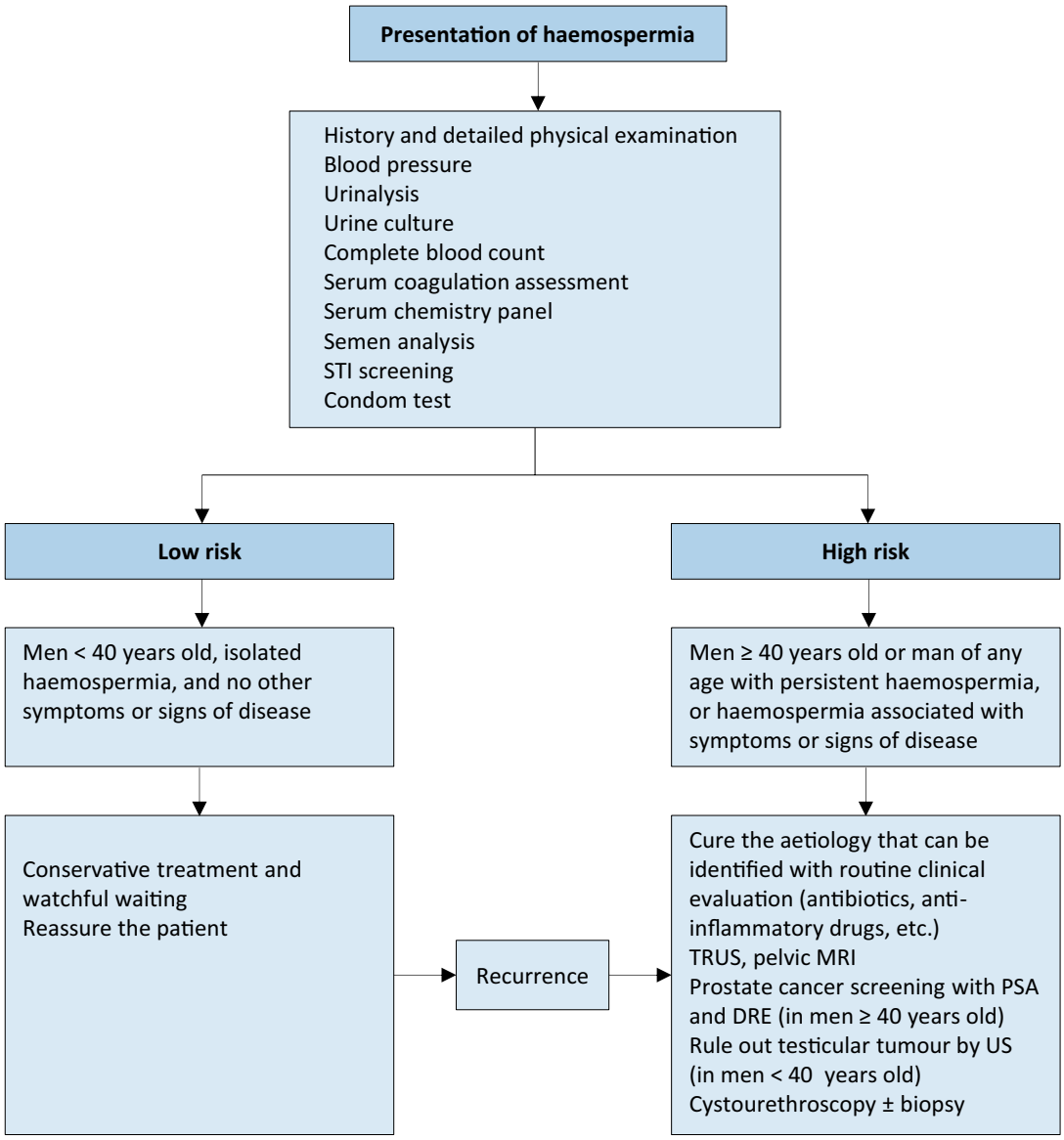
Conservative management is generally the primary treatment option when the patients are younger than 40 years of age and have a single episode of haemospermia. The primary goal of the treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [213, 850].

Patients with recurrent haemospermia and who are middle-aged, warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostate varices or angiodyplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [213]. Ejaculatory duct obstruction is managed by a transurethral incision at the duct opening [866, 867]. Systemic conditions should be treated appropriately [851, 853, 868, 869].

Defining a management algorithm for haemospermia is based on the patient age and degree of haemospermia. Patients will often find the presence of blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), whilst at the same time preventing over investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these pathologies are not commonly found after investigations have been

undertaken. However, men may be stratified into higher risk groups according to a number of factors including: men over 40 years of age, recurrent or persistent haemospermia, actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based upon the literature, a management algorithm is proposed (Figure 9) [851, 853, 868, 869].

Figure 9: Management algorithm for haemospermia [851, 853, 868, 869]



STI = Sexually transmitted infections; PSA = Prostate specific antigen; DRE = Digital rectal examination; US = Ultrasonography; TRUS = Transrectal ultrasonography; MRI = Magnetic resonance imaging.

6.9 Recommendations for the management of recurrent haemospermia

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Men ≥ 40 years of age with persistent haemospermia should be screened for prostate cancer.	Weak
Consider non-invasive imaging modalities (TRUS, MRI) in men ≥ 40 years of age or men of any age with persistent or refractory heamospermia.	Weak
Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive.	Weak

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition and classification

It has been always a challenge to define sexual desire properly because it has a complicated nature and it can be conceptualised in many different ways. According to the ICD-10, lack or loss of sexual desire should be the principal problem and no other sexual problems accompanying it such as ED [870]. In the DSM-V, male hypoactive sexual desire disorder was defined as "the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity". The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual's life [671]. According to the fourth International Consultation on Sexual Medicine, the definition of male hypoactive sexual desire disorder was proposed as a "persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)" [871].

7.2 Pathophysiology and risk factors

Several aetiological factors are considered to contribute to the pathophysiology of LSD. Levine proposed three components of sexual desire as drive (biological), motivation (psychological) and wish (cultural) [872]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [873].

*7.2.1 **Psychological aspects***

The endorsement of negative thoughts during sexual intercourse (i.e., concerns about erection, lack of erotic thoughts, and restrictive attitudes toward sexuality) predicted LSD in men [874]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving erection), characterised men with LSD as opposed to women with the same condition [875]. Psychological models testing the interplay role between biopsychosocial factors revealed that reduced male sexual desire was best predicted by negative thoughts and emotions during sex, more than general psychopathology symptoms or age [876-878]. Similarly, having a low confidence achieving erection, no attraction toward the partner, living in long-term relationships, and stress resulting from work were predictors of LSD in men [879]. On the other hand, relationship factors such as marital satisfaction, cohesion or display of affection received little support [874, 879]. Even so, it is worth noting that, despite LSD being less common in men than in women [871], it is the most frequent complaint in couples' therapy [880]. Therefore, the role of relationship factors cannot be completely ruled out. In addition, anxiety proneness has been associated with LSD in men and is expected to shift men's attention from erotic cues to worrying thoughts, thereby decreasing sexual desire [881].

*7.2.2 **Biological aspects***

Testosterone seems to be essential for a man's sexual desire; however, sexual desire does not directly relate with the circulating level of testosterone, especially in older men [882]. The biological and psychology components that take place in the pathophysiology of LSD are shown in Table 24 [873, 883]. In addition to these factors, there have been some speculations on the role of thyroid and oxytocin hormones [634, 884].

Table 24: The list of common causes of low sexual desire in men [873, 883]

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome
Renal failure
Coronary disease and heart failure
Ageing
HIV
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

*7.2.3 **Risk factors***

In an international survey aimed at estimating the prevalence and correlates of sexual problems in 13,882 women and 13,618 men from 29 countries (Global Study of Sexual Attitudes and Behaviours), risk factors for male LSD were age between 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that aging reduces sex, divorce in the past three years, financial problems in the last three years, major depression, being worried about the future of relation and less than one sexual relation in a week [188].

7.3 Diagnostic work-up

*7.3.1 **Assessment questionnaires***

Sexual Desire Inventory (SDI) is a scale aimed at evaluating different components influencing the development and expression of sexual desire [885]. This self-administered questionnaire consists of fourteen questions which weigh the strength, frequency, and significance of an individual's desire for sexual activity with others and by themselves. The SDI suggests that desire can be split into two categories: dyadic and solitary desire. While dyadic desire refers to "interest in or a wish to engage in sexual activity with another person and desire for sharing and intimacy with another", solitary desire refers to "an interest in engaging in sexual behaviour by oneself, and may involve a wish to refrain from intimacy and sharing with others" [885].

*7.3.2 **Physical examination and investigations***

Similar to other forms of sexual dysfunctions, a thorough medical and sexual history must be obtained from men who complain of LSD. The depressive symptoms of the patients must be assessed [886] and relationship problems (e.g., conflict with the sexual partner) must be questioned. In the presence of accompanying symptoms suggestive of endocrinological problems, circulating total testosterone [887], prolactin [888] and thyroid hormones [634] levels can be evaluated.

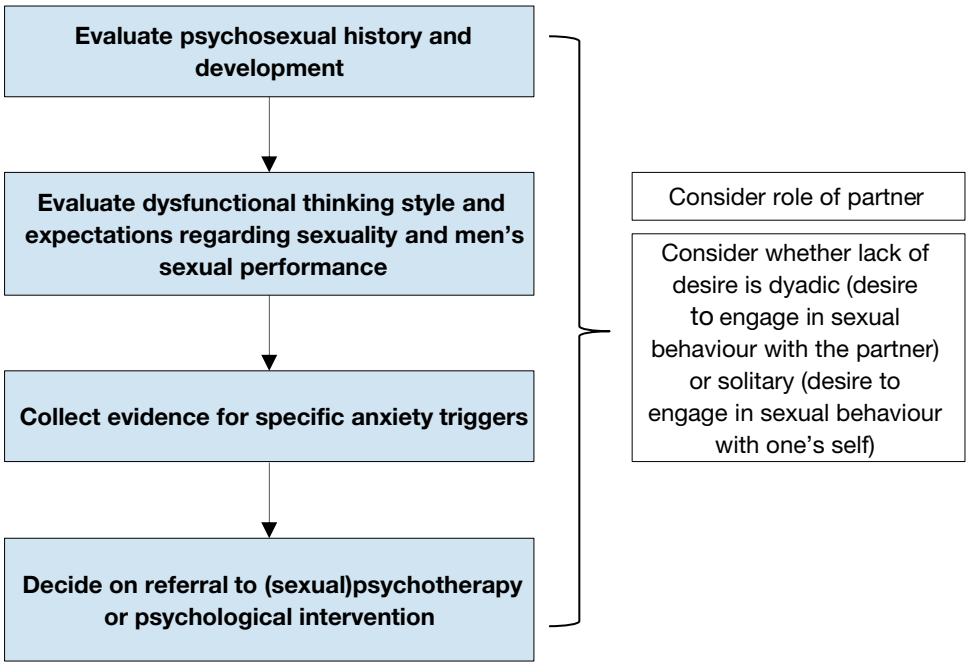
7.4 Disease management

The treatment of LSD should be tailored according to the underlying aetiology.

*7.4.1 **Psychological intervention***

Data on treatment efficacy ot psychological interventions are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for LSD in men (Figure 10) [406]. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the aging couple (thus including LSD) as a whole rather than treating the individual patient [889].

Figure 10: Flow-diagram of psychological evaluation of patients with low sexual desire



7.4.2 ***Pharmacotherapy***

Low sexual desire secondary to low testosterone levels can be treated with different formulations of testosterone administrations. The favourable effect of testosterone treatment on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [887]. The aim of the treatment should be to reach the physiological range of testosterone (see section 3.5).

Hyperprolactinaemia can also cause LSD and one of the most relevant aetiological factors is prolactin secreting pituitary adenomas. These adenomas can be easily diagnosed with MRI of the pituitary gland and can be treated with dopamine agonist agents [890]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism or diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however it should be kept in mind that antidepressants may negatively impact on sexual functioning; therefore, antidepressant compounds which have less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [891].

7.5 Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong
Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Replace testosterone if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

8. PENILE CURVATURE

8.1 Congenital penile curvature

8.1.1 Epidemiology/aetiology/pathophysiology

Congenital penile curvature (CPC) is a relatively rare condition, with a reported incidence of less than 1% [892], although there are studies which report higher prevalence rates of 4-10%, in the absence of hypospadias [893]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases, the curvature is ventral, but it can also be lateral and, more rarely, dorsal [894].

8.1.2 Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish a diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and more severe curvatures can make intercourse difficult or impossible. Physical examination during erection (alternatively photographic or preferably after intracavernous injection (ICI) of vasoactive drugs) is important to document the curvature and exclude other pathologies [894].

8.1.3 Disease management

The definitive treatment for this disorder remains surgical and can be deferred until after puberty, although results from a survey suggest that men with probable untreated ventral penile curvature reported more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems, therefore supporting surgical correction of CPC in childhood [895]. Surgical treatments for CPC generally share the same principles as in Peyronie's disease. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröeder, and others) with or without neurovascular bundle elevation (medial/lateral) and with or without complete penile degloving, have been described [896-905]. Other approaches are based on corporal body de-rotation proposed by Shaeer with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [906-909]. There are no direct comparative studies therefore, no single technique can be advocated as superior in terms of surgical correction.

8.1.4 Summary of evidence for congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination after ICI or a photograph during erection is mandatory for documentation of the curvature and exclusion of other pathologies.	3
There is no role for medical management of CPC. Surgery is the only treatment option, which can be deferred until after puberty and can be performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.5 Recommendation for the treatment congenital penile curvature

Recommendation	Strength rating
Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique.	Strong

8.2 Peyronie's Disease

8.2.1 Epidemiology/aetiology/pathophysiology

8.2.1.1 Epidemiology

Epidemiological data on Peyronie's disease (PD) are limited. Prevalence rates of 0.4-20.3% have been published, with a higher prevalence in patients with ED and diabetes [910-918]. A recent survey indicates that the prevalence of definitive and probable cases of PD in the US is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [919]. Peyronie's disease often occurs in older males with the typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), but at a lesser prevalence than older men (1.5 to 16.9%) [914, 920, 921].

8.2.1.2 Aetiology

The aetiology of PD is unknown. However, repetitive microvascular injury or trauma to the tunica albuginea is still the most widely accepted hypothesis to explain the aetiology of the disease [922]. Abnormal wound healing

leads to the remodeling of connective tissue into a fibrotic plaque [922-924]. Penile plaque formation can result in a curvature, which, if severe, may impair penetrative sexual intercourse. The genetic underpinnings of fibrotic diatheses, including PD and Dupuytren's diseases, are beginning to be understood (Table 25) [925].

Table 25: Genes with involvement in Peyronie's and Dupuytren's diseases (adapted from Herati *et al.* [925])

Gene	Gene Symbol	Chromosomal Location	Gene Function
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerisation
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein
Cortactin; amplaxin	CTTN	11q13	Organises cytoskeleton and cell adhesion structures
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics
RhoGDP dissociation inhibitor	ARHGDIA	17q25.3	Regulates Rho GTPase signaling
Pleiotrophin precursors; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organisation and translocation from cytoplasm to nucleus upon
Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells
Human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils
Bone Proteoglycan II precusor; Decorin	DCN	12q21.33	Matrix proteoglycan
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and hemostasis
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyzes matrix protein
c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes

Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits apoptosis
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerisation, negatively regulates cell differentiation
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity
Desmin	DES	2q35	Forms intra-cytoplasmic filamentous network connecting myofibrils
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence inhuman fibroblasts
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration

8.2.1.3 Risk factors

The most commonly associated comorbidities and risk factors are diabetes, hypertension, dyslipidemias, ischaemic cardiopathy, autoimmune diseases [926], ED, smoking, excessive consumption of alcohol, low testosterone levels and pelvic surgery (e.g., radical prostatectomy) [343, 914, 918, 927-929]. Dupuytren's contracture is more common in patients with PD affecting 8.3-39% of patients [915, 930-932], whilst 4-26% of patients with Dupuytren's contracture report PD [931, 933].

8.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [934]. The first is the active inflammatory phase (acute phase), which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and of the penile deformity. With time, the penile curvature is expected to worsen in 21-48% of patients or stabilise in 36-67% of patients, while spontaneous improvement has been reported in only 3-13% of patients [927, 935-937]. Overall, penile deformity is the most common first symptom of PD (52-94%). Pain is the second most common presenting symptom of PD, which presents in 20-70% of patients during the early stages of the disease [938]. Pain tends to resolve with time in 90% of men, usually during the first twelve months after the onset of the disease [935, 936]. Palpable plaques were reported as initial symptom in 39% of the patients and mostly situated dorsally [48, 938].

In addition to functional effects on sexual intercourse, men may also suffer from significant psychological distress. Validated mental health questionnaires have shown that 48% of men with PD have moderate or severe depression, sufficient to warrant medical evaluation [939].

8.2.1.5 Summary of evidence on epidemiology/aetiology/pathophysiology of Peyronie's disease

Summary of evidence	LE
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which may lead to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g., diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of PD are still unclear.	3
Two phases of the disease can be distinguished. The first phase is the active inflammatory phase (acute phase-painful erections, nodule/plaque), and the second phase is the fibrotic/calcifying phase (chronic or stable phase) with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (21-48%) or stabilisation (36-67%). Pain is usually present during the early stages of the disease, but tends to resolve with time in 90% of men within twelve months of onset.	2a

8.2.2 ***Diagnostic evaluation***

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed to be used both in clinical practice and trials. Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [940].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have active disease are those with a shorter symptom duration, pain on erection, or a recent change in penile deformity. Resolution of pain and stability of the curvature for at least three months are well-accepted criteria of disease stabilisation and patients' referral for specific medical therapy [941, 942] or surgical intervention when indicated [943].

The examination should start with a focused genital assessment which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhosen scarring of the plantar fascia [936]. Penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and the degree of curvature [944]. Measurement of the stretched or erect penile length is important because it may have an impact on the subsequent treatment decisions and potential medico-legal implications [945-947].

An objective assessment of penile curvature with an erection is mandatory. According to current literature, this can be obtained by several approaches, including a home (self) photography of a natural erection (preferably), using a vacuum-assisted erection test or an ICI using vasoactive agents. However, it has been suggested that the ICI method is superior, as it is able to induce an erection similar to or better than that which the patient would experience when sexually aroused [948-950]. Computerised Tomography and MRI have a limited role in diagnosis of the curvature and are not recommended on a routine basis. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [951]. Erectile dysfunction is common in patients with PD (30-70.6%) [952, 953]. It is mainly arterial or cavernosal (veno-occlusive) dysfunction in origin [927, 944, 954]. The presence of ED and psychological factors may also have a profound impact on the treatment strategy [953].

Ultrasound measurement of plaque size is inaccurate, and it is not recommended in everyday clinical practice [955]. Doppler US may be used for the assessment of penile haemodynamics [953].

8.2.2.1 Summary of evidence for the diagnosis of Peyronie's disease

Summary of evidence	LE
Ultrasound (US) measurement of the plaque's size is inaccurate and operator dependent.	3
Doppler US may be required for the assessment penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods to provide an objective assessment of penile curvature with an erection.	4

8.2.2.2 Recommendations for the diagnosis of Peyronie's disease

Recommendations	Strength rating
Take a medical and sexual history of patients with Peyronie's disease, include duration of the disease, pain on erection, penile deformity, difficulty in vaginal intromission due to disabling deformity and erectile dysfunction (ED).	Strong
Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g. Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use intracavernous injection (IC) method to provide an objective assessment of penile curvature with an erection in the diagnostic work-up of PD.	Weak
Use the Peyronie's disease specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory.	Weak
Do not use ultrasound, computerised tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice.	Weak
Use Doppler US only in the case of diagnostic evaluation of ED, to ascertain penile haemodynamic and vascular anatomy.	Weak

8.2.3 ***Disease management***

8.2.3.1 Conservative treatment

Conservative treatment of PD is primarily focused on patients in the early stage of the disease as an adjunct treatment to relieve pain and prevent the progression of the disease or if the patient declines other treatment options during the active phase [936, 943]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shock wave therapy (SWT) and other topical treatments (Table 26).

The results of the studies on conservative treatment for PD are often contradictory making it difficult to provide recommendations in the everyday, real-life setting [956]. The Panel does not support the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or combination of vitamin E and L-carnitine because of their lack of efficacy (tamoxifen, colchicine, vitamin E, procarbazine) or evidence (potaba, L-carnitine, pentoxyfilline) [943, 957-959]. This statement is based on several methodological flaws in the available studies. These include their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [960, 961]. Even in the absence of adverse events, treatment with these agents may delay the use of other efficacious treatments.

Table 26: Conservative treatments for PD

Oral treatments
Non-steroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5I)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment
Other
Traction devices
Multimodal treatment

8.2.3.1.1 Oral treatment

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors were first suggested as a treatment for PD in 2003 to reduce collagen deposition and increase apoptosis through the inhibition of transforming growth factor (TGF)-b1 [962, 963]. A retrospective study of 65 men suggested the use of PDE5I as an alternative for the treatment of PD. The results indicated that treatment with tadalafil was helpful in decreasing curvature and remodelling septal scar when compared to controls [964]. Another recent study concluded that sildenafil was able to improve erectile function and pain in PD patients. In the study, 39 patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for twelve weeks and significantly better outcomes in pain and IIEF score were seen in the sildenafil group [965].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD in order to manage penile pain, which is usually present in this phase. Pain levels should be periodically reassessed in monitoring treatment efficacy.

8.2.3.1.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure, particularly when a dense or calcified plaque is present.

Calcium channel antagonists: verapamil and nicardipine

The rationale for intralesional use of channel antagonists in patients with PD is based on *in vitro* research [966, 967]. Due to the use of different dosing schedules and the contradictory results obtained in published studies, the evidence is not strong enough to support the clinical use of injected channel blockers verapamil and nicardipine and the results do not demonstrate a meaningful improvement in penile curvature compared to placebo [968-973]. In fact, most of the studies did not perform direct statistical comparison between groups.

Collagenase of clostridium histolyticum

Collagenase of *clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the PD plaque [974-977]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the nonsurgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30º to 90º and non-ventrally located plaques is present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [978, 979].

The original treatment protocol in all studies consists of two injections of 0.58 mg of CCH 24-72 hours apart every six weeks for up to four cycles. Data from IMPRESS (Investigation for Maximal Peyronie´s Reduction Efficacy and Safety Studies) II and II studies [976], as well as post approval trials [980], which demonstrated the efficacy and safety of this treatment, are summarised in the Table 27.

Table 27: Clinical evidence supporting CCH treatment

Author/Year	Study type	Special considerations	Number of patients	Number of injections	Decrease in PC in CCH group
Gelbard *et al.* (2013) [981]	Phase 3 randomised double-blinded controlled trial	Pilot study	551	8 (in 78.8% of patients)	34% (17.0 ± 14.8 degrees)
Levine *et al.* (2015) [982]	Phase 3 open-label	IMPRESS based	347	≤ 8	34.4% (18.3 ± 14.02 degrees)
Ziegelmann *et al.* (2016) [983]	Prospective, double-blinded trial	IMPRESS based	69	Mean = 6	38% (22.6 ± 16.2 degrees)
Yang and Bennett (2016) [984]	Prospective study	Included patients in acute phase	37 in SP 12 in AP	Median in SP = 6 Median in AP = 2.5	32.4% (15.4 degrees) AP = 20 degrees
Nguyen *el al.* (2017) [951]	Retrospective study	Included patients in acute phase	126 in SP 36 in AP	Mean = 3.2	SP = 27,4% (15.2 ± 11.7 degrees) AP = 27,6% (18.5 ± 16.2 degrees) N/S differences in final change in curvature between group 1 (16.7º) and group 2 (15.6º) p=0.654
Anaissie *et al.* (2017) [985]	Retrospective study	Included patients in acute phase	77	Mean = 6.6	29.6% (15.3 ± 12.9 degrees)
Abdel Raheem *et al.* (2017) [986]	Prospective study	Shortened protocol	53	Mean = 3	31.4% (17.6 degrees)
Capece *et al.* (2018) [987]	Prospective multicentric study	Shortened protocol	135	Mean = 3	42.9% (19.1 degrees)

SP = Stable phase; AP = Acute phase; N/S = Non-significant.

The average improvement in curvature was 34% compared to 18.2% in the placebo group. Three adverse events of corporeal rupture were surgically repaired. The greatest chance of curvature improvement is for curvatures between 30° and 60°, longer duration of disease, an IIEF > 17, and no calcification [942]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the alleged role of plaque injection and penile modeling, regardless of the medication, in improving outcomes in men with PD as the placebo or modeling arm resulted in a relatively high curvature reduction compared to treatment.

The conclusion of the IMPRESS I and II studies is that that CCH improves PD both physically and psychologically [981]. A post hoc meta-analyses of the IMPRESS studies demonstrated better results in patients with less than 60º of curvature, more than two years of evolution, no calcification in the plaque and good erectile function [980].

A relatively new modified short protocol which consists of the administration of a single (0.9 mg, one vial) injection per cycle distributed along three lines around the point of maximum curvature up to three cycles, separated by four-weekly intervals, has been proposed, and replaces the physician modelling with a multimodal approach through penile stretching, modelling and vacuum device at home [986]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appear to decrease the

cost and duration of the treatment, although these represent non-randomised study protocols. These results were further explored in a prospective non-randomised multi-centric study [982]. In another large single-arm multi-centre clinical study using the shortened protocol, longer PD duration, greater baseline PC and basal and dorsal plaque location were identified as clinically significant predictors of treatment success [988]. Accordingly, a nomogram developed to predict treatment success after CCH for PD showed that patients with longer PD duration, greater baseline penile curvature and basal plaque location had a greater chance of treatment success [988]; however, these findings need to be externally validated.

Regarding safety concerns, the majority of PD's patients treated with CCH experienced at least one mild or moderate adverse reaction localised to the penis (penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%)) which resolved spontaneously within fourteen days of the injection [989]. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. Serious TEAE´s (0.9%) include penile haematoma and corporeal rupture that require surgical treatment. According to both IMPRESS' data and the shortened protocol, in order to prevent serious TEAE men should be advised to avoid sexual intercourse in the four weeks following the injection. Recent preliminary data suggest that treatment in the acute phase of the disease can be effective and safe [946, 979-981].

In conclusion, CCH is a safe and established treatment for active-phase disease; more recent evidence would suggest that CCH may also have a role in affecting the progression of active-phase disease, thus suggesting that the indications for CCH use could be expanded, although there is the possibility of a high placebo effect. It should also be noted that there is a large effect of traction or modelling in controlled studies, whilst studies reporting on modified protocols have small numbers of patients and are largely uncontrolled. Therefore, patients should be counselled fully on the efficacy of collagenase and the high cost of treatment.

It has been suggested that those patients with severe curvature may also benefit from CCH injections because of a potential downgrading of the penile curvature: a decrease in curvature may allow for a penile plication procedure instead of a plaque incision and grafting procedure, therefore avoiding the more negative impact on erectile function [986]. However, further investigation is needed to validate these initial findings [951, 984]. The panel has agreed to keep the whole set of information and recommendations regarding the use of CCH in men with PD despite the recent report about the official withdrawal of the product from the European market by the company.

Interferon α-2b

Interferon α-2b (IFN-α2b) has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improve the wound healing process from PD plaques *in vitro* [990]. Intralesional injections (5x10^6 units of IFN-α2b in 10 mL saline every two weeks over twelve weeks for a total of six injections) significantly improved penile curvature, plaque size and density, and pain compared to placebo. Additionally, penile blood flow parameters benefited in the IFN-α2b group [979, 991, 992]. A study showed that regardless of plaque location, IFN-α2b is an effective treatment option. Treatment with IFN-α2b provided a greater than 20% reduction in curvature in the majority of men with PD, independent of plaque location [993]. Given the mild side-effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs drugs before IFN-α2b injection, and the moderate strength of data available, IFN-α2b is currently recommended for treatment of stable-phase PD.

Steroids, hyaluronic Acid and Botulinum toxin (botox)

In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [994]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [995]. Only a case-controlled single site study and a prospective non-controlled study support the use of hyaluronic acid injections in PD, with conflicting results related to penile curvature or penile pain [996, 997]. As only a single study evaluated intralesional botox injections in men with PD, the panel conclude that there is no robust evidence available to support these treatments [998].

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is no sufficient and unequivocal evidence that topical treatments (neither verapamil, H-100 Gel [a compound with nicardipine, superoxide dismutase and emu oil] nor steroids) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration [EMDA]), result in adequate levels of the active compound within the tunica albuginea [999-1002]. Therefore, the panel does not support the use of topical treatments for PD applied to the penile shaft.

Extracorporeal shockwave treatment

The mechanical shear stress provoked by low-intensity extracorporeal shockwave treatment (LI-ESWT) on the treated tissue was deemed to induce neovascularisation and to enhance local blood flow [956]. The mechanism of action involved in ESWT for PD is still unclear, but there are two hypotheses. In the first hypothesis, shockwave therapy works by directly damaging and remodeling the penile plaque. In the second hypothesis, shockwave lithotripsy increases the vascularity of the area by generating thermodynamic changes resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [1003, 1004].

Four RCTs and one meta-analysis [1005-1009] assessed the efficacy of ESWT in the treatment of PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5I (tadalafil) [1007].

All trials showed positive findings in terms of pain relief, but no effect on penile curvature and plaque size. Inclusion criteria varied widely among studies and further investigation is needed. The results are summarised in the Table 28.

Table 28: Efficacy of ESWT in the treatment of PD

Author/Year	Nº cases/ controls	Inclusion criteria	Comparator	Follow up	Protocol of treatment	Results	AES´s
Palmieri *et al.* 2009 [1005]	50 / 50	PD <12 mo. No previous treatment	Sham therapy	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** (+5.4points) **Pain reduction** (-5.1 points) **Change in curvature** (-1.4º) **Plaque size** (-0.6 in)	No
Chitale *et al.* 2010 [1006]	16 / 20	Stable PD > 6 mo. No previous treatment	Sham therapy	6 month	1 session/week x 6 weeks. No other parameters mentioned.	**Change in IIEF** N/S **Pain reduction** N/S **Change in curvature** N/S **Plaque size** N/S	No
Palmieri *et al.* 2011 [1007]	50 / 50	PD <12 mo. Painful erections Presence of ED	ESWT + tadalafil 5 mg OD	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** Significant in both groups **Pain reduction** Significant in both groups **Change in curvature** N/S **Plaque size** N/S	No
Hatzichristodoulou *et al.* 2013 [1008]	51 / 51	Stable PD > 3 mo. Previous unsuccessful oral treatment	Sham therapy	1 month	1 session/week x 6 weeks 2000 sw, 0.29 mJ/mm^2	**Change in IIEF** N/A **Pain reduction** (-2.5 points **Change in curvature** N/S **Plaque size** N/S	Ecchymosis 4,9%

N/A = no assessed; N/S = no significant; IIEF = International index of erectile function; VAS = Visual Analogic Scale; ED = Erectile dysfunction

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been described, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [1010, 1011].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length,

which are very attractive to patients suffering from PD. However clinical evidence is limited due to the limited number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria make it impossible to draw any definitive conclusions about this therapy [1012-1016].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT therapy in patients with calcified plaques, hourglass of hinge deformities which are, theoretically, less likely to respond to PTT has not been systematically studied. In addition, the treatment can result in discomfort and be inconvenient due to use of the device for an extended period (two to eight hours daily), but has been shown to be tolerated by highly motivated patients. There were no serious adverse effects, including skin changes, ulcerations, hypoesthesia or diminished rigidity [1014, 1017].

In conclusion, PTT seems to be effective and safe for patients with PD, but there is still lack of evidence to give any definitive recommendation in terms of monotherapy for PD.

Table 29: Summary of clinical evidence of PTT as monotherapy

Author/Year	Study type	Device	Number of patients	Hours of use	Result
Levine *et al.* (2008)	Pilot Prospective, uncontrolled	Fast Size®	10	2-8h 6 months	Mean reduction in PC 33% (51°-34°) SPL: + 0.5-2 cm EG: + 0.5-1 cm IIEF: + 5.3
Gontero *et al.* (2009)	Phase II Prospective Uncontrolled	Andropenis®	15	> 5h 6 months	Mean reduction in PC: N/S SPL: + 0.8 cm (6 mo) + 1.0 cm (12 mo)
Martinez-Salamanca *et al.* (2014)	Prospective, controlled, open label Men in AP	Andropenis®	96 55 (PD) 41 (NIG)	6-9h (4.6 h/d) 6 months	Mean reduction in PC: 20° (33°-15°) p < 0.05. SPL: + 1.5 cm (6 mo) EG: + 0.9 cm (6 mo)
Moncada *el al.* (2018)	Controlled multicenter trial Men in CP	Penimaster®PRO	80 41 (PTT) 39 (NIG)	3-8h 3 months	Mean reduction in PC: 31° (50°-15°). SPL: + 1.8 cm (3 mo) EG: +0.9 cm (6 mo) IEEF: + 2.5
Ziegelmann *et al.* (2019) [1016]	Randomised, prospective, controlled, singe blind study Men in CP and contols 3:1	Restorex®	110	30-90 min/day 3 months	Mean reduction in PC (3 mo): 13.3° (PTT) +1.3° (control) p < 0.001 SPL: + 1.5 cm (PTT) + 0.cm (control) p < 0.001 IIEF: +4.3 (PTT) -0.7 (control) p=0.01

NIG = non-intervention group; IIEF = International Index of Erectile Function; N/S = Not Significant; PD = Peyronie´s Disease; AP = Acute phase; CP = Chronic phase; SPL - Stretched penile length; EG = Erect girth, mo = month.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [1018]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1a, transforming growth factor (TGF)-b1, collagenase, and apoptosis, and increases endothelial nitric oxide synthase and a-smooth muscle actin, given a role in the pathogenesis of PD [1019]. Only one clinical study assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further investigation is needed [1020].

8.2.3.1.4 Multimodal treatment

There is some data suggesting that a combination of different oral drugs can be used in the treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine, the optimum drug dosage; nor has there been a comparison of different drug combinations.

A long-term study assessing the role of multimodal medical therapy (injectable verapamil associated with antioxidants and local diclofenac) demonstrated that it is efficacious to treat PD patients. The authors concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [1019]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED have been described, however, limited data is available regarding its use [1021].

Penile traction therapy was evaluated as an adjunctive therapy to intralesional injections with interferon, verapamil, or CCH [969, 1022, 1023]. Results from these studies have failed to demonstrate statistically significant improvements in penile length or curvature, with the exception of one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours a day [1023]. A meta-analysis comparing the efficacy of PTT as an adjuvant treatment demonstrated that men who used PTT as an adjunct treatment to surgery or injection therapy in the treatment of PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunct PTT. There was no significant change in curvature between the two groups [1024].

Data available on the combined treatment of CCH and the use of VED between injection intervals reported statistically significant mean improvements in curvature (-17º) and penile length (+0.4 cm) after treatment. However, it is not possible to determine the isolated effect of VED because of a lack of control groups [986, 1024].

Recent data suggested that the combination of PDE5I (sildenafil 25 mg twice a day) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence for conservative treatment of Peyronie's disease

Summary of evidence	**LE**
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease in order to relieve symptoms and prevent progression.	3c
There is no convincing evidence supporting oral treatment with acetyl esters of carnitine, vitamin E, potassium para-aminobenzoate (potaba) and pentoxifylline.	3c
Due to adverse effects, treatment with oral tamoxifen is no longer recommended.	3c
Nonsteroidal anti-inflammatory drugs can be used to treat pain in the acute phase.	5
Intralesional treatment with calcium channel antagonists: verapamil and nicardipine are no longer recommended due to contradictory results.	1b
Intralesional treatment with collagenase of *clostridium histolyticum* showed significant decreases in penile curvature, plaque diameter and plaque length in men with stable disease.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	2b
Intralesional treatment with steroids are no longer recommended due to adverse effects include tissue atrophy, thinning of the skin and immunosuppression.	3c
No robust evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea.	3c
The use of iontophoresis is not recommended due to the absence of efficacy data.	3c
Extracorporeal shockwave treatment may be offered to treat penile pain, but it does not improve penile curvature and plaque size.	2b
Treatment with penile traction therapy alone or in combination with injectable therapy as part of a multimodal approach may reduce penile curvature and increase penile length, although studies have limitations.	3c

8.2.3.1.6 Recommendations for non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifiline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30º seeking a minimal invasive procedure.	Strong
Intralesional therapy with collagenase *clostridium histolyticum* may be offered in patients with stable PD and dorsal or lateral curvature > 30º, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage will experience a significant straightening of the penis. The aim of surgery is to correct curvature and allow penetrative intercourse. Surgery is indicated in patients with significant penile deformity and difficulty with intercourse associated with sexual bother. Patients must have a stable disease for three to six months (or more than nine to twelve months after onset of PD) [934, 943, 1025]. In addition to this requirement, there are other situations that may precipitate the indication for surgery, such as failed conservative or medical therapies, extensive penile plaque(s), or patient preference, when the disease is stable [1026, 1027].

Before considering reconstructive surgery, it is highly recommended to document the size and location of plaques, the degree of curvature, complex deformities (hinge, hourglass), the penile length and also the presence or absence of ED. The potential aims and risks of surgery should be discussed fully with the patient so that he can make an informed decision [1025]. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness and delayed orgasm, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery, including residual curvature and the risk of further penile wasting with shortening procedures [943, 1028]. Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [943]. Patient expectations from surgery must also be included in the pre-operative assessment. The main objective of surgery is to achieve a "functionally straight" penis, and this must be fully understood by the patient to achieve the best possible satisfaction outcomes after surgery [1025, 1029].

Three major types of reconstruction may be considered for PD: i) tunical shortening procedures; ii) tunical lengthening procedures; and, iii) penile prosthesis implantation, with or without adjunct straightening techniques in the presence of concomitant ED and residual curvature [1030, 1031].

Tunical shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis to make it even with the contralateral side. Tunical lengthening procedures are performed on the concave side of the penis after making an incision or partial excision of the plaque, with coverage of the defect with a graft. Although tunical lengthening procedures in real life rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication techniques of the tunica albuginea or correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening

procedures to correct the residual curvature [1032]. In patients with PD and ED not responding to medical treatments, penile prosthesis implantation can be considered with correction of the curvature including adjunct techniques (modeling, plication or incision/excision with grafting).

Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) should be considered the standard approach for all types of procedures, although modifications have been described. Only one study has suggested that circumcision is not always necessary (e.g. in cases where the foreskin is normal pre-operatively) [1033]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [1034, 1035].

There are no standardised questionnaires for the evaluation of surgical outcomes. Data from well-designed prospective studies are scarce, with low levels of evidence. Data are mainly based on retrospective single-centre studies, typically non-comparative and non-randomised, or on expert opinion [943, 1036]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormality, and non-severe curvature, a tunical shortening procedure can be considered an appropriate surgical approach. Numerous different techniques have been described, although they can be classified as excisional, incisional and plication techniques.

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite to the point of maximum curvature with a non-elastic corporal segment to treat CPC [1037]. Thereafter, this technique became a successful treatment option for PD-associated penile curvatures [1038]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature. The overall short- and long-term results of the Nesbit operation are excellent [1039-1043]. Some modifications of the Nesbit procedure have been described (partial thickness shaving instead of conventional excision; underlapped U incision) with similar results, although these are in non-randomised studies [1044-1048].

The Yachia technique, on the other hand, is based on a completely different concept, as it utilises the Heinke-Mikowitz principle where a longitudinal tunical incision is closed transversely in order to shorten the convex side of the penis. This technique, initially described by Lemberger in 1984, was popularised by Yachia in 1990, when he reported a series of ten cases [1049-1054].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions, in order to limit the potential damage to the veno-occlusive mechanism [945, 1055-1071]. Another modification has been described as the ’16-dot’ technique which consists of the application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1048, 1072-1074]. The use of non-absorbable sutures or longer lasting abdsorbable sutures may reduce recurrence of the curvature (panel expert opinion). Results and satisfaction rates are both similar to the incision/excision procedures.

In general, using these tunical shortening techniques, complete penile straightening is achieved in more than 85% of patients. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported outcome of these procedures. Shortening of 1-1.5 cm has been reported for about 22-69% of patients, which is rarely the cause of post-operative sexual dysfunction and patients may perceive the loss of length as greater than it actually is. It is therefore strongly advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used (Table 30).

As mentioned above, there are multiple techniques with small modifications and all of them reported in retrospective studies, most of them without comparison between techniques and therefore the level of evidence is not sufficient to recommend one method over another.

Table 30: Results of tunical shortening procedures for PD data from different, non-comparable studies) [945, 1044-1071]

	Tunical shortening procedures				
	Nesbit	**Modified Nesbit**	**Yachia**	**16-dot / mod16-dot**	**Simple plication**
Number of patients / studies	652 / 4	387 / 5	150 / 6	285 / 5	1068 / 18
Significant penile shortening (%)*†	8.7% (5-39)	3.2% (0-13)	3.5% (0-10)	5.9% (0-6)	8.9% (0-55)
Any penile shortening (%)*	21.8% (9-39)	58.1% (23-74)	69% (47-97)	44.6% (40-52)	33.4% (0-90)
Penile straightening (%)*	88.5% (86-100)	97.6% (92-100)	95.5% (93-100)	96.9% (95-100)	94.7% (85-100)
Post-operative *de novo* ED (%)*	6.9% (0-17)	3% (0-13)	9.6% (0-13)	3.8% (0-13)	8.1% (0-38)
Penile hypoesthesia (%)*	11.8% (2-60)	5.6% (0-31)	1% (0-3)	8.2% (6-13)	9% (0-47)
Overall satisfaction (%)*	83.5% (76-88)	95.4% (87-100)	86.8% (78-100)	94% (86-100)	86.4% (52-100)
Follow-up (months)*	(69-84)	(19-42)	(10-24)	(18-71)	(12-141)

**Data are expressed as weighted average. † Defined as > 30 degrees of curvature. Ranges are in parentheses. ED = Erectile dysfunction.*

8.2.3.2.2 Tunical lengthening procedures

Tunical lengthening surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass, hinge) but without underlying ED. The definition of a severe curvature has been proposed to be greater than 60º, although there are no studies validating this threshold. However, it may be used as an informative guide to the patient and clinician in surgical counselling and planning, although there is no unanimous consensus based on the literature that such a threshold can predict surgical outcomes (panel expert consensus opinion). On the concave side of the penis, at the point of maximum curvature, which usually coincides with the location of the plaque, an incision is made, creating a defect in the albuginea that is covered with a graft. Complete plaque removal or plaque excision may be associated with higher rates of post-operative ED due to venous leak, but partial excision in cases of florid calcification may be permissible [1075, 1076]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [1028].

Since 1974, when the first study using dermal grafting to treat PD was published [1077], a large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (not too much, to avoid aneurysmal dilations), readily available, morbidity should be minimal especially when using autografts and cost effective. No one graft material meets all of these requirements. Moreover, the studies performed do not compare different types of grafts and biomaterials and are often single-centre retrospective studies so there is not a single graft that can be recommended for surgeons [1078]. In addition, grafting procedures are associated with long term ED rates as high as 50%. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for good functional outcomes after grafting surgery [1031]. Although the risk for penile shortening appears to be less than that compared to the Nesbit, Yachia or plication procedures, it is still an issue and patients must be informed accordingly [1030]. Higher rates (3-52%) of penile hypoesthesia have also been described after these surgeries, as damage of the neurovascular bundle with dorsal curves (in the majority) is inevitable. A recent prospective study showed that 21% of patients had some degree of sensation loss at one week, 21% at one month, 8% at six months, and 3% at twelve months. [1029, 1079-1082]. The use of geometric principles introduced by Egydio may help to determine the exact site of the incision, and the shape and size of the defect to be grafted [1083].

Grafts for PD surgery can be classified into four types (Table 31) [935]:

- Autografts: taken from the individual himself, they include the dermis, vein, temporalis fascia, fascia lata, tunica vaginalis, tunica albuginea and buccal mucosa.
- Allografts: also of human origin but from a deceased donor, including the pericardium, fascia lata and dura mater.
- Xenografts: extracted from different animal species and tissues, including bovine pericardium, porcine small intestinal submucosa, bovine and porcine dermis, and TachoSil® (matrix of equine collagen).
- Synthetic grafts: these include Dacron® and Gore-Tex®.

All the autologous grafts have the inconvenience of possible graft harvesting complications. Dermal grafts are commonly associated with veno-occlusive ED (20%) due to lack of adaptability, so they have not been used in contemporary series [1077, 1078, 1084-1094]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The Saphenous vein has been the most common vein graft used [1095-1110]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have obviously perfect histological properties but have some limitations: the size that can be harvested, and the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1111-1113]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results could be obtained if a vascular flap is used [1114-1118]. Under the pretext that by placing the submucosal layer on the corpus cavernosum the graft feeds on it and adheres more quickly, the buccal mucosal graft has recently been used with good short-term results [1119-1125].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1081, 1126]. Cadaveric pericardium (Tutoplast©) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [1029, 1076, 1090, 1127, 1128]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1129-1131].

Xenografts have become more popular in recent years. Small intestinal submucosa, a type I collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine, has been shown to promote tissue-specific regeneration and angiogenesis, and supports host cell migration, differentiation and the growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1132-1141]. As mentioned above, pericardium (bovine, in this case), has very good traction resistance and adaptability, and good host tolerance [1080, 1110, 1142-1144]. Grafting by collagen fleece (TachoSil©) in PD has some major advantages such as decreased operative times, easy application and an additional haemostatic effect [1079, 1145-1149].

It is generally recommended that synthetic grafts, including polyester (Dacron®) and polytetrafluoroethylene (Gore-Tex®) are avoided, due to increased risks of infection, secondary graft inflammation causing tissue fibrosis, graft contractures, and possibility of allergic reactions [1052, 1150-1153].

Some authors recommend post-operative penile rehabilitation to improve surgical outcomes. Some studies have described using VED and PTT to prevent penile length loss of up to 1.5 cm [1154]. In addition, daily nocturnal administration of PDE5I enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED [1155]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 31: Results of tunical lengthening procedures for Peyronie's disease (data from different, non- comparable studies) [1029, 1052, 1076, 1077, 1079-1081, 1084-1149]

	Year of publication	Number of patients / studies	Success (%)*	Penile shortening (%)*	De novo ED (%)*	Follow-up (mo)*
Autologous grafts						
Dermis	1974-2019	718 / 12	81.2% (60-100)	59.9% (40-75)	20.5% (7-67)	(6-180)
Vein grafts	1995-2019	690 / 17	85.6% (67-100)	32.7% (0-100)	14.8% (0-37)	(12-120)
Tunica albuginea	2000-2012	56 / 4	85.2% (75-90)	16.3% (13-18)	17.8% (0-24)	(6-41)
Tunica vaginalis	1980-2016	76 / 5	86.2% (66-100)	32.2% (0-83)	9.6% (0-41)	(12-60)
Temporalis fascia / Fascia lata	1991-2004	24 / 2	100%	0%	0%	(3-10)
Buccal mucosa	2005-2016	137 / 7	94.1% (88-100)	15.2% (0-80)	5.3% (0-10)	(12-45)
Allografts (cadaveric)						
Pericardium	2001-2011	190 / 5	93.1% (56-100)	23.1% (0-33)	37.8% (30-63)	(6-58)
Fascia lata	2006	14 / 1	78.6%	28.6%	7.1%	31
Dura matter	1988-2002	57 / 2	87.5%	30%	17.4% (15-23)	(42-66)
Xenografts						
Porcine SIS	2007-2018	429 / 10	83.9% (54-91)	19.6% (0-66)	21.9% (7-54)	(9-75)
Bovine pericardium	2002-2016	284 / 5	88.7% (81-100)	4.3% (0-41)	24.8% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
TachoSil®	2002-2018	477 / 6	93.1%	10.9% (0-93)	10.6% (0-21)	(0-63)

**Data are expressed as weighted average. Ranges are in parentheses.*
ED = Erectile dysfunction; SIS = Small intestinal submucosa.

The results of tunical shortening and lengthening approaches are presented in Tables 30 and 31. It must be emphasised that there are no RCTs available comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [943]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised, re-activation of the condition following the development of stable disease, or the use of early re-absorbable sutures (e.g., Vicryl) that lose their strength before fibrosis has resulted in acceptable strength of the repair. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures (e.g., PDS) should be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, but this issue may be alleviated by the use of slowly re-absorbable sutures (e.g., PDS) [1039]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This will usually be a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with although rare ventral curvatures [1030].

8.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with concomitant ED not responding to conventional medical therapy (PDE5I or intracavernosal injections of vasoactive agents) [943]. Although inflatable prostheses (IPP) have been considered classically more effective in the general population with ED, some studies support the use of malleable prostheses (MPP) in these patients with similar satisfaction rates [943, 1156, 1157]. The evidence suggests that there is no real difference between the available IPPs [1158]. Surgeons can and should advise on which type of prosthesis best suits the patient but it is the patient who should ultimately choose the prosthesis to be implanted [1159].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1108, 1160]. If the curvature after placement of the prosthesis is < 30° no further action is indicated, since the prosthesis itself will act as an internal tissue expander to correct the curvature during the subsequent six to nine months. If, on the other hand, the curvature is > 30°, the first-line treatment would be modelling with the prosthesis maximally inflated (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) [1161, 1162]. If, after performing this manoeuvre, a deviation > 30° persists, next steps would be eventually incision with collagen fleece coverage or without (if the defect is small, it can be left uncovered) or plaque incision and grafting [1163-1168]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly employed in the grafting surgery (described above) which will prevent herniation and recurrent deformity due to the scarring of the defect [1169].

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modeling' over the inflated prosthesis [1161].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the "sliding" technique has been considered [1170]. Although the "sliding" technique is not recommended due to reported cases of glans necrosis because of the concomitant release of both the neurovascular bundle and the urethra, new approaches for these patients have been recently described such as the MoST (Modified Sliding Technique), MUST (Multiple-Slit Technique) or MIT (Multiple-Incision Technique) techniques, but these should only be used in the hands of experienced high-volume surgeons and after full patient counseling [1171-1173].

While patient satisfaction after IPP placement in the general population is quite high, satisfaction rates have been found to be significantly lower in those with PD. Despite this, depression rates decreased after surgery in PD patients (from 19.3% to 10.9%) [1174]. The main cause of dissatisfaction after PPI in the general population is a shortened penile length. Therefore, patients with PD undergoing penile implant surgery must be counselled that they are not designed to restore their previous length [1174, 1175].

8.2.3.2.4 Summary of evidence for non-operative treatment of Peyronie's disease

Summary of evidence	**LE**
Surgery for PD should only be offered in patients with stable disease with functional impairment.	2b
In patients with concomitant PD and ED without response to medical treatment, penile prosthesis implantation with or without additional straightening manouevres is the technique of choice.	2a
In other cases, factors such as penile length, rigidity of the erections, degree of curvature, presence of complex deformities and patient choice must be taken into account in order to decide on a tunical shortening or lengthening technique.	3

8.2.3.2.5 Recommendations for the surgical treatment of penile curvature

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to deformity.	Strong
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, non-severe curvature and absence of complex deformities (hour-glass, hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hour-glass, hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modeling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

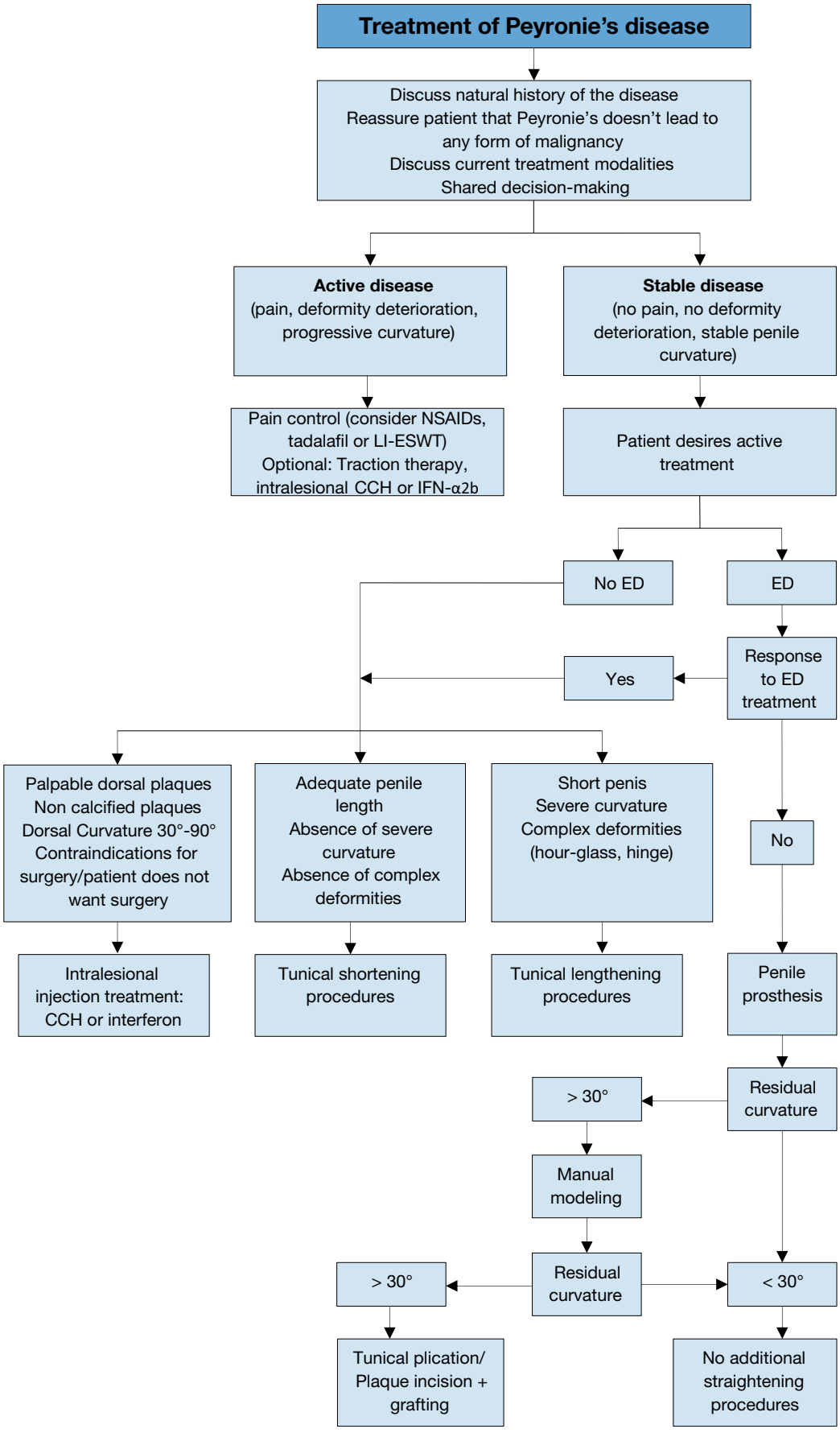
8.2.3.3 Treatment algorithm

As mentioned above, in the active phase of the disease, most therapies are experimental or with low evidence. In cases of pain, LI-ESWT, tadalafil and NSAIDs can be offered. In cases of curvature or shortening, traction therapy has demonstrated good responses.

When the disease has stabilised, intralesional treatments (mainly CCH) or surgery may be used. Intralesional treatments may reduce the indication of the surgery or change the technique to be performed but only after full patient counselling which should also include a cost benefit discussion with the patient.

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. In non-complex and non-severe deformities, tunical shortening procedures are acceptable and are usually the method of choice. This is typically the case for PC. If a severe curvature or a complex deformation is present (hourglass, or hinge), or if the penis is significantly shortened in patients with a good erectile function (preferably without pharmacological treatment), then a tunical lengthening procedure is feasible, using any of the grafts previously mentioned. If there is concomitant ED, which is not responsive to pharmacological treatment, the best option is the implantation of a penile prosthesis, with or without a straightening procedure over the penis (modeling, plication, incision or excision with or without grafting). The treatment algorithm is presented in Figure 11.

Figure 11: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= Low-intensity Extracorporeal shockwave treatment.

9. MALE INFERTILITY

9.1 Definition and classification

Infertility is the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy in one year [1176]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least twelve consecutive months having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before.

9.2 Epidemiology/aetiology/pathophysiology/risk factors

9.2.1 Introduction

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child. Three percent of women who are currently trying to conceive remain involuntarily childless, while 6% of parous women are not able to have as many children as they would wish [1177]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1176]. For this reason, all male patients belonging to infertile couples should undergo medical evaluation by an urologist trained in male reproduction.

Male fertility can be impaired as a result of [1176]:

- congenital or acquired urogenital abnormalities;
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g., as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-associated factor is found to explain impairment of sperm parameters and historically was referred to as idiopathic male infertility. These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing, although semen analysis may reveal pathological findings (see 9.3.2). On the other hand, unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters. It is now believed that idiopathic male infertility may be associated with several previously unidentified pathological factors, which include but are not limited to endocrine disruption as a result of environmental pollution, generation of reactive oxygen species/sperm DNA damage, or genetic and epigenetic abnormalities [1178].

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1179-1182]. Table 32 summarises the main male-infertility-associated factors.

Table 32: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [1183]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm auto-antibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5

Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.0
Others	0.8	1.9

CBAVD = Congenital bilateral absence of the vas deferens.

*9.2.2 **Recommendations on epidemiology and aetiology***

Recommendations	Strength rating
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	Strong

9.3 Diagnostic work-up

A focused evaluation of the male patient must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis - with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1184], and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

*9.3.1 **Medical/reproductive history and physical examination***

9.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns which could affect the male partner's fertility, such as lifestyle, family history (including, testis cancer), comorbid conditions (including, systemic diseases; e.g., hypertension; diabetes mellitus; obesity; MetS; testis cancer, etc.), genito-urinary infections (including, sexually transmitted infections), past history of surgery of the testis and excluding any potential known gonadotoxins.

Typical findings from the history of a patient with infertility include:

- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infections;
- exposure to environmental toxins;
- gonadotoxic medications (anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

9.3.1.2 Physical examination

A focused physical examination is compulsory in the evaluation of every infertile male, including presence of secondary sexual characteristics. The size, texture and consistency of the testes must be evaluated. In clinical practice, testis volume is assessed by Prader's orchidometer [1185]; orchidometry may over-estimate testis volume when compared with US assessment [1186]. There are no uniform reference values in terms of Prader's orchidometer-derived testis volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1185-1187]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0±5.0 mL [1185], whereas in infertile patients it is 18.0±5.0 mL [1185, 1188, 1189]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, the epididymis, and the vas deferens should be evaluated. Other physical alterations, such as abnormalities of the penis (e.g.,

phimosis, short frenulum, fibrotic nodules, epispadias, hypospadias, etc.), abnormal body hair distribution and gynecomastia, should also be evaluated.

Typical findings from the physical examination of a patient with characteristics suggestive for testicular deficiency include:

- abnormal secondary sexual characteristics;
- abnormal testicular volume and/or consistency;
- testicular masses (potentially suggestive of cancer);
- absence of testes (uni-bilaterally);
- gynaecomastia;
- varicocele.

*9.3.2 **Semen analysis***

A comprehensive andrological examination is always indicated if semen analysis shows abnormalities as compared with reference values (Table 33). Important treatment decisions are based on the results of semen analysis; therefore, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the most updated version of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [1190]. There is consensus that modern semen analysis must follow these guidelines. However it has also become clear from studies that more complex testing than semen analysis may be required, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or assisted reproductive technologies (ART) and men with unexplained male infertility. In these patients there is evidence that the sperm DNA may be damaged, thus resulting in pregnancy failure [1178] (see below).

Table 33: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	**Lower reference limit (range)**
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≤ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

If the results of semen analysis are normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-teratozoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1191], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In those cases, a more comprehensive assessment of the hormonal profile may be helpful to further and more accurately differentially diagnose among pathologic conditions.

In azoospermia, the semen analysis may present with normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3,000 g for fifteen minutes and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically [1190]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intracytoplasmic sperm injection (ICSI) and obviate the need to surgical intervention.

*9.3.3 **Measurement of sperm DNA Fragmentation Index (DFI)***

Semen analysis is a descriptive evaluation, and may be unable to discriminate between the sperm of fertile and infertile men. Therefore, it is now apparent that sperm DNA damage may occur in men with infertility. DNA fragmentation, or the accumulation of single- and double-strand DNA breaks, is a common property of sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception. In this context, sperm DNA damage is more common in infertile men and sperm DNA damage has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1192, 1193], including impaired embryo development [1192], miscarriage, recurrent pregnancy loss [1192, 1194], and birth defects in the offspring [1192]. Sperm DNA damage can be increased by a number of factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1193].

A number of assays have been described to measure sperm DNA damage. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict treatment outcomes from ART and controversy exists as whether to recommend them routinely for clinical use [1193, 1195]. Of those, terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labeling (TUNEL) and the alkaline comet test (COMET), are tests that directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. Sperm chromatin structure assay is still the most widely studied and one of the most commonly used techniques to detect DNA damage [1196, 1197]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI,%) [1198], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1199]. It is suggested that a threshold value of DFI of 30% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or Intra-uterine insemination (IUI) [1197]. Furthermore, DFI values of over 50% on SCSA have been associated with poorer outcomes from *in vitro* fertilisation (IVF) treatment. More recently, the mean COMET score and scores for proportions of sperm with high or low DNA damage have been shown to be of value in diagnosing male infertility and providing additional discriminatory information for the prediction of both IVF and ICSI live births [1193].

Testicular sperm has been reported to have lower levels of sperm DFI when compared to ejaculated sperm [1200]. Couples with elevated DNA fragmentation may benefit from the combination of testicular sperm extraction (TESE) and ICSI, an approach called TESE-ICSI, which may not overcome infertility when applied to an unselected population of infertile men with untested DNA fragmentation values [1197, 1200]. However, further evidence is needed to support this practice in the routine clinical setting [1200].

*9.3.4 **Hormonal determinations***

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1201]. When spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are usually within the normal range [1201]. However, for patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have both normal FSH and testis volume [1202, 1203]. Furthermore men with non-obstructive azoospermia (NOA) and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1203].

*9.3.5 **Genetic testing***

All urologists working in andrology must have an understanding of the genetic abnormalities most commonly associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can still be offered a reasonable chance of paternity, using IVF, ICSI and sperm extraction from the testes in cases of azoospermia. However, the spermatozoa of infertile men shows an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies

in spermatozoa (sperm aneuploidy) is also feasible and can be performed in selected cases (e.g., recurrent miscarriage) [1204-1206].

9.3.5.1 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations). In a survey of pooled data from eleven publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [1207]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities [1207]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a ten-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [1208, 1209]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter Syndrome) [1210, 1211].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is currently indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [1209]. This broad selection criterion has been recently externally validated, with the finding that the suggested threshold has a relatively low sensitivity, specificity, and discrimination (namely, 80%, 37%, and 59%, respectively) [1212]. In this context, a novel nomogram, with a 2% probability cut-off, which allows for a more careful detection of karyotype alterations has been developed [1212]. Notwithstanding, the clinical value of spermatozoa < 10 million/mL remains a valid threshold until further studies, evaluating the cost-effectiveness, in which costs of adverse events due to chromosomal abnormalities (e.g. miscarriages and children with congenital anomalies) are performed [1213]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

9.3.5.1.1 Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47, XXY mosaicism])

Klinefelter Syndrome is the most common sex chromosome abnormality [1214]. Adult men with Klinefelter Syndrome usually have small firm testicles along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [15]. As a whole, the phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In the vast majority of the cases infertility and reduced testis volume are the only clinical features that can be detected. Leydig cell function is also commonly impaired in men with Klinefelter Syndrome and thus testosterone deficiency is more frequently observed than that in the general population, although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [15, 1215]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1216].

The presence of germ cells and sperm production are variable in men with Klinefelter Syndrome and are more frequently observed in mosaicism, 46,XY/47,XXY. Based on sperm fluorescence *in situ* hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [1217]. The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism [1218, 1219] and in 1.36-25% of men with somatic karyotype 47,XXY [1220-1223]. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1224] [1225]. There is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1210, 1226].

Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) although the conception of one 47,XXY foetus has been reported [1214]. Although data published so far have not reported any difference in the prevalence of aneuploidies in children conceived using ICSI in Klinefelter Syndrome compared to the general population, men with Klinefelter Syndrome undergoing fertility treatments should be counselled regarding the potential genetic abnormalities in their offspring.

Regular medical follow-up of men with Klinefelter Syndrome is recommended as androgen replacement therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed. Since this syndrome is associated with a number of general health problems, appropriate medical follow-up is therefore advised [16, 1227, 1228]. In particular, men with Klinefelter Syndrome are at higher risk

of metabolic and carviovascular diseases (CVD), including venous thromoembolism (VTE). Therefore, men with Klinefelter Syndrome should be made aware of this risk, particularly when starting testosterone treatment TRT [1229]. In addition, a higher risk of haemathological malignances has been reported in men with Klinefelter Syndrome [16].

Testicular sperm extraction in peri-pubertal or pre-pubertal Klinefelter boys aiming at cryopreservation of testicular spermatogonial stem cells is to be still considered experimental and should only be performed within a research setting [1230]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1231].

9.3.5.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter Syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring. However, the use of this genetic test is largely limited by the availability of laboratories able to perform this analysis [1232]. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1233, 1234].

9.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1235]. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis. Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations and was also found in ~2% of men with obstructive azoospermia [1236]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD, particularly those with a semen volume < 1.0 mL and acidic pH < 7.0 [1237-1239]. Approximately 1,500 mutations are listed on the CFTR database http://www.genetsickkids.on.ca/cftr/.

The most frequently found mutations are the F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1240, 1241]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1242], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a very low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the male's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [1243].

9.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1244]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is extremely rare for patients who have CBAVD and CFTR mutations [1245]. An abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CTFR mutations. Findings may range from unilateral absence of the vas deferens with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1246].

9.3.5.3 Y microdeletions - partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1247]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [1248]. In each AZF region,

there are several spermatogenesis candidate genes [1249]. Deletions occur *en bloc* (i.e. removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a "fine tuner" of sperm production, and its specific screening is not advised [1250].

9.3.5.3.1 Clinical implications of Y microdeletions

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [1251].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1252, 1253].
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%).
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%) [1254].
- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete deletions of the AZFb region is associated with spermatogenic arrest. Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm at the time of TESE and sperm is not found in these patients. Therefore, TESE should not be attempted in these patients [1255, 1256].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Sperm can be found in up to 50%-75%of men with AZFc microdeletions [1255-1257].
- Men with AZFc microdeletions who are oligozoospermic or in whom sperm is found at the time of TESE must be counselled that any male offspring will inherit the deletion.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [1258, 1259].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1258].

9.3.5.3.1.1 Testing for Y microdeletions

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A recent single meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligozoospermic men in thirty-seven European and North American studies (n = 12,492 oligozoospermic men) showed that the majority of microdeletions occur in men with sperm concentrations of ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1259]. In this context, whilst an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are less than 5 million sperm/mL, but should be necessarily tested if less than ≤1 million sperm/mL.

With the efforts of the European Academy of Andrology (EAA) guidelines and the European Molecular Genetics Quality Network external quality control program (http://www.emqn.org/emqn/), Yq testing has become more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [1260].

9.3.5.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son will have the same microdeletion [1260], but occasionally the son may have a more extensive deletion [1261]. The extent of spermatogenic failure (still in the range of azoo-/oligozoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity on reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [1262, 1263], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [1264]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [1258, 1260]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

9.3.5.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [1265]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [1260, 1266-1268]. The frequency of gr/gr deletion in oligozoospermic patients is ~5% [1269].

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [1267-1269]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplo-groups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multicenter study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [1242]. However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [1270].

9.3.5.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (e.g., Prader-Willi Syndrome [1271], Bardet-Biedl Syndrome [1272], Noonan's Syndrome, Myotonic dystrophy, dominant polycystic kidney disease [1273, 1274], 5 α-reductase deficiency [1275-1278], etc). Pre-implantation genetic screening (PGS) may be necessary in order to improve the ART outcomes among men with autosomal chromosomal defects [1279, 1280].

9.3.5.4 Sperm chromosomal abnormalities

Sperm can be examined for their chromosomal constitution using FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [1207, 1281-1283] and with translocations and may lead to recurrent pregnancy loss (RPL) or recurrent implantation failure [1284]. In a large retrospective series, couples with normal sperm FISH had similar outcomes from IVF and ICSI on PGS. However, couples with abnormal FISH had better clinical outcomes after PGS, suggesting a potential contribution of sperm to aneuploidic abnormalities in the embryo [1285]. In men with sperm aneuploidy, PGS combined with IVF and ICSI can increase chances of live births [1206].

9.3.5.5 Measurement of Oxidative Stress

Oxidative Stress (OS) is considered to be central in male infertility by affecting sperm quality, function, and the integrity of sperm as well [1286]. Oxidative Stress may lead to sperm DNA damage and poorer sperm DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1287, 1288]. Spermatozoa are vulnerable to OS and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [1289]. However, this data has never been supported by RCTs. Furthermore, there are no standardised testing methods for reactive oxygen species (ROS) and the duration of antioxidant treatments. Although ROS can be measured by various assays (e.g., chemiluminescence), routine measurement of ROS testing should remain experimental until these tests are validated in randomised controlled studies [1290].

9.3.5.6 Outcomes from assisted reproductive technology and long-term health implications to the male and offspring

It is estimated that more than four million babies have been born with ART since the first baby conceived by IVF in 1978 [1291]. As the number of couples undergoing ART has increased [1292, 1293], safety concerns related to ART have been raised. Assisted reproductive technology-conceived offspring have poorer prenatal outcomes, such as lower birth weight, lower gestational age, premature delivery, and higher hospital admissions compared with naturally conceived offspring [1294, 1295]. However, the exact mechanisms resulting in these complications remain obscure. Birth defects have also been associated with children conceived via ART in numerous studies [1296-1298]. Furthermore, a 30%-40% increase of major malformations were linked with ART in meta-analyses [1299-1301]. However, debate still continues as to whether the increased risk of birth defects are related to parental age, ART or the intrinsic defects in spermatogenesis in infertile men [1302-1307].

As for the long-term outcomes, post-natal growth patterns are mostly not associated with ART [1296, 1308, 1309]. However, a number of studies showed that ART children are taller [1310, 1311]. This may be important as there is evidence showing that rapid weight gain during early childhood is linked with higher blood pressure levels in children conceived via ART [1312]. It is also suggested that ART-conceived children have similar

childhood illnesses and hospital services rates as compared with naturally conceived children [1313-1315]. Furthermore, some studies showed an increased risk for retinoblastoma [1316] and hepatoblastoma in children after ART. However, these studies have been challenged with other studies which have not supported these findings [1317]. The current evidence for cancer risk in children conceived with ART is inadequate and further studies are warranted [1318, 1319]. Finally, a number of epigenetic alterations seem to be caused by ART, which might be the molecular basis to a some complex traits and diseases [1320].

*9.3.6 **Imaging in the infertile male***

In addition to physical examination, a scrotal US may be helpful in: i) measuring testis volume; ii) assessing testicular anatomy and testicular structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to an impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testis tumours; and, iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1186]. In clinical practice, Prader's orchidometer-derived testis volume is considered a reliable surrogate of US-measured testis volume, is easier to perform and is cost-effective [1185]. Nevertheless, scrotal US has a relevant role in testis volume assessment when Prader's orchidometer is unreliable (e.g., large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin; small testis, where the epididymis is large in comparison to the total testis volume [1185, 1186]. US-patterns of testicular inhomogeneity [1321, 1322] is usually associated with ageing, although it has also been reported in association with testis atrophy and fibrosis [1186]. At present, a diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1321, 1322].

9.3.6.1 Testicular neoplasms

Scrotal US is widely used in everyday clinical practice in patients with oligozoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1323, 1324]. In one study, men with infertility had an increased risk of testicular cancer (hazard rate [HR] 3.3). When infertility was refined according to individual semen parameters, oligozoospermic men had an increased risk of cancer compared with fertile control subjects (HR 11.9) [1325]. Furthermore, in a recent SR infertile men with testicular microcalcification (TM) were found to have an ~18-fold higher prevalence of testicular cancer [1326]. However, the utility of US as a routine screening tool in men with infertility to detect testis cancer remains a matter of debate [1323, 1324].

One issue in undertaking routine screening for testicular neoplasms in this cohort of patients is the risk of overdiagnosis and the increased detection of indeterminate lesions of the testis. These testicular lesions are often detected during the diagnostic work-up of infertile men and are difficult to characterise as benign or malignant based only upon US criteria, including size, vascularity and echogenicity.

A dichotomous cut-off of certainty in terms of lesion size that may definitely distinguish benign from malignant testicular masses is currently not available. However, in a recent study 81 patients with a lesion size < 10 mm on histology were identified and of these, 56 (69%) were benign lesions, although of note one-third were malignant. Overall, 100% of lesions < 5 mm in diameter were benign [1327]. Overall, available data suggest that the smaller the nodule, the less likely that it is malignant [1328], and lesions < 5 mm could be monitored, as they have a low probability of malignancy.

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testis inhomogeneity after previous pathologic conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral testicular microcalcifications, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of /contralateral tumour) [1186].

In the case of interval growth of a lesion and/or of the presence of additional risk factors for malignancy, testicular biopsy/surgery may be considered, although the evidence for adopting such a management policy is limited. In 145 men referred for azoospermia who underwent US before testicular biopsy, 49 (34%) had a focal sonographic abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions less than 5 mm all of which were confirmed to be benign. All other patients with hyperechoic or heterogeneous areas on US with subsequent tissue diagnoses were found to have benign lesions. The authors concluded that men with severe infertility who are found to have incidental testicular lesions and negative tumour markers and lesions less than 5 mm, may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1329].

Other studies have suggested that if a testicular lesion is hyperechoic and non-vascular on colour Doppler US and associated with negative tumour markers, the likelihood of malignancy is low and consideration can be given to regular testicular surveillance, as an alternative to radical surgery. In contrast, hypoechoic and vascular lesions are more likely to be malignant [1330-1334]. However, most lesions cannot be characterised by US (indeterminate), and histology remains the only certain diagnostic tool. A multidisciplinary team discussion (MDT), including invasive diagnostic modalities, should therefore be considered in these patients.

The role of US-guided intra-operative frozen section analysis in the diagnosis of testicular cancer in indeterminate lesions remains controversial, although a number of authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1335]. Whilst, the default treatment after patient counselling and MDT discussion may be radical orchidectomy, an US-guided biopsy with intra-operative frozen section analysis may be offered as an alternative to radical orchidectomy and potentially obviate the need for removal of the testis in a patient seeking fertility treatment. In those men who have severe abnormalities in semen parameters (e.g., azoospermia), a concurrent mTESE can also be performed at the time of diagnostic biopsy (panel recommendations).

In summary, if an indeterminate lesion is detected incidentally on US in an infertile male, a MDT discussion is highly recommended. Based upon the current literature, lesions < 5 mm in size are likely to be benign and serial US and self-examination can be performed. However, men with larger sized lesions (> 5 mm), which are hypoechoic or demonstrate vascularity, may be considered for open US-guided testis biopsy, testis sparing surgery with tumour enucleation for frozen section examination or radical orchidectomy. Therefore, in making a definitive treatment decision for surveillance versus intervention, consideration should be given to the size of the lesion, echogenicity, vascularity and previous history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]). If intervention is to be undertaken in men with severe hypospermatogenesis (e.g., azoospermia), then a simultaneous TESE can be undertaken, along with sperm banking.

9.3.6.2 Varicocele

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal color Doppler US is useful in assessing venous reflux and diamater, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1186]. Furthermore, definitive evidence of reflux and venous diameter may be utilised in the decision process to treat.

9.3.6.3 Transrectal US

For patients with a low seminal volume, acidic pH and severe oligozoospermia or azoospermia, in whom obstruction is suspected, scrotal and transrectal US are of clinical value in detecting CBAVD, presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, TRUS has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies related to the ejaculatory ducts obstruction, such as ejaculatory duct cysts, SV dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1186, 1336].

*9.3.7 **Recommendations for the diagnostic work-up of male infertility***

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention)	Strong
A complete medical history taking, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong
Prader's orchidometer-derived testis volume is a reliable surrogate of ultrasound (US)-measured testis volume in everyday clinical practice.	Weak
Perform semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) indications and reference criteria.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone FSH/Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome microdeletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong
Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but should be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the male and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter Syndrome offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong
Perform scrotal ultrasound in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testis biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal ultrasound if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.	Strong

9.4 Special Conditions and Relevant Clinical Entities

*9.4.1 **Cryptorchidism***

Cryptorchidism is the most common congenital abnormality of the male genitalia; at one year of age nearly 1% of all full-term male infants have cryptorchidism [1337]. Approximately 30% of undescended testes are non-

palpable and may be located within the abdominal cavity. This guideline will only deal with the management of cryptorchidism in adults.

9.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testis. If the undescended testicle has been identified from birth then this is termed congenital whilst the diagnosis of acquired is used in males that have been previously noted to have testicles situated within the scrotum. Cryptorchidism is categorised on whether it is bilateral or unilateral and the location of the testicle (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormone profiles, semen analysis and testicular volumes [1338, 1339]. However, testicular volume and hormone function have been reported to be reduced in adults treated with congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1340].

9.4.1.1.1 Aetiology and pathophysiology

It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy, including exposure to endocrine disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig/Sertoli cell dysfunction [1341]. Cryptorchidism has also been linked with maternal gestational smoking [1342] and premature birth [1343].

9.4.1.1.2 Pathophysiological effects in maldescended testes

9.4.1.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies, depending on the position of the testis [1344]. During the second year, the number of germ cells declines. Early treatment is therefore recommended (surgery should be performed within the subsequent year) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [1345]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1346, 1347]. It has been reported that hCG treatment may be harmful to future spermatogenesis therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend it use on a routine basis [1348]. See also the EAU Guidelines on Paediatric Urology [1349].

There is increasing evidence to suggest that in cases of a unilateral undescended testicle, the contralateral normal descended testicle may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and a dark spermatogonia) [1338, 1350]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

9.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1351]. Early surgical treatment may have a positive effect on subsequent fertility [1352]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity falls to 35-53% [1353]. It is also important to screen for hypogonadism, as this is a potential long-term sequelae of cryptorchidism and could contribute to impaired fertility and potential problems such as testosterone deficiency and MetS [1354].

9.4.1.1.2.3 Germ cell tumours

As a component of the TDS, cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcifications and intratubular germ cell neoplasia *in situ* (GCNIS), formerly known as carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [1355]. The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [1337]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1356]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [1357]. Therefore all men with a history of cryptorchidism should be warned that they are at increased risk of developing testis cancer and should perform regular testicular self-examination [1358].

9.4.1.2 Disease management

9.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood. Although some studies have recommended the use of hormonal stimulation as an adjunct to orchidopexy to improve fertility preservation, there is a lack of long-term data and also concerns regarding impairment to spermatogenesis with the use of these drugs [1359].

9.4.1.2.2 Surgical treatment

In adolescence removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1360]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered in this setting as there is evidence that the undescended testicle confers a higher risk of GCNIS and future development of GCT [1361] and regular testicular self-examination is not an option in these patients. In those patients with unilateral undescended testis (UDT) and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered in this setting to preserve androgen production and fertility if surgically feasible. However, multiple biopsies of the UDT are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT (panel consensus opinion). As indicated above, the correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men and therefore may be considered in these patients, if surgically feasible and or in patients who place a high utility on fertility preservation [1362]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1363]. At the time of orchidectomy in the treatment of GCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (i.e. history of cryptorchidism, < 12 mL. testicular volume, poor spermatogenesis [1364]).

9.4.1.3 Summary of evidence recommendations for cryptorchidism

Summary of evidence	**LE**
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	2a
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and GCTs and patients should be counselled appropriately.	2b
Paternity in men with unilateral cryptorchidism is almost equal to men without cryptorchidism.	1B
Bilateral cryptorchidism significantly reduces the likelihood of paternity and patients should be counselled appropriately.	1B

Recommendations	**Strength rating**
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

9.4.2 ***Germ cell malignancy and male infertility***

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of sub-fertile men [1365]. The lifetime risk of TGCT varies between ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and nonseminomas are preceded by GCNIS, and untreated GCNIS will eventually progress to invasive cancer [1366-1368]. There has been a general decline in male reproductive health and an increase in testicular cancer seen in western countries [1369, 1370]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1258, 1371]. This has been postulated to be related to the so-called TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in

pregnancy. As detailed above, the adverse sequelae of TDS include cryptorchidism hypospadias, infertility and an increased risk of testicular cancer [1341]. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1372] and abnormal semen parameters [1373]. These cancers arise from premalignant gonocytes or GCNIS [1374]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1326, 1375, 1376].

9.4.2.1 Testicular germ cell cancer and reproductive function

Overall, sperm, cryopreservation is considered standard practice in patients with cancer, not only with testicular cancer [1377, 1378]. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery which may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiation therapy; retroperitoneal surgery).

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 5-8% of men with TGCT [1379] and oligospermia in 50% [1380]. Given that the average ten-year survival rate for testicular cancer is 98% and it is the most common cancer in men of reproductive potential, it is mandatory to include counselling regarding fertility preservation prior to any gonadotoxic treatment [1380, 1381]. Semen analysis and cryopreservation is therefore recommended prior to any gonadotoxic cancer treatment and all patients should be offered cryopreservation of ejaculated sperm or sperm extracted surgically (e.g., c/mTESE) if shown to be azoospermic or severely oligozoospermic. Given the fact that a significant number of men with testis cancer at the time of first presentation will have severe semen abnormalities (i.e., severe oligozoospermia/azoospermia) even prior to (any) treatment [1374], it is recommended that men should undergo sperm cryopreservation prior to orchidectomy. As mentioned above, in those who are either azoospermic or severely oligozospermic this will allow an opportunity to perform TESE prior to further potential gonadotoxic/ablative surgery [1380]. The use of cryopreservation has been demonstrated to be the most cost effective strategy for fertility preservation in patients undergoing potential gonadotoxic treatments [1382, 1383]. In cases of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (Onco-TESE) potential. The surgical principles in Onco-TESE do not differ from the technique of mTESE for men with infertility (e.g., NOA) [1384, 1385]. In this context, referral to an urologist adept in microsurgery is desirable with facilities for sperm cryopreservation.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify the azoospermic or severely oligozoospermic patient at diagnosis who may eventually benefit from fertility-preserving procedures (e.g., Onco-mTESE at the time of orchidectomy). Therefore, counselling about fertility preservation is a priority and needs to be broached earlier in men with testis cancer [1380]. There are controversial arguments that performing cryopreservation prior to orchidectomy may delay subsequent treatment and have an adverse impact on survival. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Treatment of TGCT can result in additional impairment of semen quality [1386] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1387]. Chemotherapy is also associated with DNA damage and an increased DNA fragmentation rate [1388]. However, sperm aneuploidy levels will often decline to pre-treatment levels 18-24 months post treatment [1387] and several studies reviewing the offspring of cancer survivors has not shown a significant increased risk of genetic abnormalities in the context of chemotherapy and radiotherapy treatment [1389].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1390]. The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol may help to stratify those patients at increased risk of hypogonadism and provide a baseline for post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should be advised that they may be at increased risk of developing hypogonadism, as a result of an age-related decrease in testosterone production and could potentially develop MetS; there is no current long term data supporting this. The risk of hypogonadism is increased in the survivors of testis cancer and serum testosterone levels should be evaluated during the management of these patients [1391]. However, this risk is greatest at six to twelve months post-treatment and suggests that there may be some improvement in Leydig cell function post treatment and it is therefore reasonable to delay initiation of TRT, until the patient shows continuous signs or symptoms of testosterone deficiency [1366]. The risk of low libido and ED is also increased in TGCT patients [1392]. Furthermore, patients treated for TGCT are also at increased risk of CVD [1388]. Therefore, patients may require a MDT approach and in this context, survivorship programmes incorporating a holistic view of patients psychological, medical and social needs could be beneficial to the patient. In those patients who place a high utility on fertility potential, the use of TRT in men

with symptoms suggestive for TDS will need to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of SERM (e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off label treatments in this particular clinical setting.

9.4.2.2 Testicular microcalcification

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1393, 1394]. Although the true incidence of testicular microcalcification (TM) in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been associated in men with TGCT, cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudohermaphroditism and varicocele [1395]. The incidence reported seems to be higher with high-frequency US machines [1396]. The relationship between TM and infertility is unclear, but may relate to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification with hydroxyapatite occurs. Testicular microcalcification is found in testes at risk of malignant development, with a reported incidence of TM in men with TGCT of 6-46% [1397-1399]. A recent SR and meta-analysis of case-control studies indicated that the presence of TM is associated with a ~18-fold higher odds ratio for testicular cancer in infertile men (pooled OR:18.11, 95%CI: 8.09, 40.55; $p < 0.0001$) [1326].

Testicular microcalcification should therefore be considered pre-malignant in this setting and patients counselled accordingly. Testicular biopsies from men with TM have found a higher prevalence of GCNIS, especially in those with bilateral microcalcifications [1400]. However, TM can also occur in benign testicular conditions and the microcalcification itself is not malignant. Therefore, the association of TM and TGCT is controversial and the challenge is to identify those men at risk of harbouring GCNIS and future risk of TGCT. Further investigation of the association between TM and GCNIS will require testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, the clinician and patient should be reassured that testicular cancer will not develop in the majority of men with asymptomatic TM [1376] and available data indicates that only men in whom TM is found by US, and who have an increased risk of TGCT, should be offered testicular biopsy to exclude GCNIS. Men potentially at high-risk of harbouring or developing GCNIS includes men with infertility, atrophic testes, undescended testes, a history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1370, 1375]. The normal mean testicular volume is estimated to range between 12-30 mL and less than 12 mL is considered small [1393]. Patients with a history of TGCT and TM in the contralateral testis and sub-fertile patients have been demonstrated to have an increased risk of GCNIS [1376], whilst there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1370, 1394, 1401]. A useful algorithm has been proposed [1370] to stratifying those patients at increased risk of GCNIS who may benefit from testicular biopsy. However, when undertaking a biopsy in this setting the full risks and complications of adopting this strategy must be explained to the patient. With the lack of availability of large cohort studies, these recommendations must be treated with caution given the risk of overtreatment (i.e. biopsy) in these patients.

Decastro *et al.* [1402] suggested that testicular cancer will not develop in the majority of men with TM (98.4%) during a five-year follow-up. As such, an extensive screening program would only benefit men at significant risk. In this context it would be prudent to advise those patients with TM and risk factors for developing testicular cancer to at least undergo regular testicular examination. It has been suggested that these patients could also be offered annual physical examination by a urologist and US follow-up, although follow up protocols may be difficult to implement in this invariably young cohort of patients [1395]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1370]. However, the majority of patients who are azoospermic will be undergoing therapeutic biopsy (i.e. sperm retrieval) and therefore a definitive diagnosis can be made and there is a lack of evidence demonstrating a higher prevalence of testicular cancer in patients with both TM and testicular atrophy. In those patients with incidental TM, the risk of GCNIS will be low and a logical approach would be to instruct patients to perform regular testicular self-examination.

9.4.2.3 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	Strength rating
Men with testicular microcalcification (TM) should learn to perform self-examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound, measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (less than 12 mL), history of undescended testes and TGCT.	Weak
If there are suspicious findings on physical examination or ultrasound in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multidisciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular (CV) risk. Men should be managed in a multidisciplinary team setting with a dedicated late effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testis cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction at the time of radical orchidectomy.	Weak

9.4.3 ***Varicocele***

Varicocele is a common genital abnormality, which may be associated with the following andrological conditions:

- male subfertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

9.4.3.1 Classification

The following classification of varicocele [1176] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsalva manoeuvre, but can be shown by special tests (Doppler US studies).
- Grade 1: palpable during Valsava manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

Overall, the prevalence varicocele in one study was 48%. Of 224 patients, 104 had unilateral, 120 had bilateral varicoceles; 62 (13.30%) were grade 3, 99 (21.10%) were grade 2, and 63 (13.60%) were grade 1 [1403, 1404]. Worsening semen parameters are associated with a higher grade of varicocele and age [1405, 1406].

9.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and if this examination is inconclusive scrotal Doppler US is indicated [1176, 1407]. A number of radiological thresholds for venous diameter on US are used to diagnose significant varicoceles, although multiple spermatic veins > 3 mm in the upright position and during the Valsalva manoeuvre correlate with the presence of a clinically significant varicocele [1408a].

9.4.3.3 Basic considerations

9.4.3.3.1 Varicocele and fertility

Varicocele is present in almost 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35-40% of men presenting with infertility (1,3,7,9). The incidence of varicocele among men with primary infertility is estimated at 35-44%, whereas the incidence in men with secondary infertility is 45-81% [1176, 1409].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased OS and DNA damage [1409].

A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal parameters [1408b]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1409, 1410].

9.4.3.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of RCTs and observational studies in men with only clinical varicoceles showed that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters, including men with NOA with hypo-spermatogenesis or late maturation (spermatid) arrest on testicular pathology [1411-1415]. Moreover, pain resolution after varicocelectomy occurs in 48-90% of the patients [1416].

In RCTs varicocele repair in men with a subclinical varicocele was found to be ineffective in increasing the chances of spontaneous pregnancy [1417]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found in favour of treatment over observation. A Cochrane review from 2012 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance for spontaneous pregnancy [1418]. In two recent meta-analysis of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, the analyses favoured treatment, with a combined OR of 2.39-4.15 (95% CI 1.56 to 3.66) (95% CI, 2.31 to 7.45) [1415, 1418]. A recent meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI 0.95 to 3.02) [1419].

9.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment since most adolescents with a varicocele will have no problem achieving pregnancy later in life [1420]. Prophylactic treatment is only advised in case of documented testicular growth deterioration confirmed by serial clinical or Doppler US examinations and/or abnormal semen analysis [1421, 1422].

More novel considerations for varicocelectomy are patients with NOA, hypogonadism and DNA damage are described below:

Varicocelectomy and NOA

A number of studies have suggested that varicocelectomy may lead to sperm appearing in the ejaculate in men with azoospermia. In one such study, microsurgical varicocelectomy in men with NOA men led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1423]. There were further beneficial effects on sperm retrieval rates and ICSI outcomes. Meta-analyses have further corroborated these findings; 468 patients diagnosed with NOA and varicocele underwent surgical varicocele repair or percutaneous embolisation. In patients who underwent varicocelectomy, sperm retrieval rates (SRR) increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69-4.14; $p< 0.001$). In 43.9% of the patients (range: 20.8%-55.0%), sperm were found in postoperative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR and overall 44% of the treated men will have sperm in the ejaculate and may avoid sperm retrieval. However, the quality of evidence available is low and the risks and benefits of varicocele repair must be discussed fully with the patient with NOA and a clinically significant varicocele prior to embarking upon treatment intervention [1413].

Varicocelectomy and hypogonadism

Evidence would also suggest that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. In one meta-analysis studying the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone, 712 patients were included for analysis. The combined analysis of seven studies demonstrated that the mean post-operative serum testosterone improved by 34.3 ng/dL (95% CI: 22.57-46.04, $p < 0.00001$, $I^2 = 0.0\%$) compared with their pre-operative levels. In an analysis of surgery versus untreated control results showed that mean testosterone among hypogonadic patients increased by 105.65 ng/dL (95% CI: 77.99-133.32), favouring varicocelectomy [1424]. However, results must be treated with caution and adequate cost benefit analysis must be undertaken to determine the risks and benefits of surgical intervention over TRT in this setting. Whilst, varicocelectomy may be offered in hypogonadal men with clinically significant varicoceles, patients must be advised that the full benefits of treatment in this setting must be further evaluated with prospective randomised controlled studies.

9.4.3.3.4 Varicocelectomy for assisted reproductive technology and for raised DNA fragmentation

Varicocelectomy can improve sperm DNA integrity, with a mean difference of -3.37% (95% CI, -2.65 to -4.09) [1425]. There is now increasing evidence that varicocele treatment may improve DNA fragmentation

and outcomes from ART [1419, 1420]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to also include men with raised DNA fragmentation. If a patient has failed ART (e.g., failure of implantation, embryogenesis or recurrent pregnancy loss) there is an argument that if DNA damage is raised, consideration could be given to varicocele intervention after extensive counselling [1426] and exclusion of other causes of raised DNA fragmentation [1420, 1427]. The dilemma is whether varicocele treatment is indicated in men with raised DNA fragmentation and normal semen parameters.

In a meta-analysis study of non-azoospermic infertile men with clinical varicocele by Estevez *et al.*, four retrospective studies were included of men undergoing ICSI, and included 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR = 1.59, 95% CI: 1.19-2.12, I^2 = 25%) and live birth rates (OR = 2.17, 95% CI: 1.55-3.06, I^2 = 0%) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy. A further study [1419] evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligospermia or azoospermia and a varicocele. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR = 8.360).

9.4.3.4 Disease management

Several treatments are available for varicocele (Table 34). Current evidence indicates that microsurgical varicocelectomy is the most effective method among the different varicocelectomy techniques [1420, 1428]. Unfortunately, there are no large prospective RCTs comparing the efficacy of the various interventions for varicocele. However, microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques based upon case series [1429]. This procedure, however, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1430].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive widely used approaches, although higher recurrence rates compared to microscopic varicocelectomy have been reported (4-27%) [1409]. Robot-assisted varicocelectomy has similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1431-1433].

Table 34: Recurrence and complication rates associated with treatments for varicocele

Treatment	Ref.	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy	[1434, 1435]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema.
Retrograde sclerotherapy	[1436, 1437]	6-9.8	Hydrocele (3.3%) wound infection, scrotal pain	Technical failure 6-7.5%, adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, venous perforation
Retrograde embolisation	[1436, 1438]	3-11	Hydrocele (10%) haematoma, wound infection	Technical failure 7-27%, pain due to thrombophlebitis, radiological complications (e.g., reaction to contrast media), misplacement or migration of coils (to femoral vein or right atrium), retroperitoneal haemorrhage, fibrosis, ureteric obstruction, venous perforation
Open operation				
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	
Inguinal approach	[1439, 1440]	2.6-13	Hydrocele (7.3%), testicular atrophy, epididymo-orchitis, wound complications	Post-operative pain due to incision of external oblique fascia, genitofemoral nerve damage
Open retroperitoneal high ligation	[1428, 1441]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal edema	External spermatic vein ligation failure
Microsurgical inguinal or subinguinal	[1429, 1439, 1442, 1443]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy	[1406, 1428, 1429, 1444, 1445]	3-6	Hydrocele (7-43%) epididymitis, wound infection, testicular atrophy due to injury of testicular artery, bleeding	External spermatic vein ligation failure, intestinal, vascular and nerve damage; pulmonary embolism; pneumoscrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum)

9.4.3.5 Summary of evidence and recommendations for varicocele

Summary of evidence	LE
The presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment: the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair may be effective in men with abnormal semen parameters, a clinical varicocele and otherwise unexplained male factor infertility.	1a
Although there are no prospective randomised studies evaluating this, meta-analysis suggest that varicocele repair may lead to sperm appearing in the ejaculate in men with non-obstructive azoospermia	2
Microscopic approach (inguinal/subinguinal) may have lower recurrence and complications rates than non-microscopic approaches (retroperitoneal and laparoscopic), although no RCTs are available yet.	2a
Varicocele is associated with raised DNA fragmentation and intervention has been shown to reduce DNA fragmentation	2a

Recommendations	Strength rating
Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicocele in infertile men who have normal semen analysis and in men with a subclinical varicocele.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

*9.4.4 **Male accessory gland infections and infertility***

9.4.4.1 Introduction

Infections of the male urogenital tract are potentially curable causes of male infertility [1446-1448]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1446]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1449]. A SR assessing the relationship between sexually transmitted diseases, such as *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae, Trichomonas vaginalis* and viral infections, and infertility was unable to draw a strong association between STDs and male infertility due to the limited quality of reported data [1450].

9.4.4.2 Diagnostic evaluation

9.4.4.2.1 Semen analysis

Semen analysis (see Section 9.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CP/CPPS) (NIH IIa versus NIH 3b National Institutes of Health classification for CP/CPPS).

9.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), > 10^6 peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In these cases, a semen culture or PCR analysis should be performed for common urinary tract pathogens. A concentration of > 10^3 CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1451]. The sampling should be delivered the same day to the laboratory because the sampling time can influence the rate of positive micro-organisms in semen and the frequency of isolation of different strains [1452]. The ideal diagnostic test for isolating *C. trachomatis* in semen has not yet been established [1453], but the most accurate method is PCR analysis [1454-1456].

Historical data showed that *Ureaplasma urealyticum* is pathogenic only in high concentrations (> 10^3 CFU/mL ejaculate). Less than 10% of samples analysed for ureaplasma exceeded this concentration [1457]. Normal colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1458].

A recent meta-analysis indicates that *Ureaplasma parvum* and *Mycoplasma genitalium* are not associated with male infertility, but a significant relationship existed between *Ureaplasma urealyticum* (OR 3.03 95% CI: 1.02-8.99) and *Mycoplasma hominis* (OR 2.8; 95% CI: 0.93- 3.64) [1459].

The prevalence of Human papilloma virus (HPV) in the semen ranges from 2-31% in the general population and is higher in men with unexplained infertility (10-35,7%) [1460,1461]. Recent systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1462-1464]. However, data still needs to be prospectively validated to clearly define the clinical impact of HPV infection in semen. Additionally, seminal presence of Herpes Simplex virus (HSV)-2 in infertile men may be associated with lower sperm quality compared to HSV-negative infertile men [1449]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

9.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1465]. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator [1466]. According to the WHO classification, leukocytospermia is defined as > 10^6 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [1467, 1468]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3b). Furthermore, leukocytospermia should be further confirmed by performing a peroxidase test on the seminal analysis. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms will improve conception rates [1469].

9.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology has been demonstrated in a recent SR based on case-controlled studies [1470]. Both *C. trachomatis* and *Ureoplasma spp*. can cause decreased sperm density, motility, altered morphology and increased DNA damage. HPV can also induce changes in sperm density, motility and DNA damage [1460, 1461]. *Mycoplasma spp*. can cause decreased motility and development of antisperm antibodies [1449].

9.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1448, 1471, 1472]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function through different pathways but no correlations have been found [1473-1475].

The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process [1476]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) [1477].

9.4.4.2.6 Glandular secretory dysfunction

The secretory function of the prostate gland can be evaluated by measuring seminal plasma pH, citric acid, or γ-glutamine transpeptidase levels; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1478].

9.4.4.2.7 Reactive oxygen species

Reactive oxygen species may be increased in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* infection, with subsequent decrease in ROS upon antibiotic treatment. However, the levels of ROS in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen were low, making it difficult to draw any firm conclusions [1479]. Chronic urogenital infections are also associated with increased leukocyte numbers [1480]. However, their biological significance in prostatitis remains unclear [1448].

9.4.4.2.8 Disease management

Treatment of CP/CPPS is usually targeted at relieving symptoms [1481, 1482]. The indications and aims of therapy are:

- reduction or eradication of micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters associated with fertility impairment [1483].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has providedsymptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [1483], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1448, 1484].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated to impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1479].

9.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* [1485, 1486]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with urinary tract infection and occurs more often in men aged > 35 years [1487].

9.4.4.3.1 Diagnostic evaluation

9.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive motility can be observed [1485, 1488, 1489]. Semen culture might help to identify pathogenic micro-organisms. Development of stenosis of the epididymal ducts, reduction of sperm count, and azoospermia are more important potential sequelae to consider in the follow-up of bilateral epididymitis (see Chapter 9.3.2).

9.4.4.3.1.2 Disease management

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to also refer their sexual partners for evaluation and treatment [1490].

9.4.4.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	**LE**
Male accessory gland infections are not clearly associated with impaired natural conception.	3
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities.	2a
Although antibiotic treatment for MAGIs may result in improvement in sperm quality, it does not enhance the probability of conception.	2a

Recommendations	**Strength rating**
Treating male accessory gland infections (MAGIs) may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Data is insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia may improve fertility outcomes.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

9.5 Non-Invasive Male Infertility Management

*9.5.1 **Idiopathic male infertility and OATS***

Oligo-astheno-teratozoospermia (OAT) is a clinical condition, with a reduced number of spermatozoa in the ejaculate, which is also characterised by a reduced motility and morphology; often referred to as OAT syndrome (OATs). Several conditions can cause OATs, although the aetiology may be unknown in a significant number of cases [73, 1324].

*9.5.2 **Empirical treatments***

9.5.2.1 Life-style

Studies suggest that environmental and lifestyle factors may contribute to idiopathic infertility acting additively on a susceptible genetic background [73, 1324]. Hence, lifestyle improvement can have a positive effect on sperm parameters (see below).

9.5.2.1.1 Weight loss

Few authors have investigated the role of weight loss on male fertility outcomes. Non-controlled studies have suggested that weight loss can result in improved sperm parameters [73, 1491, 1492]. However, data derived from RCTs are more conflicting. In particular, a meta-analysis including a total of 28 cohort studies and 1,022 patients, documented that bariatric surgery had no effects in improving sperm quality and function in morbidly obese men [1493]. Data on ART outcomes are lacking. However, it is important to recognise that weight loss is able to improve obesity-related secondary hypogonadism which may result in better outcomes in couples seeking medical care for infertility and is important for the general health of the male partner [1491, 1493].

9.5.2.1.2 Physical activity

Regular physical activity is recommended by the WHO in order to prevent and reduced the risk of several long-term chronic diseases [1494]. A recent meta-analysis has documented that moderate-intensity (20-40 METs-h/week) or even high-intensity (40-80 METs-h/week) recreational physical activity can result in better semen parameters [1495]. In addition, similar to what is observed form weight loss improvements in hormonal profile have also been reported [1496].

9.5.2.1.3 Smoking

Epidemiological data has indicated that about one in three men of reproductive age smokes, with the highest prevalence observed in Europe among all the WHO regions [1497]. Data derived from a large meta-analysis including twenty studies and 5,865 participants has clearly documented a negative association between smoking and sperm parameters [1497]. Experimental studies performed in rats showed that nicotine has a dose-dependent deleterious effect on the sperm, which can be improved by nicotine cessation [1498]. Data in men are lacking and only one case report has indicated an improvement of sperm parameters after a three months smoking cessation program [1499]. Similar data have been reported in a recent non-controlled study, which showed a possible benefit on ART after the male partner stopped smoking [1500].

9.5.2.1.4 Alcohol consumption

Data derived from a recent meta-analysis including fifteen cross-sectional studies and 16,395 men suggested that moderate alcohol did not adversely affect semen parameters whereas higher alcohol intake can result in a detrimental effect on male fertility [1501]. Similar to what has been reported for weight loss, however, heavy chronic ethanol consumption (defined as > two drinks per day [1502]) can reduce testosterone levels which can be restored by alcohol cessation [1503].

9.5.2.2 Antioxidant treatment

Inflammation is a positive reaction of the human body to overcome potential noxious stimuli. However, chronic inflammation can induce several negative biochemical and metabolic effects contributing to the development of several medical conditions. Oxidative stress (OS) is considered one of the most important contributing factors in the pathogenesis of idiopathic infertility. ROS, the final products of OS, can impair sperm function acting at several levels including plasma membrane lipid peroxidation and which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased DNA fragmentation [1504]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1505]. Despite this, evidence for the role of antioxidant therapy in male patients with infertility is still conflicting. In a meta-analysis Cochrane Data Base Systemic Review including 34 RCTs and 2,876 couples using various antioxidant compounds, it was concluded that antioxidant therapy had a positive impact on live birth and pregnancy rates in sub-fertile couples undergoing ART cycles [1506]. Similar results were also reported in the most recent meta-analysis including 61 studies with a total population of 6,264 infertile men, aged between 18 and 65 year [1507]. However, all the aforementioned studies also recognised important limitations. In particular, data were derived

from low-quality RCTs with serious risk of bias due to poor methods of reporting randomisation, failure to report on the clinical outcomes including live birth rate and clinical pregnancy rate, high attrition rates, and also imprecision due to often low event rates and small overall sample sizes [1507]. In addition, no clear conclusion regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate were possible [1507].

9.5.2.3 Selective oestrogen receptor modulators (SERMs)

Selective oestrogen receptor modulators (SERMs) have been advocated as a possible empiric treatment in male idiopathic infertility. The proposed mechanism of action is based on the activity of these compounds to block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion leading to an increase in pituitary gonadotropin release. The latter effect, by stimulating spermatogenesis, represents the rational basis for SERM administration to patients with reduced sperm number [1508]. In an initial meta-analysis including eleven RCTs, in which only five were placebo-controlled, it was concluded that SERMs were not associated with an increased pregnancy rate in the 459 patients analysed [1509]. In a subsequent Cochrane review published one year later, these findings were confirmed, in a larger number of studies (n=10 and 738 men), although positive effects on hormonal parameters were documented. More recently, Chua *et al.* meta-analysed data derived from eleven RCTs showing that the use of SERM was associated with a statistically significant increased pregnancy rate [1510]. In addition, a significant improvement in sperm parameters and hormonal parameters were detected. Similar results were confirmed in the latest updated meta-analysis including sixteen studies [1508]. However, it should be recognised that the quality of the papers included is low and only a few studies are placebo-controlled. In conclusion, although some positive results relating to the use of SERMs in men with idiopathic infertility have been reported, no conclusive recommendations can be drawn due to poor quality of the available evidence. Furthermore, complications from the use of SERM are under reported.

9.5.2.4 Aromatase inhibitors

Aromatase, a cytochrome p450 enzyme, is present in the testes, prostate, brain, bone, and adipose tissue of men; it converts testosterone and androstenedione to estradiol and estrone, respectively. Estradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, AIs may decrease oestrogen production by reversibly inhibiting cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex; inhibiting the negative feedback of oestrogen on the hypothalamus resulting in stronger GnRH pulses that stimulate the pituitary to increase production of FSH [1511-1514]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to estradiol ratio. In this context, Aromatase inhibitors (AIs) have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1515]. Either steroidal (testolactone) or non-steroidal (anastrozole and letrozole) AIs were found to statistically improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these medications in this clinical setting [1513, 1515].

Recommendations	Strength rating
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although anti-oxidant use may improve semen parameters.	Weak
No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn.	Weak
No conclusive recommendations on the use of either steroidal (testolactone) or non-steroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery.	Weak

9.5.3 ***Hormonal therapy***

9.5.3.1 Gonadotrophins

Follicle Stimulating Hormone is primarily involved in the initiation of spermatogenesis and testicular growth during puberty. The role of FSH post puberty has not been clearly defined. Luteinising Hormone stimulates testosterone production in the testes, but due to its short half-life is not suitable for clinical use. Human Chorionic Gonadotrophin acts in a similar manner to LH and can be used pharmacologically to stimulate testosterone release in men with failure of their hypothalamic-pituitary axis. Human Chorionic Gonadotrophin

can adequately stimulate spermatogenesis in men whom have developed hypopituitarism after a normal puberty. Therefore, the treatment of men with secondary hypogonadism depends on whether or not they developed hypothalamic-pituitary failure before or after puberty [5].

9.5.3.2 Secondary Hypogonadism

(a) Pre-Pubertal-Onset

Congenital causes resulting in low gonadotropin production are associated with testicular size < 4 mL and/or cryptorchidism. Testes size of < 4 mL occurs when they have not been exposed to any gonadotropins at all. These conditions require combination therapy with both hCG and FSH with subcutaneous administration or GnRH by pulsed delivery using a subcutaneous pump [1516]. However, GnRH treatment requires a pulsatile secretion using specific devices for either intravenous or subcutaneous administration, which may limit patient compliance. Moreover, GnRH therapy should be limited to subjects with a residual pituitary gonadotropic activity [5].

As for the type of gonadotropin treatment, it is usual to commence hCG first and titrate the dose to achieve testosterone levels within the normal physiological range. However, FSH can be given first or in combination with hCG [105]. Human Chorionic Gonadotrophin is given twice weekly and in patients with congenital secondary hypogonadism in high dose, commencing at 1,000 IU twice weekly. Testosterone levels can be assayed every two weeks with dosage increases until ideally mid-range testosterone is achieved. Dose increases can be to 2,000 IU, 3,000 IU, 4,000 IU and 5,000 IU all two to three times a week, until normal testosterone levels are achieved [1517-1520]. Failure to achieve normal testosterone status at the high dose would indicate that primary testicular failure is present, probably as a result of cryptorchidism or failure of testicular development. Human Chorionic Gonadotrophin is also used to stimulate testicular descent into the scrotum in subjects with cryptorchidism. Once the hCG dose giving a normal level testosterone is established with the implication that intra-testicular testosterone has occurred FSH 75-150 IU three times per week subcutaneously should be commenced. Usually the higher 150 IU dose three times weekly is needed to be successful in men with testes size < 4mL. The trophic response of the testes to FSH is variable in these patients and it may range from no effect to achieving testicular sizes of 12-15 mL [1521]. A trophic response is usually an indication of an increase in spermatogenesis. The production of new spermatogenesis may be evident after three months of FSH therapy, but could occur even up to eighteen months of treatment [1519-1521]. A low baseline sperm concentration does not indicate a poor response to gonadotropin therapy [1522]. Semen analysis can be assessed at three monthly intervals. These patients can be fertile with low sperm counts much less than 20 million/mL as there is a high proportion of motile sperm. Follicle-stimulating hormone SH therapy prior to GnRH is also effective in stimulating testicular growth and fertility in men with congenital hypogonadotrophic hypogonadism [1523]. A larger initial testicular volume is the best prognostic factor for induction of successful spermatogenesis [1524].

(b) Post-Pubertal Onset Secondary

If secondary hypogonadism develops after puberty, hCG alone is usually required first to stimulate spermatogenesis. Doses of subcutaneous hCG required may be lower than those used in individuals with pre-pubertal onset; therefore, a starting dose of 250 IU twice weekly is suggested, and if normal testosterone levels are reached, hCG doses may be increased up to 2,000 IU twice weekly as per pre-pubertal onset above. Again, semen analysis should be performed every three months to assess response, unless conception has taken place. If there is a failure of stimulation of spermatogenesis, then FSH can be added (75 IU three times per week, increasing to 150 IU three times per week if indicated). Similarly, a combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with secondary hypogonadism [105]. No difference in outcomes have been observed when urinary-derived, highly purified FSH was compared to recombinant FSH [105].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotrophin treatment [1524]. Data had suggested that previous testosterone therapy could negatively impact on gonadotropins treatment outcomes in men with secondary hypogonadism [1524]. However, this observation had been subsequently refuted by a meta-analysis which did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting of men [105].

In the presence of hyperprolactinaemia, causing suppression of gonadotrophins resulting in sub-fertility the treatment independent of aetiology (including a pituitary adenoma) is dopamine agonist therapy or withdrawal of a drug which causes the condition. Dopamine agonists used include bromocritpine, cabergoline and quinagolide.

9.5.3.3 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there is no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [74, 1525].

9.5.3.4 Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 - 8 mIU/mL). It has also been reported that FSH may improve sperm DNA fragmentation rates as well as ameliorating AMH and inhibin levels [1526-1529]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses. A Cochrane Database Systemic Review including six RCTs with 456 participants, different treatment protocols and follow-up periods concluded that FSH treatment resulted in higher live birth and pregnancy rates compared to either placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1530]. In a more recent meta-analysis including fifteen trials with more than 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1531]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved sperm retrieval rates and higher pregnancy and fertilisation rates in men treated with FSH compared to non-treated subjects [1532]. In men with NOA, the combination of hCG/FSH therapy has in only one study been shown to increase sperm retrieval rates [1533]. Human Chorionic Gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on sperm retrieval rates [1534].

9.5.3.5 Anabolic Steroid Abuse

Oligospermia or azoospermia as a result of anabolic abuse should be treated initially by withdrawal of the anabolic steroid. There is no common indication for treating this disorder; the management is based on case reports and clinical experience. Usually, adequate sperm numbers and quality will improve over a six to twelve month period. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to try and stimulate spermatogenesis [1535].

9.5.3.6 Recommendations for treatment of male infertility with hormonal therapy

Recommendations	Strength rating
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed Gonadotropin-releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given on the use of high dose FSH in men with idiopathic infertility prior (m)TESE and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In the presence of hyperprolactinaemia dopamine agonist therapy may improve spermatogenesis.	Weak

9.6 Invasive Male Infertility Management

*9.6.1 **Obstructive azoospermia***

Obstructive azoospermia is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1536]. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia [1537, 1538]. Men with OA usually have a normal FSH, testes of normal size and epididymal enlargement [1539]. Of clinical relevance, men with late maturation arrest may present with normal gonadotrophins and testis size and may be only be distinguished from OA at the time of surgical exploration.

The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

9.6.1.1 Classification of obstructive azoospermia

9.6.1.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [1540]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic) (Table 35).

9.6.1.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [1540-1543]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [1543]. Other congenital forms of epididymal obstruction include chronic sinu-pulmonary infections (Young's syndrome) [1544]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most commonly due to infections [1545, 1546]. Other causes may be trauma or surgical intervention (Table 35) [1547, 1548].

9.6.1.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy (Table 35) [1545]. Approximately 2-6 % of these men request vasectomy reversal (see section from EAU Guidelines on Male Infertility 2019 for this topic). Vasal obstruction may also occur after hernia repair [1549, 1550]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [1245].

9.6.1.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-5% of cases of OA and is classified as either cystic or post-inflammatory or calculi of one or both ejaculatory ducts (Table 35) [1380, 1551]. Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [1552], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [1553]. Paramedian or lateral intraprostatic cysts are rare [1554]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethroprostatitis [1555]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose, and acidic pH. The seminal vesicles (anterior-posterior diameter > 15 mm) and ejaculatory duct (> 2.3 mm in width) are usually dilated [1551, 1555-1557].

9.6.1.1.4.1 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neurogenic dysfunction [1558]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport can be observed as idiopathic or due to spinal cord injury, multiple sclerosis, retroperitoneal lymph node dissection, pelvic surgery and selective serotonin re-uptake inhibitors (SSRI), α-blockers and typical antipsychotic medication [1559].

Table 35: Causes of obstruction of the genitourinary system

Epydidimis
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA; hydrocelectomy; other scrotal surgery)
Congenital epididymal obstruction (usually manifests as congenital bilateral absence of the vas deferens [CBAVD])
Other congenital forms of epididymal obstruction (Young's syndrome)
Vas deferens
Vasectomy
Vasotomy/vasography (with improper technique)
Post-surgical iatrogenic obstruction (i.e., scrotal surgery; herniorraphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular; prostatic; seminal vesicular)
Infection (acute/chronic epididymitis)

Traumatic
Postsurgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

9.6.1.2 Diagnostic evaluation

9.6.1.2.1 Clinical history

Clinical history taking should follow the investigation and diagnostic evaluation of infertile men (See section 10.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

9.6.1.2.2 Clinical examination

Clinical examination should follow the guidelines for the diagnostic evaluation of infertile men. Obstructive azoospermia is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- Obstructive azoospermia and concomitant partial testicular failure;
- enlarged and dilated epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas.

9.6.1.2.3 Semen analysis

Azoospermia means the inability to detect spermatozoa after centrifugation at ×400 magnification. At least two semen analyses must be carried out [1536, 1560] (see section 10.3). When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in the semen pellet suggest complete seminal duct obstruction.

9.6.1.2.4 Hormone levels

Hormones including FSH and inhibin-B should be normal, but do not exclude other causes of testicular azoospermia (e.g., NOA). Although inhibin-B concentration is a good index of Sertoli cell integrity reflecting closely the state of spermatogenesis, its diagnostic value is no better than that of FSH and its use in clinical practice has not been widely advocated [1561].

9.6.1.2.5 Genetic Testing

Inability to palpate the vas on one or both sides should raise concern for a CFTR mutation. Any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis should be offered CFTR testing [1562].

9.6.1.2.6 Testicular biopsy

Testicular biopsy must be combined with TESE for cryopreservation. Although studies suggest that a diagnostic or isolated testis biopsy [1563] is the most important prognostic predictor of spermatogenesis and sperm retrieval, the panel recommends not to perform testis biopsies (including fine needle aspiration [FNA]) without performing simultaneously a therapeutic sperm retrieval, as this will require a further invasive procedure after biopsy. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1564, 1565].

9.6.1.3 Disease management

Sperm retrieval

9.6.1.3.1 Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

9.6.1.3.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1566] is indicated in men with CBAVD. Testicular sperm extraction (TESE) and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1567]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction does not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1568]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [1569] and it produces high pregnancy and fertilisation rates [1570]. In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1571]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1572].

Anatomical recanalisation following surgery may require 3 to 18 months. A recent systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogenous and vary between 1-50% [1573]. Before microsurgery, and in all cases where recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for subsequent ICSI procedures [1555]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1548, 1574]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates and larger studies are needed [1431].

9.6.1.3.3 Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedure patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1548, 1574]. The average time to patency is 1.7 to 4.3 months and late failures are uncommon (0-12%) [1573]. Robot-assisted vasovasostomy has similar success rates and larger studies are needed to establish its benefits over standard microsurgical procedures including cost-benefit analysis [1431].

The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas has a thick “toothpaste” appearance; in this case microsurgical EV may be indicated [1575-1577]. A simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

9.6.1.3.4 Vas deferens obstruction at the inguinal level

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy. In these cases, TESE/MESA/PESA or proximal vas deferens sperm aspiration [1578] can be used for cryopreservation for future ICSI. Prostate cancer patients who express an interest in future fertility should be counselled for cryopreservation [1579].

9.6.1.3.5 Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1551, 1555]. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision, unroofing or aspiration of the cyst is required [1551, 1555].

Intra-operative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the seminal vesicles (chromotubation) can help to confirm intra-operative opening of the ducts. Pregnancy rates after TURED are approximately 20-25% [1380, 1551, 1580]. Complications following TURED include epididymitis, urinary tract infection, gross haematuria, haematospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1551].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1581]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

9.6.1.4 Summary of evidence and recommendations for obstructive azoospermia

Summary of evidence	**LE**
Obstructive lesions of the seminal tract are frequent in azoospermic or severely oligozoospermic patients, usually with normal-sized testes and normal reproductive hormones.	3

Recommendations	**Strength rating**
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA, TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

9.6.2 ***Non-obstructive azoospermia***

Non-obstructive azoospermia (NOA) is defined as the absence of sperm at the semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed at least at two consecutives semen analyses [1582]. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

9.6.2.1 Investigation of Non-obstructive azoospermia

The diagnosis of NOA is based on the evidence of two consecutive semen analyses confirming azoospermia. Moreover, causes of OA should be ruled out. Patients with NOA should undergo a comprehensive assessment aimed to identify genetically transmissible conditions, potential treatable causes of azoospermia, and potential health-relevant comorbidities (e.g., testis cancer and hypogonadism [any type]). A detailed medical history (e.g., history of cryptorchidism, previous gonadotoxic treatments for cancer), also including socio-demographic characteristics [1583], along with a comprehensive physical examination should be performed in every patient to detect conditions potentially leading to azoospermia, while ruling out comorbidities frequently associated with azoospermia. Indeed, NOA could be the first sign of pituitary tumours or germ cell tumours of the testis [1584-1586]. Patients with NOA have been shown to be also at increased risk of being further diagnosed with cancer [1587]. Moreover, other systemic conditions such as metabolic syndrome, type 2 diabetes, osteoporosis and cardiovascular diseases (CVDs) have been more frequently observed in patients with NOA compared to normozoospermic men [1588-1590]. Therefore investigation of the infertile male provides an opportunity for long-term risk stratification for other co-morbid conditions [1591].

Genetic tests should be performed in patients with NOA to detect genetic abnormalities. As discussed (see section 10.3), patients should undergo karyotype analysis [1208, 1209], along with a screening of Y-chromosome microdeletions [1259, 1592] and of the gene coding for CFTR in order to exclude concomitant mutations, and to rule out CBAVD [1240, 1241]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

As detailed, all patients should undergo a complete hormonal investigation to exclude a concomitant hypogonadism, which has been found in about 30% of patients with NOA [341, 1593, 1594]. A correct definition of the type of the associated hypogonadism (i.e., hypogonadotropic hypogonadism versus hypergonadotropic vs. compensated hypogonadism) is fundamental to differentiate diagnostic and therapeutic approaches to the patient [1595].

Scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testis tumours. Testicular volume may be a predictor of spermatogenic function [1186] and is usually, but not invariably, low in patients with NOA. Some authors advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1596]; however, to date data are inconsistent to suggest a routine role of testis Doppler evaluation before TESE.

9.6.2.2 Surgery for non-obstructive azoospermia

Surgical treatment for NOA is mostly aimed to retrieve vital sperm directly from the testis (either uni- or bilaterally). This treatment is normally part of assisted reproductive technology (ART) protocols, including IVF cycles via intracytoplasmic sperm injection (ICSI). Techniques and indications for surgical sperm retrieval in patients with NOA are discussed below. As detailed, any surgical approach aimed at sperm retrieval must be considered not a routine and simple biopsy; in this context, performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate.

9.6.2.3 Indications and techniques of sperm retrieval

Spermatogenesis within the testis may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive sperm retrieval rates have been reported in up to 50% of patients with NOA [1597, 1598]. Numerous predictive factors for positive sperm retrieval have been investigated, although no definitive factors have been demonstrated to predict sperm retrieval [1598].

Historically, there is a good correlation between the histology found at testicular biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval [1563, 1599, 1600]. The presence of hypospermatogenesis at testicular biopsy showed a good accuracy in predicting positive sperm retrieval after either single or multiple conventional TESE or mTESE compared to maturation arrest pattern or a SCOS [1563, 1599, 1600]. However, a diagnostic biopsy is not recommended in this clinical setting for the reasons outlined above.

Hormonal levels, including FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes at surgery, and data from retrospective series are still controversial [1601-1607]. Similarly, conflicting results have been published regarding testicular volume as a predictor of positive sperm retrieval [1563, 1604, 1605]. Therefore, no clinical variable may be currently considered as a reliable predictor for positive sperm retrieval throughout ART patient work-up [1598].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is zero and therefore TESE procedures are contraindicated [1258]. Conversely, patients with Klinefelter syndrome [1225] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1604].

Historically, surgical techniques for retrieving sperm in men with NOA include testicular sperm aspiration (TESA), single or multiple conventional TESE (cTESE) and mTESE.

Fine needle aspiration (FNA)

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1608]. The procedure is performed under local anaesthesia in the office and percutaneous aspiration is performed with 23G needle in multiple sites, ranging from 4 to 18 [1608]. The retrieved tissue is sent for cytological and histological evaluation in order to provide information on the presence of mature sperm and on testicular histological pattern. Moreover, given that focal spermatogenesis may occur within the testis of patients with NOA, FNA mapping may provide information on the sites with the higher probability of retrieving sperms, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). Turek *et al.* have shown that a higher number of aspiration sites may increase the chance of finding sperm [1609, 1610]. The extent and type of subsequent sperm retrieval procedure can be tailored according to the FNA mapping results: TESA or TESE could be suggested in case of multiple positive sites for sperm, while a more precise and potentially more invasive technique, such as mTESE, could be considered for patients with only few positive sites at FNA [1608]. However, there are no RCTs comparing the diagnostic yield from FNA vs. mTESE. Furthermore, a positive FNA will require a secondary therapeutic surgical approach, which may increase the risk of testis damage and without appropriate cost-benefit analysis is not justifiable. Furthermore, there are no studies evaluating the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping cannot be recommended as a primary therapeutic intervention in men with NOA until further RCTs are undertaken.

Testicular sperm aspiration

Testicular sperm aspiration (TESA) is a minimally invasive, office-based, procedure in which testicular tissue is retrieved with a biopsy needle under local anaesthesia. Reported sperm retrieval rates with TESA range from 11 to 60% according to patients' profile and surgical techniques [1611-1614]. Data have shown that using larger needles with (18-21G) with multiple passes could yield a higher chance of positive sperm retrieval [1614]. Complications after TESA are very uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1614].

As a less invasive and less-costly procedure TESA has been proposed as a possible first-line approach before sending patients to a more invasive procedure [1614]. To date there are no RCTs comparing sperm retrieval rates from TESA, cTESE or mTESE. A recent meta-analysis including data from case-control studies, reported that TESE was two times (95% CI 1.8-2.2) more likely to result in successful sperm retrieval as compared with TESA [1598]. Given the low success rates compared to TESE, TESA is no longer recommended in men with NOA.

Conventional TESE

Conventional TESE (cTESE) requires a scrotal incision and an open biopsy of the testis. Reported sperm retrieval rates in single-arm studies are about 50% [1597]. However, pooled data analysis of case-control studies comparing conventional TESE with mTESE showed a lower unadjusted sperm retrieval rate of 35% (95% CI 30-40) for cTESE [1598]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1597, 1615].

The probability of finding vital sperm at TESE varies also according to testicular histology: data from non-randomised studies comparing cTESE with mTESE have shown a higher chance of sperm retrieval with mTESE only for patients with an histological finding of SCOS [1616]: in such cases results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE versus cTESE, respectively [1616]. Conversely, no difference between the two techniques has been found when comparing patients with a histology suggestive for maturation arrest [1616]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1617]. In light of these findings some authors have advocated that cTESE could be the technique of choice in patients with a histological finding of maturation arrest or hypospermatogenesis [1598, 1616].

Conventional TESE has been associated with a higher rate of complications compared to other techniques [1597]. A total of 51.7% of patients have been found with intratesticular haematoma at scrotal US three months after surgery, with testicular fibrosis observed in up to 30% of patients at 6-month assessment [1618].

A recent meta-analysis has investigated the risk of hypogonadism after TESE due to testicular atrophy [1619]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline in a time frame between 18 and 26 months.

Microdissection TESE)

Microdissection TESE (mTESE) is aimed at identifying sites of focal spermatogenesis within the testis by performing focal biopsies in areas where larger dilated (and opaque) tubules are present by using optical magnification (20-25x) [1620]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of sampled tissue and a consequent lower risk of complications.

Unadjusted sperm retrieval rate after mTESE was 52% (95% CI 47-58) in a pooled data analysis of studies comparing cTESE with mTESE [1598]. Specifically, mTESE resulted in a 1.5 higher chance of retrieving sperm compared to the conventional technique [1598]. In a study assessing the role of salvage mTESE after a previously failed cTESE or TESA, sperm were successfully retrieved in 46.5% of cases [1565]. Lower rates of complications have been observed with mTESE as compared to cTESE, both in terms of haematoma and fibrosis [1616]. Both procedures have shown a recovery of baseline testosterone levels at long-term follow-up [1617].

A recent meta-analysis of the currently available studies comparing cTESE vs. mTESE in patients with NOA showed a mean sperm retrieval rate of 47% (95% CI 45;49). No differences were observed when mTESE was compared to cTESE (46[range 43;49]% for cTESE versus 46[range 42;49]% for mTESE, respectively). Meta-regression analysis demonstrated that SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testis volume. Retrieved sperms resulted in a live birth rate of up to 28% per ICSI cycle [1621].

Although no difference between cTESE/mTESE techniques in subjects with NOA was found, to conclusively clarify if one technique is superior to the other, there is a need for a sufficiently powered and well-designed RCTs to compare mTESE to cTESE; therefore, a clear recommendation regarding the technique of choice cannot be given. Several variables should be considered before counselling patients for one specific technique including surgical skills, testicular histology, costs of the procedure and risk of complications.

Follow-up after TESE

When compared with cTESE, mTESE has been reported to have fewer post-operative complications and negative effects on testicular function. In a recent meta-analysis analysing the complications of TESE, men with Klinefelter syndrome and NOA had the largest decrease in total testosterone levels 6 months after TESE (mean decrease of 4.1 and 2.7 nmol/l) respectively, which recovered to baseline levels 26 and 18 months after TESE, respectively [1619]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism, particularly for patients with Klinefelter syndrome; testosterone levels assessment could be offered in asymptomatic men at 18 months post TESE or in those men who become symptomatic for hypogonadism after surgery [1622].

Hormonal therapy prior to surgical sperm retrieval approaches

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of sperm retrieval at the time of surgery in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. There is evidence that treatment with hCG can lead to an increase in ITT [1528] and Leydig cells within the testis [1623]. Moreover, it has been shown that in azoospermic patients with elevated gonadotropins levels, administration of HCG and/or FSH can lead to a so-called “gonadotropins reset”, with a reduction in FSH plasma concentrations and an improvement in Sertoli cells function [1624]. Similarly, clomiphene citrate may increase pituitary secretion by blocking feedback inhibition of estradiol, thus inducing an increase in FSH and LH in patients with NOA [1625]. Overall, whilst azoospermic patients with secondary hypogonadism should be treated accordingly to stimulate sperm production [341], there is currently no RCT showing a benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA. In a large multicentre case-control study, 496 patients with idiopathic NOA treated with a combination of clomiphene, HCG and human menopausal gonadotropin according to hormonal profile, were compared to 116 controls subjected to mTESE without receiving any pre-operative treatment [1533]. A total of 11% of treated patients had sperm in the ejaculate at the end of treatment; of the remaining patients, 57% had positive sperm retrieval at mTESE as compared with 33% in the control group. Likewise, a small case-control study including 50 men with idiopathic NOA, of whom 25 were treated with recombinant FSH before mTESE,

the authors observed a 24% sperm retrieval rate compared to 12% in the control group [1532]. Conversely, Gul *et al.* [1626] failed to find any advantage of pre-operative treatment with HCG compared to no treatment, in 34 idiopathic NOA patients candidates for mTESE.

Moreover, hormonal therapy has been proposed to increase the chance of sperm retrieval at salvage surgery after a previous failed cTESE or mTESE. Retrospective data have shown that treatment with HCG and recombinant FSH could lead to a 10-15% sperm retrieval rate at salvage mTESE [1528, 1627]. In a small case-control study 28 NOA patients were treated with HCG with or without FSH for 4-5 months before salvage mTESE and compared with 20 controls subjected to salvage surgery [1628]. Sperm retrieval rate was 21% in the treated group compared to 0% in the control group. The histological finding of hypospermatogenesis emerged as predictor of sperm retrieval at salvage surgery after hormonal treatment [1628]. Further prospective trials are needed to elucidate the effect of hormonal treatment before salvage surgery in NOA patients, with a previously failed cTESE or mTESE. However, patients should be counselled that the evidence for the role of hormone stimulation prior to sperm retrieval surgery in men with idiopathic NOA is limited [1629]. Currently, it is not recommended in routine practice.

9.6.2.4 Recommendations for Non-Obstructive Azoospermia

Recommendations	Strength rating
Patients with non-obstructive azoospermia should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated comorbidities. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for ART (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE.	Weak
Fine needle aspiration as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional TESE (cTESE) or microdissection TESE (mTESE) are the techniques of choice for retrieving sperm in patients with NOA.	Weak
No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

9.7 Assisted Reproductive Technologies

*9.7.1 **Types***

Assisted reproductive technology consists of procedures that involve the *in vitro* handling of both human oocytes and sperm, or of embryos, with the objective of establishing a pregnancy [1630].

Once couples have been prepared for treatment, the following are the steps that make up an ART cycle:

1. Pharmacological stimulation of growth of multiple ovarian follicles, while at the same time other medications are given to suppress the natural menstrual cycle and down-regulate the pituitary gland.
2. Careful monitoring at intervals to assess the growth of the follicles.
3. Ovulation triggering: when the follicles have reached an appropriate size, a drug is administered to bring about final maturation of the eggs.
4. Egg collection (usually with a trans-vaginal US probe to guide the pickup) and, in some cases of male infertility, sperm retrieval.
5. Fertilisation process, which is usually completed by IVF or ICSI.
6. Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching etc.
7. The embryos are then placed into the uterus. Issues of importance here include endometrial preparation, the best timing for embryo transfer, how many embryos to transfer, what type of catheter to use, the use of US guidance, need for bed rest etc.
8. Then there is luteal phase support, for which several hormonal options are available.

Fertility treatments are complex and each cycle consists of several steps. If one of the steps is incorrectly applied, conception may not occur [1630].

Several ART techniques are available:

9.7.1.1 Intra-uterine insemination (IUI): IUI is an infertility treatment that involves the placement of the prepared sperm into the uterine cavity timed around ovulation. This can be done in combination with ovarian stimulation or in a natural cycle. The aim of the stimulated cycle is to increase the number of follicles available for fertilisation and to enhance the accurate timing of insemination in comparison to the natural cycle IUI [1631-1633].

Intra-uterine insemination is generally, though not exclusively, used when there is at least one patent fallopian tube with normal sperm parameters and regular ovulatory cycles (unstimulated cycles) and when the female partner is less than 40 years of age.

The global pregnancy rate (PR) and delivery rate (DR) per IUI cycles with husband sperm are 12.0% and 8.0%, respectively. Using donor sperm the resultant PR and DR per cycle are 17.0% and 12.3%, respectively [1634]. The rates of successful treatment cycles for patients decrease with the increase in age, and the birth rates across all age groups have remained broadly stable over time. The highest birth rates were reported in patients younger than 38 years (14% in patients younger than 35 years and 12% in patients aged 35-37 years). The rates of successful treatments are low for patients older than 42 years. The multiple pregnancy rate (MPR) for IUI is approximately 8% [1632]. IUI is not recommended in couples with unexplained infertility, male factor and mild endometriosis, unless the couples have religious, cultural or social objections to proceed with IVF [1635].

Intra-uterine insemination with ovarian stimulation is a safe, cheaper, patient-friendly and non-inferior alternative to IVF in the management of couples with unexplained and mild male factor infertility [1631, 1632]. A recent RCT showed lower multiple pregnancy rates and comparable live birth rates in patients submitted to IUI with hormonal stimulation when compared to women undergoing IVF with single embryo transfer [1636]. Additionally, IUI was found to be a more cost-effective treatment than IVF for couples with unexplained or mild male subfertility [1637].

9.7.1.2 In vitro fertilisation IVF involves using controlled ovarian hyperstimulation to recruit multiple oocytes during each cycle from the female partner. Follicular development is monitored ultrasonically, and ova are harvested before ovulation with the use of US-guided needle aspiration. The recovered oocytes are mixed with processed semen to perform *in-vitro* fertilisation. The developing embryos are incubated for two to three days in culture and then placed trans-cervically into the uterus.

The rapid refinement of embryo cryopreservation methods has resulted in better perinatal outcomes of frozen-thawed embryo transfer (FET) and make it a viable alternative to fresh embryo transfer (ET) [1638, 1639]. FET

seems to be associated with lower risk of gestational complications than fresh ET. Individual approaches remain appropriate to balance the options of FET or fresh ET at present [1640].

Generally, only 20% to 30% of transferred embryos result in clinical pregnancies. The global PR and DR per aspiration for non-donor IVF is 24.0% and 17.6%, respectively [1634].

According to the NICE guidelines, IVF treatment is appropriate in cases of unexplained infertility for women who have not conceived after two years of regular unprotected sexual intercourse [1641].

9.7.1.3 Intracytoplasmic sperm injection is a procedure through which a single sperm is injected directly into the egg using a glass micropipette.

The difference between ICSI and IVF is the method used to achieve fertilisation. In conventional IVF, oocytes are incubated with sperm in a Petri dish, and the male gamete fertilises the oocyte naturally. In ICSI, the cumulus-oocyte complexes go through a denudation process in which the cumulus oophorus and corona radiata cells are removed mechanically or by an enzymatic process. This step is essential to enable microscopic evaluation of the oocyte regarding its maturity stage, as ICSI is performed only in metaphase II oocytes [1642]. A thin and delicate glass micropipette (injection needle) is used to immobilise and pick up morphologically normal sperm selected for injection. A single spermatozoon is aspirated by its tail into the injection needle, which is inserted through the zona pellucida into the oocyte cytoplasm. The spermatozoon is released at a cytoplasmic site sufficiently distant from the first polar body. During this process, the oocyte is held still by a glass micropipette [1642].

With this technique the oocyte can be fertilised independently of the morphology and/or motility of the spermatozoon injected.

Intracytoplasmic sperm injection is currently the most commonly used assisted reproductive technology, accounting for 70-80% of the cycles performed [1643].

The procedure was first used in cases of fertilisation failure after standard IVF or when an inadequate number of sperm cells were available. The consistency of fertilisation independent of the functional quality of the spermatozoon has extended the application of ICSI to immature spermatozoa retrieved surgically from the epididymis and testis [1644]. ICSI is the natural treatment for couples with severe male factor infertility and is also used for a number of non-male factor indications (Table 36) [1645].

Moreover, the need to denude the oocyte has allowed assessment of the nuclear maturity of the oocyte. ICSI is also preferred in conjunction with pre-implantation genetic diagnosis and has recently been used to treat HIV discordant couples, where there is a pressing need to minimise the exposure of the oocyte to a large number of spermatozoa [1644].

The global PR and DR per aspiration for ICSI is 26.2% and 19.0%, respectively [1634]. For all ages and with all the different sperm types used, fertilisation after ICSI is at approximately 70% to 80% and it ensures a clinical pregnancy rate of up to 45% [1643, 1644].

Existing evidence does not support ICSI in preference over IVF in the general non-male factor ART population; however, in couples with unexplained infertility, ICSI is associated with lower fertilisation failure rates than IVF [1645].

Overall, pregnancy outcomes from ICSI are comparable between epididymal and testicular sperm and also between fresh and frozen-thawed epididymal sperm in men with OA [1646]. However these results are from studies of low evidence [1645].

Sperm injection outcomes with fresh or frozen-thawed testicular sperm have also been compared in men with NOA. In a meta-analysis of 11 studies and 574 ICSI cycles, no statistically significant difference was observed between fresh and frozen-thawed testicular sperm with regards to fertilisation rate (RR 0.97, 95% CI 0.92-1.02) and clinical pregnancy rates (RR 1.00, 95% CI 0.75-1.33) [1647]. However, no meta-analysis was performed on data regarding implantation rate, miscarriage rate, and low birth rate.

Testicular sperm in men with raised DNA fragmentation in ejaculated sperm

The use of testicular sperm for ICSI is associated with possibly improved outcomes compared to ejaculated

sperm in men with high sperm DNA fragmentation [1200, 1645]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure from ARTs, although they should be counselled that live birth rates are under reported in the literature and patients must weigh up the risks of performing an invasive procedure in a potentially normozoospermic or unexplained condition. The advantages of the use of testicular sperm in men with cryptozoospermia have not yet been confirmed in large scale randomised studies [1648].

In terms of a practical approach, Urologists may offer the use of testicular sperm in patients with high DNA fragmentation. However, patients should be counselled regarded the low levels of evidence for this (i.e., non-randomised studies). Furthermore, testicular sperm should only be used in this setting once the common causes of oxidative stress have been excluded including varicoceles, dietary/lifestyle factors and accessory gland infections.

Table 36: Fertilisation methods for male-factor and non-male factor infertility (adapted from [1645]**)**

	Fertilisation method
Male Factor Infertility	
Sperms derived from men with azoospermia	ICSI mandatory
Severe OAT	ICSI highly recommended
Moderate OAT	IVF and ICSI equally effective
Isolated teratozoospermia	IVF and ICSI equally effective
Absolute asthenozoospermia	ICSI mandatory
Globozoospermia	ICSI mandatory
Anti-sperm antibodies	IVF and ICSI equally effective
Sperm DNA fragmentation	ICSI recommended
Non-male factor infertility	
Unexplained infertility	Equally effective. Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. It should be noted for clarification that in the absence of male factors, ICSI should not be offered in the first treatment cycle [1649].
General non-male factor population	Equally effective, slightly in favour of IVF
Poor quality oocytes and advanced maternal age	Equally effective, slightly in favour of IVF
Pre-implantational genetic testing	ICSI highly recommended
Poor responders	Equally effective, slightly in favour of IVF
Tubal ligation	IVF preferable
Sero-discordant couples	Equally effective

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; OAT = oligo-asthenoter-atozoospermia

ICSI is carried out using viable sperm populations. A number of semen processing techniques have been developed to select the optimal sperm fraction for ICSI. The density gradient centrifugation (DGC) and the swim-up procedures have been used as standard semen preparation techniques for ICSI for more than two decades [1650]. However, these traditional sperm selection techniques are unable to select sperm fractions with optimal DNA integrity and functional characteristics. Advanced sperm selection techniques have been introduced to optimise the selection of high quality sperm for ICSI [1651]. These selection methods are based on sperm surface charge (electrophoresis and Zeta potential), apoptosis (magnetic-activated sperm cell sorting (MACS) and glass wool), membrane maturity (hyaluronic acid binding), or ultra-morphological sperm assessment [1652].

9.7.1.4 Intra-cytoplasmic morphologically selected sperm injection (IMSI) was first introduced in 2002 as a modification of the ICSI technique [1653]. This technology introduced the magnification of sperm to more than 6,000 times its size, the purpose of which is to perform the motile sperm organelle morphology examination (MSOME), a method used to select spermatozoa that have the choicest morphology in couples with the most severe male factor. Bartoov *et al.* showed that, for patients with histories of ICSI failure, the addition of IMSI resulted in a 60% pregnancy rate, compared with a 30% rate for patients not using IMSI [1654]. Moreover, the pregnancy rate following IVF-IMSI was significantly higher and the miscarriage rate significantly lower,

than in the routine IVF-ICSI procedure (60.0% vs. 25.0%, and 14% vs. 40%, respectively) [1655]. However, a meta-analysis reviewed nine RCTs evaluating 2,014 couples and concluded that the current evidence does not adequately support the use of IMSI [1656].

Because IMSI is also a costly procedure, more studies with larger sample sizes are needed to confirm its value before recommending it for ART.

9.7.1.5 PICSI technique: a selection based on membrane maturity of sperm

The human oocyte is surrounded by hyaluronic acid, which acts as a natural selector. In fact, only mature sperm that express receptors specific to HA can reach the oocyte and fertilise it. Those sperm have normal shapes, low DNA fragmentation rates, and low frequency of chromosomal aneuploidies [1657]. Several studies have attempted to verify whether sperm selection based on HA binding could affect IVF outcomes. A meta-analysis included six prospective randomised studies and one retrospective study, all of which used either the PICSI sperm selection dish (a plastic culture dish with microdots of HA hydro gel on its inner surface) or the Sperm Slow method (a viscous medium containing HA). No improvements in fertilisation and pregnancy rates were recorded, although embryo quality was superior in PICSI compared with conventional ICSI [1657]. A recent large-sample multicentre randomised trial provided conclusive evidence against the use of PICSI in ART (PICSI live birth rate versus ICSI: OR 1.12, 95% CI 0.95-1.34) [1658]. A time-lapse study found no difference in embryo development dynamics in oocytes fertilised via HA-ICSI vs. conventional ICSI [1659].

9.7.1.6 Magnetic-activated cell sorting (MACS) is an advanced sperm selection technique used to isolate sperm that do not show signs of apoptosis and, therefore, are presumed to have a lower rate of DNA damage [1651]. Use of MACS after density gradient centrifugation (DGC) has been found to improve sperm morphology and decrease DNA fragmentation and apoptotic markers, but it reduces the motility of the selected sperm [1651, 1652]. Magnetic-activated cell sorting failed to improve ICSI outcomes compared with DGC or swim-up, although a slightly higher pregnancy rate (RR) 1.5, 95% CI 1.14-1.98) was observed in MACS patients relative to the control group [1660]. No difference in implantation or miscarriage rate was noted (RR 1.03 [95% CI 0.8-1.31] and 2 [95% CI 0.19-20.9], respectively).

Finally, another randomised controlled trial performed on infants conceived via ovum-donation IVF cycles did not report any differences in terms of obstetrical and perinatal outcomes between pregnancies or babies conceived with sperm selected via MACS or swim-up [1661].

9.7.2 ***Safety***

The most significant risk of pre-implantation ART treatment is the ovarian hyperstimulation syndrome, a potentially life-threatening condition resulting from excessive ovarian stimulation during ART techniques, ranging from 0.6% to 5% in assisted reproduction cycles [1662].

Other problems include the risk of multiple pregnancies due to the transfer of more than one embryo and the associated risks to mother and baby, including multiple and preterm birth. The most prevalent maternal complications include pre-eclampsia, gestational diabetes, placenta previa, placental abruption, postpartum haemorrhage, and preterm labour and delivery [1663-1665]. The risks of foetal demise during the third trimester, perinatal mortality, preterm birth, and low birth weight increase with the number of foetuses in the pregnancy. The foetal consequences of preterm birth (cerebral palsy, retinopathy, and broncho-pulmonary dysplasia) and foetal growth restriction (polycythemia, hypoglycemia, and necrotizing enterocolitis) are significant [1666].

The average number of embryos transferred in fresh non-donor IVF and ICSI cycles in 2011 was 1.91, compared with 2.09 in 2008, 2.00 in 2009, and 1.95 in 2010, reflecting a continuing decrease from previous years. The average number of embryos transferred in frozen ET cycles decreased from 1.72 in 2008 to 1.65 in 2009 to 1.60 in 2010 and to 1.59 in 2011 [1667].

The global multiple birth rate for fresh cycle transfer has decreased from 21.5% in 2010 to 20.5% in 2011 and for frozen ET cycles from 12.0% to 11.5% [1634].

In 2011, the rate of early pregnancy loss was 20.1% after fresh ET, compared with 25.4% after frozen ET. Both rates showed wide regional variation [1634]. The multiple birth rates after fresh non-donor ET was 19.6% (twins) and 0.9% (triplets and higher order births); for frozen ET non-donor cycles, twin and triplet and higher order birth rates were 11.1% and 0.4%, respectively [1634].

Rates of premature delivery and perinatal mortality were lower for frozen ETs than for fresh ETs. The global preterm DR after non-donor fresh ET was 19.1%, and after frozen ET was 13.1%. The perinatal mortality rate per 1,000 births after non-donor fresh ET was 16.3 and after frozen ET was 8.6.

In terms of potential adverse effects of ICSI-conceived offspring, a greater neonatal morbidity, obstetric complications and congenital malformations compared to spontaneous conceptions [1668-1670]. Additionally, epigenetic disorders and impaired neurodevelopment have been observed in infants born using ICSI compared with naturally conceived children [1645]. Among singleton infants born at 37 weeks of gestation or later, those following IVF had a risk of low birth weight that was 2.6 times (95% CI 2.4-2.7) than in the general population (absolute risk of low birth weight with spontaneous versus resulting from IVF was 2.5% versus 6.5%) [1295]. Singleton infants after IVF were 39% more likely (adjusted RR of 1.39, 95% CI 1.21-1.59) to have a non-chromosomal birth defect (particularly gastrointestinal and musculoskeletal) compared with all other singleton births. No single ART procedure (e.g., ICSI, fresh, or frozen ETs) was found to substantially increase the risk of birth defects.

Analyses from the Massachusetts Outcome Study of ART reported a 50% increase (adjusted prevalence ratio of 1.5, 95% CI 1.3-1.6) in birth defects in infants after IVF vs. spontaneous pregnancy, and a 30% increase (adjusted prevalence ratio of 1.3, 95% CI 1.1-1.5) in birth defects in infants after subfertility vs. spontaneous pregnancy [1671-1673]. No difference in risk of cancer was found between ART-conceived children and those spontaneously conceived [1674].

Health differences between ICSI and IVF conceptions have not been comprehensively assessed and results are contradictory. Some authors found a significantly reduced risk of birth defects in IVF- compared to ICSI conceived infants [1298] (while two meta-analyses demonstrated no difference in risk of congenital malformations between IVF and ICSI conception) [1301, 1675]. Data about ICSI- and IVF-conceived adolescents or young adults is scarce but it seems that there is no difference in outcomes between the two techniques. Further research into health outcomes in adolescence and adulthood is required before conclusions can be drawn about the long-term safety of ICSI compared to IVF [1676].

10. LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH

The EAU Guidelines Panel of Sexual and Reproductive Health have extensively reviewed the literature to provide guidance on: i) late effects of urological diseases (both occurring during childhood and adulthood) on male sexual and reproductive health; ii) late and long-term effects of cancers on male sexual and reproductive health; and, iii) future directions to support personalised medicine strategies for promotion and raising the awareness of overall male sexual and reproductive health.

A systematic literature search for original English-language publications and review articles published up to December 2019 was performed using both Pubmed and Google, yielding only a very limited number of papers addressing the role of health care professionals in supporting male patients who have suffered from cancers in terms of sexual and reproductive health, or the concept of Men's Health programmes.

Despite considerable public health initiatives over the past decades, the panel observed that there is still a significant gender gap between male and female in life expectancy [1677, 1678]. The main contributors to male mortality in Europe are non-communicable diseases (namely cardiovascular diseases [CVD)], cancer, diabetes and respiratory disease) and injuries [1679], as highlighted in a recent WHO report disproving the prevailing misconception that the higher rate of premature mortality amongst men is a natural phenomenon [1678, 1679].

The WHO report also addresses male sexual and reproductive health which is considered under reported, linking in particular male infertility, as a proxy for overall health, to serious diseases in men [1583, 1589, 1680-1684]. These data suggest that health care policies should redirect their focus to preventive strategies and in particular pay attention to follow-up of men with sexual and reproductive complaints [1685]. Considering that the infertile male seems to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1686]. The Panel aim to develop a concept of a more streamlined and holistic approach to Men's health.

For these guidelines, the panel aimed to challenge clinicians to look beyond the pathology of disorders alone and consider the potential associations with other health disorders; f.i. men with varicoceles have a higher incidence of heart disease, a higher risk of diabetes and hyperlipidaemia following diagnosis [1685]. A diagnosis of infertility may have a profound psychological impact on men (and their partners), potentially resulting in anxiety, enduring sadness, anger, and a sense of personal inadequacy and "unmet masculinity" [1688]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [1687].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [351]. Due to new therapeutic approaches, survival rates have improved significantly [1689] and as men live longer, health-related quality of life and related sexual well-being will become increasingly important [1691]. Regardless of the type of treatment used [1692], sexual dysfunction is one of the most common post-treatment complications [342, 343, 1690].

Furthermore, relatively little is known about the relevance of fertility and fertility preservation strategies in cancer survivors [1693, 1694, 1695-1697]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [1698]. Therefore urologists dealing with sexual and reproductive health are primed to act as a vanguard for cancer survivorship programmes.

Finally, the relationship between ED and heart disease has been firmly established for well over two decades now [288, 289, 291, 1710-1713]. Cadiovascular disease is the leading cause of both male mortality and premature mortality [1699-1702]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [1703-1709]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [291], it provides urologists with the unique opportunity for CVD screening and health modification and to optimise CVD risk factors, whilst treating men's primary complaint (e.g., ED). Currently, both the EAU and AUA guidelines recommend screening for CVD risk factors in men with ED and late onset hypogonadism [1714-1716] (see sections 3.7.3 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and to assess the impact of primary and secondary preventive strategies. The EAU Guidelines panel off Male sexual and reproductive health aims to promote and develop a long-term strategy to raise men's health at a global level.

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12. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website http://www.uroweb.org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

13. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Urological Infections

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urinary tract infections (UTIs) and male accessory gland infections. These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship. Separate EAU guidelines documents are available addressing paediatric urological infections [1] and infections in patients with neurological urinary tract dysfunction [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of a multi-disciplinary group of urologists, with particular expertise in this area, an infectious disease specialist and a clinical microbiologist. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/.

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. This 2020 document presents a limited update of the 2019 publication.

2. METHODS

2.1 Introduction

For the 2020 Urological Infections Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for sections 3.4, 3.6, 3.7 and 3.10. Broad and comprehensive literature searches, covering these sections were performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries. The time frames covered and the number of unique records identified, retrieved and screened for relevance for each section were:

Section	No. of unique records	Search time frame
3.4 Uncomplicated cystitis	694	Jan 1st 2014 – Feb 1st 2019
3.7 Complicated UTI	1,331	
3.10 Urethritis	488	
3.6 Uncomplicated pyelonephritis	1,006	Jan 1st 2015 – Feb 1st 2019

Detailed search strategies are available online: http://uroweb.org/guideline/urological-infections/?type=-appendices-publications. For the 2021 Urological Infections Guidelines the following sections will be updated:

- 3.5 Recurrent UTI;
- 3.8 Catheter associated UTI.

The 2020 edition of the EAU Guidelines uses a modified GRADE methodology [3]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and on the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

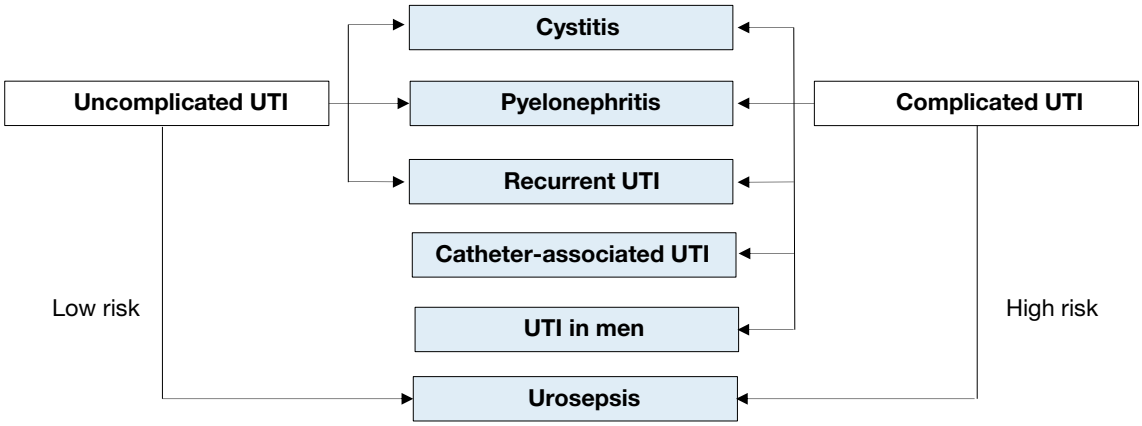
This document was subject to independent peer review prior to publication in 2019.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centres for Disease Control and Prevention (CDC) [6], Infectious Diseases Society of America (IDSA) [7], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [8] as well as the U.S. Food and Drug Administration (FDA) [9, 10]. Current UTI guidelines frequently use the concept of uncomplicated and complicated UTI with a number of modifications (Figure 1). In 2011 the EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, the anatomical level of the UTI, the grade of severity of the infection, the categorisation of risk factors and availability of appropriate antimicrobial therapy [11].

Figure 1: Concept of uncomplicated and complicated UTI



The following classification of UTIs is adopted in the EAU Urological Infections Guidelines:

Classification of UTI	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or has had a catheter in place within the past 48 hours.
Urosepsis	Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs [12].

3.2 Antimicrobial Stewardship

Although the benefits to patients of antibiotic use are clear, overuse and misuse have contributed to the growing problem of resistance amongst uropathogenic bacteria, which is a serious threat to public health [13, 14]. In acute care hospitals, 20-50% of prescribed antibiotics are either unnecessary or inappropriate [15]. In response, a worldwide initiative seeks to incorporate Antimicrobial Stewardship programs in healthcare [16]. Antimicrobial Stewardship aims to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections including *Clostridium difficile*, toxicity, selection of virulent organisms and emergence of resistant bacterial strains [17].

Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance. These include persuasive actions such as education and feedback together with restricting availability linked to local formularies. A Cochrane review of effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients, updated in 2017, found high-certainty evidence that such interventions are effective in increasing adherence with antibiotic policy leading to reduced antibiotic treatment duration and that it may also reduce hospital stay. The review found no evidence that reduced antibiotic usage increased mortality [18].

The important components of antimicrobial stewardship programs are [19]:

- regular training of staff in best use of antimicrobial agents;
- adherence to local, national or international guidelines;
- regular ward visits and consultation with infectious diseases physicians and clinical microbiologists;
- audit of adherence and treatment outcomes;
- regular monitoring and feedback to prescribers of their performance and local pathogen resistance profiles.

A 2016 systematic review of evidence for effectiveness of various Antimicrobial Stewardship interventions in healthcare institutions identified 145 studies of nine Stewardship objectives. Guideline-driven empirical therapy using a restricted choice of antibiotics and including de-escalation, intravenous to oral switch, therapeutic drug monitoring, and bedside consultation resulted in a 35% (95% CI 20-46%) relative risk reduction (RRR) in mortality. Use of de-escalation (tailoring to a more narrow spectrum agent), showed a RRR of 56% (95% CI 34 – 70%) for mortality [20].

To facilitate local initiatives and audit, a set of valid, reliable, and applicable indicators of the quality of antibiotic use in the treatment of hospitalised patients with complicated UTI was developed [21]. Its use in the Netherlands appeared to result in shortened hospital stay [22]. A literature search of Pubmed from April 2014 [20], to February 2017 identified no further randomised controlled trials (RCTs) relating to stewardship

programmes for UTIs. Studies to provide high-quality evidence of effectiveness of Stewardship programmes in urology patients are urgently needed.

3.3 Asymptomatic bacteriuria in adults

*3.3.1 **Evidence question***

What is the most effective management for people with asymptomatic bacteriuria?

*3.3.2 **Background***

Urinary growth of bacteria in an asymptomatic individual (asymptomatic bacteriuria - ABU) is common, and corresponds to a commensal colonisation [23]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [24, 25]. The aim of this section is to support the clinician in deciding when ABU should or should not be treated.

*3.3.3 **Epidemiology, aetiology and pathophysiology***

Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females. Increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and in 23-89% in patients with spinal cord injuries [26]. Asymptomatic bacteriuria in younger men is uncommon, but when detected, chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence of risk factors (see sections 3.4 and 3.7).

*3.3.4 **Diagnostic evaluation***

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine showing bacterial growth ≥ 10^5 cfu/mL in two consecutive samples in women [27] and in one single sample in men [28]. In a single catheterised sample, bacterial growth may be as low as 10^2 cfu/mL to be considered representing true bacteriuria in both men and women [26, 29]. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remark. If persistent growth of urease producing bacteria, i.e. *Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [30]. In men, a digital rectal examination (DRE) has to be performed to investigate the possibility of prostate diseases (see section 3.11).

*3.3.5 **Evidence summary***

A systematic search of the literature from January 2000 to November 2016 identified 3,582 titles of which 224 were selected for full text review and 50 were included [31]. For the subgroups of pregnancy, prior to urologic surgeries, post-menopausal women and institutionalised elderly patients only data from RCTs were included, on which a meta-analysis was performed [31]. For the other subgroups non-RCTs were also included in the narrative analysis [31]. The following patient populations were not covered by the systematic review: immuno-compromised patients; patients with candiduria; patients with dysfunctional and/or reconstructed lower urinary tracts; and patients with indwelling catheters. For these groups the guideline was updated using a structured PubMed search.

*3.3.6 **Disease management***

3.3.6.1 Patients without identified risk factors

Asymptomatic bacteriuria does not cause renal disease or damage [32]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [33], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in most high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

3.3.6.2 Patients with ABU and recurrent UTI, otherwise healthy

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI without identified risk factors [25] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI; therefore, treatment of ABU is not recommended.

3.3.6.3 Pregnant women

3.3.6.3.1 Is treatment of ABU beneficial in pregnant women?

Twelve RCTs comparing antibiotic treatments of ABU with placebo controls or no treatment [34-45], with different antibiotic doses and regimens were identified, ten published before 1988 and one in 2015. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [34, 36-44, 46]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average RR 0.22, 95% CI 0.12 to 0.40).

Six RCTs reported on the resolution of bacteriuria [34-36, 38, 41, 43]. Antibiotic treatment was effective in the resolution of bacteriuria compared to placebo (average RR 2.99, 95% CI 1.65 to 5.39; n=716). Eight RCTs reported on the rate of low birthweights [34, 36-39, 42, 45, 46]. Antibiotic treatment was associated with lower rates of low birthweight compared to placebo or no treatment (average RR 0.58, 95% CI 0.36 to 0.94; n=1689). Four RCTs reported on the rate of preterm deliveries [42, 43, 45, 46]. Antibiotic treatment was associated with lower rates of preterm delivery compared to placebo or no treatment (average RR 0.34, 95% CI 0.18 to 0.66; n=854).

Based on the beneficial maternal and foetal effects of antibiotic treatment pregnant women should be screened and treated for ABU. However, the panel would like to emphasise that most available studies have low methodological quality and are from the 60s to 80s. Diagnostic and treatment protocols and accessibility to medical services have dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In a newer study of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [46]. Therefore, it is advisable to consult national recommendations for pregnant women.

3.3.6.3.2 Which treatment duration should be applied to treat ABU in pregnancy?

Sixteen RCTs comparing the efficacy of different antibiotic treatments in pregnant women with ABU were identified [47-62]. There was significant heterogeneity amongst the studies. Studies compared different antibiotic regimens or the same antibiotic regimens with different durations. The duration of treatment ranged from single dose to continuous treatment (until delivery). For practical purposes the grouping strategy used by the previously published Cochrane Review by Widmer et al. was adopted with some modifications [63]. The following treatment groups were used for comparison:

1. single dose (single day);
2. short course (2-7 days);
3. long course (8-14 days);
4. continuous (until delivery).

Nine studies compared single dose to short course treatment [48, 52, 53, 57-62], one study compared single dose to long course treatment [56] and one study compared long course to continuous treatment [49]. As long term and continuous antibiotic treatment is not used in current practice, only studies comparing single dose to standard short course treatment are presented.

3.3.6.3.2.1 Single dose vs. short course treatment

Three RCTs reported on the rate of symptomatic UTIs [52, 61, 62], with no significant difference between the two durations (average RR 1.07, 95% CI 0.47 to 2.47; n=891). Nine RCTs reported on the rate of ABU resolution [48, 52, 53, 57-62], with no significant difference between the two durations (average RR 0.97, 95% CI 0.89 to 1.07; n=1,268). Six RCTs reported on the rate of side effects [48, 52, 57, 58, 60, 61]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.40, 95% CI 0.22 to 0.72; n=458). Three RCTs reported on the rate of preterm deliveries [52, 54, 62], with no significant difference between the two durations (average RR 1.16, 95% CI 0.75 to 1.78; n=814). One RCT reported on the rate of low birthweights [62]. There were significantly more babies with low birthweight in the single dose duration compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; n=714).

According to the data analysis, single dose treatment was associated with a significantly lower rate of side effects but a significantly higher rate of low birthweight. Therefore, standard short course treatment should be applied to treat ABU in pregnancy; however, it should be emphasised that the overall quality of the scientific evidence backing this recommendation is low.

3.3.6.4 Patients with identified risk-factors

3.3.6.4.1 Diabetes mellitus

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [64]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both

groups. Furthermore, untreated ABU did not correlate to diabetic nephropathy [65]. Screening and treatment of ABU in well-controlled diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

3.3.6.4.2 ABU in post-menopausal women

Elderly women have an increased incidence of ABU [66]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic doses and regimens [67-70]. Women in these studies were mostly nursing home residents, which may bias the results of this analysis. Three RCTs reported on the rate of symptomatic UTIs (average RR 0.71, 95% CI 0.49 to 1.05; 208 women) and the resolution of bacteriuria (average RR 1.28, 95% CI 0.50 to 3.24; 203 women) [52, 61, 62], with no significant benefit of antibiotic treatment. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women.

3.3.6.4.3 Elderly institutionalised patients

The rate of ABU is 15-50% in elderly institutionalised patients [71]. Differential diagnosis of ABU from symptomatic UTI is difficult in the multi-diseased and mentally deteriorated patient, and is probably a cause of unnecessary antibiotic treatment [72, 73]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [67-70, 74-76].

Three RCTs reported on the rate of symptomatic UTIs [67, 69, 74]. Antibiotic treatment was not significantly beneficial in reducing the rate of symptomatic UTIs compared to placebo or no treatment (average RR 0.68, 95% CI 0.46 to 1.00; n=210). Six RCTs reported on the resolution of bacteriuria [67, 69, 70, 74-76]. There was no benefit of antibiotic treatment compared to placebo in the resolution of ABU (average RR 1.33, 95% CI 0.63 to 2.79; n=328). One RCT compared the rates of incontinence in this patient group before and after the eradication of ABU, and found no effect of antibiotic treatment [77]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.6.4.4 Patients with renal transplants

Two RCTs and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [78-81]. Meta-analysis of the two RCTs did not find antibiotic treatment beneficial in terms of reducing symptomatic UTIs (RR 0.86, 95% CI 0.51 to 1.45; n=200). The two retrospective studies reached the same conclusion. Furthermore, there were no significant differences in the rate of ABU clearance, graft loss or change in renal function during long-term follow-up up to 24 months [78-81]. Therefore, treatment of ABU is not recommended in renal transplant recipients.

3.3.6.4.5 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD) (e.g. neurogenic bladder patients secondary to multiple sclerosis, spinal cord injury patients, patients with incomplete bladder emptying, patients with neo-bladder and ileo-cystoplasty, patients using clean intermittent catheterisation (CIC), and patients with ileal conduits, orthotopic bladder replacement and continent reservoirs) frequently become colonised [82, 83]. Studies have shown no benefit in ABU treatment in these patient groups [84, 85]. Furthermore, in LUTD patients who do not spontaneously develop ABU, deliberate colonisation with an ABU strain (*Escherichia coli* 83972) has shown a protective effect against symptomatic recurrences [84, 85]. Screening and treatment of ABU in these patient groups is therefore, not recommended. If these patient groups develop recurrent symptomatic UTI (see section 3.5) the potential protective effect of a spontaneously developed ABU against lower UTI must be considered before any treatment.

3.3.6.4.6 Patients with catheters in the urinary tract

Patients with indwelling or suprapubic catheters and nephrostomy tubes invariably become carriers of ABU, with antibiotic treatment showing no benefit [86]. This is also applicable for patients with ABU and indwelling ureteral stents [87]. Routine treatment of catheter-associated bacteriuria is not recommended. For detailed recommendations see section 3.8.

3.3.6.4.7 Patients with ABU subjected to catheter placements/exchanges

In patients subjected to uncomplicated placement/exchanges of indwelling urethral catheters ABU is not considered a risk factor and should not be screened or treated [88]. In patients subjected to placement/exchanges of nephrostomy tubes and indwelling ureteral stents, ABU is considered a risk factor for infectious complications [89]; therefore, screening and treatment prior to the procedure is recommended.

3.3.6.4.8 Immuno-compromised and severely diseased patients, patients with candiduria

These patient groups have to be considered individually and the benefit of screening and treatment of ABU

should be reviewed in each case. Patients with asymptomatic candiduria may, although not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended [90].

3.3.6.5 Prior to urological surgery

In diagnostic and therapeutic procedures not entering the urinary tract, ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary. On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor.

Two RCTs [91, 92] and two prospective non-randomised studies [93, 94] compared the effect of antibiotic treatment to no treatment before transurethral prostate or bladder tumour resections. Antibiotic treatment significantly reduced the number of post-operative symptomatic UTIs compared to no treatment in the meta-analysis of the two RCTs (average RR 0.20, 95% CI 0.05 to 0.86; n=167). The rates of post-operative fever and septicaemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs. One RCT including patients with spinal cord injury undergoing elective endoscopic urological surgeries found no significant difference in the rate of post-operative UTIs between single-dose or 3-5 days short term pre-operative antibiotic treatment of ABU [95].

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment is recommended.

3.3.6.6 Prior to orthopaedic surgery

One RCT (n=471) and one multicentre cohort study (n=303) comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [96, 97]. Neither of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection (3.8% vs. 0% and 3.9% vs. 4.7%, respectively). The cohort study reported no significant difference in the rate of post-operative symptomatic UTI (0.65% vs. 2.7%) [97]. Therefore, treatment of bacteriuria is not recommended prior to arthroplasty surgery.

3.3.6.7 Pharmacological management

If the decision is taken to eradicate ABU, the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (section 3.4.4.4) or complicated (section 3.7.5) UTI can be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical.

*3.3.7 **Follow-up***

There are no studies focusing on follow-up after treatment of ABU.

*3.3.8 **Summary of evidence and recommendations for the management of ABU***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria is not beneficial in the following conditions:	
• women without risk factors;	3b
• patients with well-regulated diabetes mellitus;	1b
• post-menopausal women;	1a
• elderly institutionalised patients;	1a
• patients with dysfunctional and/or reconstructed lower urinary tracts;	2b
• patients with renal transplants;	1a
• patients prior to arthoplasty surgeries.	1b
Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections.	1b
Treatment of asymptomatic bacteriuria is beneficial prior to urological procedures breaching the mucosa.	1a
Treatment of asymptomatic bacteriuria in pregnant women was found to be beneficial by meta-analysis of the available evidence; however, most studies are old. A recent study reported lower rates of pyelonephritis in low-risk women.	1a

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthoplasty surgeries; • patients with recurrent urinary tract infections.	Strong
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	Strong
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	Weak

3.4 Uncomplicated cystitis

*3.4.1 **Introduction***

Uncomplicated cystitis is defined as acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.

*3.4.2 **Epidemiology, aetiology and pathophysiology***

Almost half of all women will experience at least one episode of cystitis during their lifetime. Nearly one in three women will have had at least one episode of cystitis by the age of 24 years [98]. Risk factors include sexual intercourse, use of spermicides, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The majority of cases of uncomplicated cystitis are caused by *E. coli*.

*3.4.3 **Diagnostic evaluation***

3.4.3.1 Clinical diagnosis

The diagnosis of uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge [99, 100]. In elderly women genitourinary symptoms are not necessarily related to cystitis [101, 102].

3.4.3.2 Differential diagnosis

Uncomplicated cystitis should be differentiated from ABU, which is considered not to be infection but rather a commensal colonisation, which should not be treated and therefore not screened for, except if it is considered a risk factor in clearly defined situations (see section 3.3).

3.4.3.3 Laboratory diagnosis

In patients presenting with typical symptoms of an uncomplicated cystitis urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy [103]. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of an uncomplicated cystitis diagnosis [104, 105]. Taking a urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy [106, 107].

3.4.3.4 Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis

Summary of evidence	LE
An accurate diagnosis of uncomplicated cystitis can be based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation.	2b

Recommendations	Strength rating
Diagnose uncomplicated cystitis in women who have no other risk factors for complicated urinary tract infections based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge or irritation.	Strong
Use urine dipstick testing for diagnosis of acute uncomplicated cystitis.	Weak
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after the completion of treatment; • women who present with atypical symptoms; • pregnant women.	Strong

*3.4.4 **Disease management***

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [108]. In female patients with mild to moderate symptoms, symptomatic therapy (e.g. Ibuprofen), as an alternative to antimicrobial treatment, may be considered in consultation with individual patients [109-112]. The choice of antimicrobial therapy should be guided by [99]:

- spectrum and susceptibility patterns of the aetiological pathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- costs;
- availability.

According to these principles and the available susceptibility patterns in Europe, oral treatment with fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin (e.g. nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for five days), should be considered for first-line treatment, when available [113-116].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily for three days) or trimethoprim (200 mg twice daily for five days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [117, 118].

Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *E. coli* resistance. Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [119, 120].

Important notice:

On March 11, 2019 the European Commission implemented stringent regulatory conditions regarding the use of fluoroquinolones due to their disabling and potentially long-lasting side effects [121]. This legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics. In uncomplicated cystitis a fluoroquinolone should only be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections [121].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [122], but not all antimicrobials are suitable during pregnancy. In general, penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimenon) and sulphonamides (not in the last trimenon), can be considered.

3.4.4.2 Cystitis in men

Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. Therefore, treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim sulfamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [123].

3.4.4.3 Renal insufficiency

In patients with renal insufficiency the choice of antimicrobials may be influenced by decreased renal excretion; however, most antimicrobials, have a wide therapeutic index. No adjustment of dose is necessary until glomerular filtration rate (GFR) is < 20 mL/min, with the exception of antimicrobials with nephrotoxic potential, e.g. aminoglycosides. The combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m2 as accumulation of the drug leads to increased side effects as well as reduced urinary tract recovery, with the risk of treatment failure [124].

3.4.4.4 Summary of evidence and recommendations for antimicrobial therapy for uncomplicated cystitis

Summary of evidence	**LE**
Clinical success for the treatment of uncomplicated cystitis is significantly more likely in women treated with antimicrobials than placebo.	1b
Aminopenicillins are no longer suitable for antimicrobial therapy in uncomplicated cystitis because of negative ecological effects, high resistance rates and their increased selection for extended spectrum beta-lactamase (ESBL)-producing bacteria.	3

Recommendations	**Strength rating**
Prescribe fosfomycin trometamol, pivmecillinam or nitrofurantoin as first-line treatment for uncomplicated cystitis in women.	Strong
Do not use aminopenicillins or fluoroquinolones to treat uncomplicated cystitis.	Strong

Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis.
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d	5 days	
Pivmecillinam	400 mg t.i.d	3-5 days	
Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy
Treatment in men			
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

SD = single dose; b.i.d = twice daily; t.i.d = three times daily.

3.4.5 ***Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [26]. In women whose symptoms do not resolve by end of treatment, and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed [125]. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a seven-day regimen using another agent should be considered [125].

3.5 Recurrent UTIs

*3.5.1 **Introduction***

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated aetiology.

*3.5.2 **Diagnostic evaluation***

Recurrent UTIs are common. Risk factors are outlined in Table 2. Diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc. is not routinely recommended as the diagnostic yield is low [126]. However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.

Table 2: Age-related associations of rUTI in women [71, 101, 127]

Young and pre-menopausal women	Post-menopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocele
History of UTI during childhood	Increased post-void urine volume
Blood group antigen secretory status	Blood group antigen secretory status
	Urine catheterisation and functional status
	deterioration in elderly institutionalised women

*3.5.3 **Disease management and follow-up***

Prevention of rUTIs includes counselling regarding avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis [125]. These interventions should be attempted in this order. Any urological risk factor must be identified and treated. Significant residual urine should be treated optimally, including by CIC when judged to be appropriate.

3.5.3.1 Behavioural modifications

A number of behavioural and personal hygiene measures (e.g. reduced fluid intake, habitual and post-coital delayed urination, wiping from front to back after defecation, douching and wearing occlusive underwear) have been suggested to decrease the risk of rUTI. However, studies that have explored underlying behavioural risk factors have consistently documented the lack of association with rUTI [125].

3.5.3.2 Non-antimicrobial prophylaxis

There are many non-antimicrobial measures recommended for rUTIs but only a few are supported by well-designed studies [128, 129].

3.5.3.2.1 Hormonal replacement

In post-menopausal women vaginal oestrogen replacement, but not oral oestrogen, showed a trend towards preventing rUTI [128, 130].

3.5.3.2.2 Immunoactive prophylaxis

OM-89 is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials with a good safety profile. Therefore, it can be recommended for immunoprophylaxis in female patients with rUTIs [128, 131-133]. Efficacy in other groups of patients relative to antimicrobial prophylaxis remains to be established.

3.5.3.2.3 Prophylaxis with probiotics (Lactobacillus spp.)

Pooled data from a recent meta-analysis shows no convincing benefit of lactobacillus products as prophylaxis for rUTI [134]. However, differences in effectiveness between available preparations suggest further trials are needed before any definitive recommendation for or against their use can be made.

3.5.3.2.4 Prophylaxis with cranberry

Limited studies have suggested that cranberry is useful in reducing the rate of lower UTIs in women [135, 136]. However, a meta-analysis including 24 studies and comprising 4,473 participants showed that current

cranberry products did not significantly reduce the occurrence of symptomatic UTI for women with rUTI [137]. Due to these contradictory results, no recommendation on the daily consumption of cranberry products can be made.

3.5.3.2.5 Prophylaxis with D-mannose

In a randomised placebo-controlled non-blinded clinical trial, it was shown that a daily dose of 2 g D-mannose was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing rUTI [138]. This is indicative but not sufficient for a recommendation; therefore, D-mannose should at present only be used within the context of clinical investigations.

3.5.3.2.6 Endovesical instillation

Endovesical instillations of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI [139]. A review of 27 clinical studies concluded that large-scale trials are urgently needed to assess the benefit of this type of therapy [140]; therefore, no general recommendation is possible at this stage.

3.5.3.3 Antimicrobials for preventing rUTI

3.5.3.3.1 Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis

Antimicrobials may be given as continuous low-dose prophylaxis for longer periods (three to six months), or as post-coital prophylaxis, as both regimens reduce the rate of rUTI [141]. It is mandatory to offer both options after counselling, and when behavioural modifications and non-antimicrobial measures have been unsuccessful. Regimens include nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every ten days, trimethoprim 100 mg once daily and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [125, 142]. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [143].

3.5.3.3.2 Self-diagnosis and self-treatment

In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [144]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

3.5.4 Summary of evidence and recommendations for the diagnostic evaluation and treatment of rUTIs

Summary of evidence	**LE**
Extensive routine workup including cystoscopy, imaging, etc. has a low diagnostic yield for the diagnosis of rUTI.	3
Studies that have investigated behavioural risk factors in the development of rUTIs have consistently documented the lack of association with rUTI.	3
Vaginal oestrogen replacement has shown a trend towards preventing rUTI in post-menopausal women.	1b
OM-89 has been shown to be more effective than placebo for immunoprophylaxis in female patients with rUTIs in several randomised trials with a good safety profile.	1a
Both continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis, have been shown to reduce the rate of rUTI.	1b
A prospective cohort study showed that intermittent self-start therapy is effective, safe and economical in women with rUTIs.	2b

Recommendations	**Strength rating**
Diagnose recurrent UTI by urine culture.	Strong
Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors.	Weak
Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.	Weak
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	Weak
Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	Strong
Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects.	Strong
For patients with good compliance self-administered short-term antimicrobial therapy should be considered.	Strong

3.6 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant urological abnormalities or comorbidities.

*3.6.1 **Diagnostic evaluation***

3.6.1.1 Clinical diagnosis

Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [145]. Pregnant women with acute pyelonephritis need special attention, as this kind of infection may not only have an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn child with more frequent preterm labour and birth [146].

3.6.1.2 Differential diagnosis

It is vital to differentiate as soon as possible between uncomplicated and complicated mostly obstructive pyelonephritis, as the latter can rapidly lead to urosepsis. This differential diagnosis should be made by the appropriate imaging technique (see section 3.6.1.4).

3.6.1.3 Laboratory diagnosis

Urinalysis including the assessment of white and red blood cells and nitrite, is recommended for routine diagnosis [147]. In addition, urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis.

3.6.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary tract obstruction or renal stone disease in patients with a history of urolithiasis, renal function disturbances or a high urine pH [148]. Additional investigations, such as a contrast enhanced computed tomography (CT) scan, or excretory urography should be considered if the patient remains febrile after 72 hours of treatment, or immediately if there is deterioration in clinical status [148]. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus [148].

*3.6.2 **Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis***

Summary of evidence	**LE**
Urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis.	4
A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.	2b
Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4

Recommendations	**Strength rating**
Perform urinalysis (e.g. using the dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	Strong
Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong

*3.6.3 **Disease management***

3.6.3.1 Outpatient treatment

Fluoroquinolones and cephalosporines are the only antimicrobial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis [149]. However, oral cephalosporines achieve significantly lower blood and urinary concentrations than intravenous cephalosporines. Other agents such as nitrofurantoin, oral fosfomycin, and pivmecillinam should be avoided as there is insufficient data regarding their efficacy [150]. In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg) or an oral beta-lactam, if the uropathogen is known to be

susceptible. If such agents are used in the absence of antimicrobial susceptibility results, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered. A short outpatient antibiotic course of treatment, for acute pyelonephritis, has been shown to be equivalent to longer durations of therapy in terms of clinical and microbiological success. However, this is associated with a higher recurrence rate of infection within four to six weeks and needs to be tailored to local policies and resistance patterns [151].

3.6.3.2 Inpatient treatment

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen e.g. a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin [152]. Ceftolozane/tazobactam achieved a clinical response rate of over 90% in patients with uncomplicated pyelonephritis [153, 154]. It also demonstrated significantly higher composite cure rates than levofloxacin among levofloxacin-resistant pathogens [155]. Ceftazidime-avibactam combination has been shown to be effective for treating ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* UTIs [156].

Novel antimicrobial agents include imipenem/cilastatin, cefiderocol, meropenem-vaborbactam and plazomicin. Imipenem/cilastatin has been investigated in a phase 2 randomised trial and showed good clinical response rates [157]. Cefatazidime-avibactam and doripenem showed similar efficacy against ceftazidime non-susceptible pathogens and may offer an alternative to carbapenems in this setting [158]. Meropenem-vaborbactam has been shown to be non-inferior to piperacillin-tazobactam in a phase 3 RCT [159]. It was also effective for treating carbapenem-resistant Enterobacteriaceae with cure rates of 65% compared to best available treatment [160]. Once daily plazomicin was non-inferior to meropenem for the treatment of cUTIs and acute pyelonephritis caused by Enterobacteriaceae, including multidrug-resistant strains [161]. Cefiderocol was non-inferior to imipenem/cilastatin for the treatment of complicated UTI in people with multidrug-resistant Gram-negative infections in a phase 2 RCT [162].

Carbapenems and novel broad spectrum antimicrobial agents should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms. The choice between these agents should be based on local resistance patterns and optimised on the basis of drug susceptibility results. In patients presenting with signs of urosepsis empiric antimicrobial coverage for ESBL-producing organisms is warranted [163]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [164].

3.6.3.2.1 Summary of evidence and recommendations for the treatment of uncomplicated pyelonephritis

Summary of evidence	**LE**
Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis.	1b
Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin.	1b
Carbapenems should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms.	4
The appropriate antimicrobial should be chosen based on local resistance patterns and optimised on the basis of drug susceptibility results.	3

Recommendations	**Strength rating**
Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first-line treatment.	Strong
Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially.	Strong
Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

Table 3: Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobial	Daily dose	Duration of therapy	Comments
Ciprofloxacin	500-750 mg b.i.d	7 days	Fluoroquinolone resistance should be less than 10%.
Levofloxacin	750 mg q.d	5 days	
Trimethoprim sulfamethoxazol	160/800 mg b.i.d	14 days	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	
Ceftibuten	400 mg q.d	10 days	

b.i.d = twice daily; q.d = every day.

Table 4: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobials	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/tazobactam	2.5-4.5 g t.i.d	
Gentamicin	5 mg/kg q.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	
Last-line alternatives		
Imipenem/cilastatin	0.5 g t.i.d	Consider carbapenems only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Cefiderocol	2g t.i.d	
Meropenem-vaborbactam	2g t.i.d	
Plazomicin	15mg/kg o.d	

b.i.d = twice daily; t.i.d = three times daily; q.d = every day; o.d = once daily.

In pregnant women with pyelonephritis, outpatient management with appropriate parenteral antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [165, 166]. In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of seven to ten days. In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of two weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent [167].

*3.6.4 **Follow-up***

Post-treatment urinalysis or urine cultures in asymptomatic patients post-therapy are not indicated.

3.7 Complicated UTIs

*3.7.1 **Introduction***

A complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [168-170]. New insights into the management of cUTIs also suggest to consider infections caused by multi-drug resistant uropathogens [171]. The underlying factors that are generally accepted to result in a cUTI are outlined in Table 5. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs

is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [172].

Table 5: Common factors associated with complicated UTIs [171-174]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes mellitus
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections
Isolated ESBL-producing organisms	Isolated multi-drug resistant organisms

*3.7.2 **Diagnostic evaluation***

3.7.2.1 Clinical presentation

A cUTI is associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may be atypical for example, in neuropathic bladder disturbances, CA-UTI or patients who have undergone radical cystectomy with urinary diversion. In addition, all patients with nephrostomy may have an atypical clinical presentation. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Clinicians must also recognise that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as, for example, benign prostatic hyperplasia and autonomic dysfunction in patients with spinal lesions and neurogenic bladders. Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

3.7.2.2 Urine culture

Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI.

*3.7.3 **Microbiology (spectrum and antimicrobial resistance)***

A broad range of micro-organisms cause cUTIs. The spectrum is much larger than in uncomplicated UTIs and the bacteria are more likely to be resistant (especially in treatment-related cUTI) than those isolated in uncomplicated UTIs [173, 174]. *E. coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Serratia* spp. and *Enterococcus* spp. are the most common species found in cultures. Enterobacteriaceae predominate (60-75%), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another [175].

*3.7.4 **General principles of cUTI treatment***

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

3.7.4.1 Choice of antimicrobials

Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs [176]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [176].

Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin, or an extended-spectrum penicillin with or without an aminoglycoside [172]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [150]. These recommendations are not only suitable for pyelonephritis, but for all other cUTIs.

Alternative regimens for the treatment of cUTIs, particularly those caused by multidrug-resistant pathogens have been studied. Ceftolozane/tazobactam 1.5 g every eight hours demonstrated high clinical

cure rates for cUTIs caused by ESBL-producing Enterobacteriaceae in a pooled analysis of phase 3 clinical trials [177]. Cefiderocol (2 g) three times daily was non-inferior to imipenem-cilastatin (1 g) three times daily for the treatment of cUTI in patients with multidrug-resistant Gram-negative infections [162]. Imipenem/cilastatin plus relebactam (250 or 125 mg) was as effective as imipenem/cilastatin alone for treatment of cUTI in a phase 2 RCT [157]. Ceftazidime/avibactam has been shown to be as effective as carbapenems for the treatment of cUTI in a systematic review reporting a baseline of 25% for ESBL-producing Enterobacteriaceae, but more severe adverse events were reported in the ceftazidime/avibactam group [178]. Once-daily plazomicin was shown to be non-inferior to meropenem for the treatment of cUTIs caused by Enterobacteriaceae, including multidrug-resistant strains [161].

In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months [179]. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials. Intravenous levofloxacin 750 mg once daily for five days has been shown to be non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms) [180].

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven [181] to fourteen days (for men fourteen days when prostatitis cannot be excluded) [182] is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality. When the patient is hemodynamically stable and afebrile for at least 48 hours, a shorter treatment duration (e.g. seven days) may be considered in patients where a short-course treatment is desired due to relative-contraindications to the administered antibiotic [180].

*3.7.5 **Summary of evidence and recommendations for the treatment of complicated UTIs***

Summary of evidence	**LE**
Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen chosen based on local resistance data and previous urine culture results from the patient, if available. The regimen should be tailored on the basis of susceptibility result.	1b
If the prevalence of fluoroquinolone resistance is thought to be < 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with complicated pyelonephritis.	2
In the event of hypersensitivity to penicillin a cephalosporins can still be prescribed, unless the patient has had systemic anaphylaxis in the past.	2
In patients with a cUTI with systemic symptoms, empirical treatment should cover ESBL-producing organisms if there is an increased likelihood of ESBL infection based on prevalence in the community, earlier collected cultures and prior antimicrobial exposure of the patient.	2
Intravenous levofloxacin 750 mg once daily for five days, is non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms).	2

Recommendations	**Strength rating**
Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	Strong
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	Strong
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months.	Strong
Manage any urological abnormality and/or underlying complicating factors.	Strong

3.8 Catheter-associated UTIs

*3.8.1 **Introduction***

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours. The urinary catheter literature is problematic as many published studies use the term CA-bacteriuria without providing information on what proportion are CA-ABU and CA-UTI, and some studies use the term CA-UTI when referring to CA-ABU or CA-bacteriuria [173]. The following recommendations are based on the SWAB Guidelines from the Dutch Working Party on Antibiotic Policy [172] as well as the IDSA Guidelines [173].

*3.8.2 **Epidemiology, aetiology and pathophysiology***

Catheter-associated UTIs are the leading cause of secondary healthcare-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [183]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [184-188]. The duration of catheterisation is the most important risk factor for the development of a CA-UTI [189, 190]. Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder. Indwelling urinary catheters facilitate colonisation with uropathogens by providing a surface for the attachment of host cell binding receptors recognised by bacterial adhesins, thus enhancing microbial adhesion. In addition, the uroepithelial mucosa is disrupted, exposing new binding sites for bacterial adhesins, and residual urine in the bladder is increased through pooling below the catheter bulb [191]. Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens.

*3.8.3 **Diagnostic evaluation***

3.8.3.1 Clinical diagnosis

Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness [172]. In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI [172, 173].

3.8.3.2 Laboratory diagnosis

Microbiologically, CA-UTI is defined by microbial growth of ≥ 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours. In catheterised patients, pyuria is not diagnostic for CA-UTI. The presence, absence, or degree of pyuria should not be used to differentiate CA-ABU from CA-UTI. Pyuria accompanying CA-ABU should not be interpreted as an indication for antimicrobial treatment. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI [173].

3.8.3.3 Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	**LE**
Patients with indwelling or suprapubic catheters become carriers of ABU, with antibiotic treatment showing no benefit.	1a
In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI.	2
Microbiologically CA-UTI is defined by microbial growth of ≥ 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose catheter has been removed within the previous 48 hours.	3

Recommendations	**Strength rating**
Do not carry out routine urine culture in asymptomatic catheterised patients.	Strong
Do not use pyuria as sole indicator for catheter-associated UTI.	Strong
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	Strong

3.8.4 *Disease management*

A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for presumed CA-UTI due to the wide spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. The urine culture should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy [173]. Based on the global prevalence on infections in urology (GPIU) study, the causative micro-organisms in CA-UTI are comparable with the causative micro-organisms in other cUTIs; therefore, symptomatic CA-UTIs should be treated according to the recommendations for cUTI (see section 3.7.5) [192].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [173]. A five-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. Data are insufficient to make such a recommendation about other fluoroquinolones.

A three-day antimicrobial regimen may be considered for women aged ≤ 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed. If an indwelling catheter has been in place for two weeks at the onset of CA-UTI and is still indicated, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI. If use of the catheter can be discontinued, a culture of a voided mid-stream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [173]. Long-term indwelling catheters should not be changed routinely. Follow appropriate practices for catheter insertion and care [193].

3.8.4.1 *Recommendations for disease management and prevention of CA-UTI*

Recommendations	Strength rating
Treat symptomatic catheter-associated UTI according to the recommendations for complicated UTI (see section 3.7.5).	Strong
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	Strong
Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong
Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	Strong
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong
The duration of catheterisation should be minimal.	Strong

3.8.5 *Removal of indwelling bladder catheter*

3.8.5.1 *Evidence question*

1. Does antibiotic prophylaxis reduce the rate of symptomatic UTI in adults following indwelling bladder catheter removal?

3.8.5.2 *Review of evidence*

A structured literature search identified one systematic review and meta-analysis [194] with a search date of November 2012 and one subsequent RCT [195]. Marschall *et al.*, identified seven RCTs with 1,520 participants. Meta-analysis showed overall benefit for use of prophylaxis RR (95%CI) = 0.45 (0.28-0.72); ARR 5.8% (from 10.5% to 4.7%) with a number needed to treat (NNT) of 17. Results for individual trials were inconsistent with five trials including the possibility of no benefit [194]. The trial reported by Fang *et al.*, recruited 172 participants undergoing laparoscopic radical prostatectomy randomised to seven days of ciprofloxacin (n=80) or no treatment (n=80). At the time of catheter removal which, occurred at a mean of nine days post-operatively, there was no difference in infective complications recorded at up to four weeks after catheter removal. More isolates obtained from the prophylaxis group (11) were resistant to ciprofloxacin compared to the no treatment group (3) [195].

3.8.5.3 Summary of evidence and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	LE
A meta-analysis showed overall benefit for use of prophylaxis for reduction of infective complications after catheter removal; however, results from individual trials were inconsistent with five out of seven trials including the possibility of no benefit.	1a
A subsequent RCT found no benefit of antibiotic prophylaxis for reduction of infective complications at up to four weeks after catheter removal.	1b

Recommendation	Strength rating
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal.	Weak

3.9 Urosepsis

*3.9.1 **Introduction***

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a cUTI. Systemic inflammatory response syndrome (SIRS), characterised by fever or hypothermia, leukocytosis or leukopenia, tachycardia and tachypnoea, has been recognised as a set of alerting symptoms [196, 197]; however, SIRS is no longer included in the recent terminology of sepsis (Table 6) [12]. Mortality is considerably increased the more severe the sepsis is.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders [198]. Source control by decompression of any obstruction and drainage of larger abscesses in the urinary tract is essential [198]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Urosepsis is seen in both community-acquired and healthcare associated infections. Nosocomial urosepsis may be reduced by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urinary catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily aseptic techniques to avoid cross-infection.

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia (Table 6).

*3.9.2 **Epidemiology, aetiology and pathophysiology***

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in a very short time.

Mortality rates associated with sepsis vary depending on the organ source [199] with urinary tract sepsis generally having a lower mortality than that from other sources [200]. Sepsis is more common in men than in women [201]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [199], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [202]. Although the rate of sepsis due to Gram-positive and fungal organisms has increased, Gram-negative bacteria remain predominant in urosepsis [192, 203].

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response.
Patients who are more likely to develop urosepsis include elderly patients, diabetics, immunosuppressed patients, such as transplant recipients and patients receiving cancer chemotherapy or corticosteroids. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract.

*3.9.3 **Diagnostic evaluation***

For diagnosis of systemic symptoms in sepsis either the full Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, or the quickSOFA score should be applied (Table 6). Microbiology sampling should be applied to urine, two sets of blood cultures [204], and if appropriate drainage fluids. Imaging investigations, such as sonography and CT-scan should be performed early [205].

Table 6. Definition and criteria of sepsis and septic shock [12, 196, 197]

Disorder	Definition
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification a quickSOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

3.9.4 ***Physiology and biochemical markers***

E. coli remains the most prevalent micro-organism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [203]. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection.

3.9.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis [200]. They are molecules that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [200].

3.9.4.2 Biochemical markers

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [206]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Mid-regional proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [207]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [206, 208]. In addition, serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [209]. Serum lactate should therefore also be monitored in patients with severe infections.

3.9.5 ***Disease management***

3.9.5.1 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Urosepsis treatment requires a combination of treatment including source control (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [200, 205]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3.9.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [210, 211] they include:

- Isolation of patients with multi-resistant organisms following local and national recommendations.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. Long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [212]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3.9.5.1.2 Appropriate peri-operative antimicrobial prophylaxis

For appropriate peri-operative antimicrobial prophylaxis see section 3.15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

3.9.5.2 Treatment

Early goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomised, controlled, single-centre study [213]. However, follow-up studies in an improved emergency medicine background have not achieved positive effects with this strategy [214-216]. An individual patient data meta-analysis of the later three multicentre trials concluded that early goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalisation costs [217].

3.9.5.2.1 Antimicrobial therapy

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [198, 205]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with appropriate adjustment for renal function [198]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis [198].

3.9.5.2.2 Source control

Obstruction in the urinary tract is the most frequent urological source of urosepsis. Drainage of obstruction and abscesses, and removal of foreign bodies, such as urinary catheters or stones is therefore the most important source control strategy. These are key components of the strategy. This condition is an absolute emergency.

3.9.5.2.3 Adjunctive measures

The most important adjunctive measures in the management of sepsis are the following [198, 205]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure: passive leg raising-induced changes in cardiac output and in arterial pulse pressure are predictors of fluid responsiveness in adults [218];
- as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction;
- hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg;
- blood products should be given to target a haemoglobin level of 7-9 g/dL;
- mechanical ventilation should be applied with a tidal volume 6 mL/kg and plateau pressure ≤ 30 cm H_2O and a high positive end-expiratory pressure;
- sedation should be given minimally, neuromuscular blocking agents should be avoided;
- glucose levels should be target at ≤ 180 mg/dL;
- deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously;
- stress ulcer prophylaxis should be applied in patients at risk, using protone pump inhibitors;
- enteral nutrition should be started early (< 48 hours).

In conclusion, sepsis in urology remains a severe situation with a considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [198, 205, 219]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antimicrobial treatment provide the best conditions for improving patient survival. The prevention of sepsis is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

3.9.5.3 Summary of evidence and recommendations for the diagnosis and treatment of urosepsis

Summary of evidence	LE
Initial high dose empiric antimicrobial therapy, administered within the first hour, should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available.	2b
Source control interventions should be implemented as soon as possible to control or eliminate diagnosed and/or suspected infectious foci.	3

Recommendations	Strength rating
Perform the quickSOFA score to identify patients with potential sepsis.	Strong
Take a urine culture and two sets of blood cultures before starting antimicrobial treatment.	Strong
Administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis.	Strong
Adapt initial empiric antimicrobial therapy on the basis of culture results.	Strong
Initiate source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.	Strong
Provide immediate adequate life-support measures.	Strong

Table 7: Suggested regimens for antimicrobial therapy for urosepsis.

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d	7-10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1-2 g t.i.d	
Ceftriaxone	1-2 g q.d	
Cefepime	2 g b.i.d	
Piperacillin/tazobactam	4.5 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Gentamicin*	5 mg/kg q.d	
Amikacin*	15 mg/kg q.d	
Ertapenem	1 g q.d	
Imipenem/cilastatin	0.5 g t.i.d	
Meropenem	1 g t.i.d	

** Not studied as monotherapy in urosepsis*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.10 Urethritis

*3.10.1 **Introduction***

Urethritis can be of either infectious or non-infectious origin. Inflammation of the urethra presents usually with LUTS and must be distinguished from other infections of the lower urinary tract. Urethral infection is typically spread by sexual contact.

*3.10.2 **Epidemiology, aetiology and pathogenesis***

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) caused by *Neisseria gonorrhoeae* must be differentiated from non-gonococcal urethritis (NGU). Non-gonococcal urethritis is a non-specific diagnosis that can have many infectious aetiologies. Causative pathogens include *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum* and *Trichomonas vaginalis*. The role of *Ureaplasma* spp. as urethritis

causative pathogens is controversial. Recent data suggests that *U. urealyticum*, but not *U. parvum* is an aetiological agent in NGU [220]. The prevalence of isolated causative pathogens are: *C. trachomatis* 11-50%; *M. genitalium* 6-50%; Ureaplasmas 5-26%; *T. vaginalis* 1-20%; and adenoviruses 2-4% [221].

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women [222].

Mucopurulent or purulent discharge, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

*3.10.3 **Evidence Questions***

1. In patients with urethritis what is the best method of detecting the causative pathogen?
2. In patients with urethritis what are the best treatment strategies for clinical or microbiological cure?

*3.10.4 **Evidence Summary***

A systematic search of the literature form January 2014 until February 2019 identified 488 titles of which 71 were selected for full text review. Thirteen systematic reviews or guidelines based on systematic literature searches [220-232], and seventeen original publications [233-249] were selected for further analysis. In addition, a further eleven relevant publications were identified from the references of the reviewed literature [250-260].

*3.10.5 **Diagnostic evaluation***

In symptomatic patients the diagnosis of urethritis can be made based on the presence of any of the following criteria [221, 222]:

- Mucoid, mucopurulent, or purulent urethral discharge.
- Gram or methylene-blue stain of urethral secretions demonstrating inflammation. Five or more polymorphonuclear leucocytes (PMNL) per high power field (HPF) is the historical cut-off for the diagnosis of urethritis. A threshold of ≥ 2 PMNL/HPF was proposed recently based on better diagnostic accuracy [237, 250-252], but this was not supported by other studies [236]. Therefore, in line with the 2016 European Guideline on the management of NGU [221] the use of ≥ 5 PMNL/HPF cut-off level is recommended until the benefit of alternative cut-off levels is confirmed.
- The presence of ≥ 10 PMNL/HPF in the sediment from a spun first-void urine sample or a positive leukocyte esterase test in first-void urine.

Evidence of urethral inflammation in the Gram stain of urethral secretions with gonococci located intracellularly as Gram-negative diplococci indicates GU. Non-gonococcal urethritis is confirmed when staining of urethral secretions indicates inflammation in the absence of intracellular diplococci. Clinicians should always perform point-of-care diagnostics (e.g. Gram staining, first-void urine with microscopy, leukocyte esterase testing) if available to obtain objective evidence of urethral inflammation and to guide treatment [221, 222, 235]. Recent studies showed that processing time of point-of-care diagnostics is highly relevant in terms of patient compliance and real-life applicability [233, 234].

Men who meet the criteria for urethritis should be tested for *C. trachomatis, M. genitalium and N. gonorrhoea* with nucleic acid amplification tests (NAAT), even if point-of-care tests are negative for gonorrhoeae [221, 224]. The sensitivity and specificity of NAATs is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections [225, 253]. The performance of first-catch urine is non-inferior to urethral swabs [253]. In case of delayed treatment, if a NAAT is positive for gonorrhoea, a culture using urethral swabs should be performed before treatment to assess the antimicrobial resistance profile of the infective strain [222]. *N. gonorrhoeae and C. trachomatis* cultures are mainly used to evaluate treatment failures and monitor developing resistance to current treatment. *Trichomonas* spp. can usually be identified microscopically [222] or by NAATs [227].

Non-gonococcal urethritis is classified as persistent when symptoms do not resolve within three to four weeks following treatment. When this occurs NAATs should be performed for urethritis pathogens including *T. vaginalis* four weeks after completion of therapy [221, 238].

*3.10.6 **Disease management***

For severe urethritis empirical treatment should be started following diagnosis. If the patients symptoms are mild, delayed treatment guided by the results of NAATs is recommended. All sexual partners at risk should be assessed and treated whilst maintaining patient confidentiality [221, 241].

3.10.6.1 Gonococcal urethritis

For GU, a combination treatment using two antimicrobials with different mechanisms of action is recommended to improve treatment efficacy and to hinder increasing resistance to cephalosporins [222]. Ceftriaxone 1 g intramuscularly or intravenously with azithromycin 1 g single oral dose should be used as first-line treatment. Azithromycin is recommended because of its favourable susceptibility rates compared to other antimicrobials, good compliance with the single-dose regimen and the possibility of a *C. trachomatis* co-infection [222]. In case of azithromycin allergy, doxycycline can be used instead in combination with ceftriaxone or cefixime [222]. A 400 mg oral dose of cefixime is recommended as an alternative regimen to ceftriaxone; however, it has less favourable pharmacodynamics and may lead to the emergence of resistance [223, 259].

A number of alternative regimens for the treatment of GU have been studied. In a randomised, open label, non-comparative clinical study dual treatment with a combination of intramuscular gentamicin 240 mg plus oral azithromycin 2 g (n=202) single doses and a combination of oral gemifloxacin 320 mg plus oral azithromycin 2 g (n=199) single doses were associated with microbiological cure rates of 100% and 99.5%, respectively [255]. A 2014 systematic review focusing on the use of single-dose intramuscular gentamicin concluded that there is insufficient data to support or refute the efficacy and safety of this regimen in the treatment of uncomplicated gonorrhoea [229]. In three prospective single arm studies enrolling men with GU the use of extended-release azithromycin 2 g single oral dose resulted in microbiological cure rates of 83% (n=36), 93.8% (n=122) and 90.9% (n=33), respectively [245, 246, 248]. However, azithromycin monotherapy is generally not recommended because of its effect on increasing macrolide resistance rates [222]. Intramuscular spectinomycin 2 g single dose shows microbiological cure rates above 96% [256, 259] in urogenital gonorrhoeal infections where available, it can be a valid treatment alternative. An open label, randomised trial compared oral fosfomycin trometamol 3 g on days one, three and five (n=60) with intramuscular ceftriaxone 250 mg plus oral azithromycin 1 g single dose (n=61) in men with uncomplicated GU. In the per-protocol analysis clinical and microbiologic cure rates were 96.8% and 95.3% respectively [249].

The worldwide increase in gonorrhoeal antimicrobial resistance and the emergence of multidrug-resistant gonorrhoeal strains is a globally recognised healthcare crisis which emphasises the importance of guideline adherence [228, 240, 260].

3.10.6.2 Non-gonococcal urethritis

For NGU without an identified pathogen oral doxycycline 100 mg twice daily for seven days should be used as first-line treatment. Alternatively, single dose oral azithromycin 500 mg day one and 250 mg days two to four can be used. This regimen provides better efficacy compared to azithromycin 1 g single dose for *M. genitalium* infections, in which azithromycin 1 g single dose treatment is associated with the development of increasing macrolide resistance significantly decreasing the overall cure rate [221, 224, 230, 244]. However, a retrospective cohort study did not find significant difference between the extended and 1 g single dose azithromycin regimen regarding cure rates and the selection of macrolide resistance in *M. genitalium* urethritis [242]. If macrolide resistant *M. genitalium* is detected moxifloxacin 400 mg can be used for seven to fourteen days [221, 222, 231]. In case of failure after both azithromycin and moxifloxacin treatment, pristinamycin (registered in France) is the only antimicrobial agent with documented activity against *M. genitalium* [224, 243, 254]. Josamycin 500 mg three times a day for ten days is used in Russia, but will not eradicate macrolide-resistant strains [224].

For chlamydial urethritis azithromycin 1 g single dose and doxycycline 100 mg twice daily for seven days are both effective options [258]. A Cochrane review found that in men with urogenital *C. trachomatis* infection regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure [232]. Fluoroquinolones, such as ofloxacin or levofloxacin, may be used as second-line treatment only in selected cases where the use of other agents is not possible [257].

For *U. urealyticum* infections the efficacy of doxycycline 100 mg twice daily for seven days is similar to azithromycin 1 g single dose treatment [221, 239]. For urethritis caused by *T. vaginalis* oral metronidazole or tinidazole 2 g single dose is recommended as first-line treatment. For treatment options for persistent or recurrent *T. vaginalis* infection refer to the review of Sena *et. al.*, [227]. In case of persistent NGU treatment should cover *M. genitalium* and *T. vaginalis* [221, 222].

3.10.7 ***Follow-up***

Patients should be followed-up for control of pathogen eradication after completion of therapy only if therapeutic adherence is in question, symptoms persist or reoccurrence is suspected. Patients should be instructed to abstain from sexual intercourse for seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and source tracing should

be done in accordance with national guidelines and in cooperation with specialists in venereology, whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV [226].

3.10.8 Summary of evidence and recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis

Summary of evidence	**LE**
A Gram stain of urethral discharge or a urethral smear that shows ≥ 5 leukocytes per high power field (× 1,000) and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis.	3b
Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections.	2a
For GU dual treatment with ceftriaxone and azithromycin is the most effective combination.	2a
In case of urogenital *C. trachomatis* infection in men azithromycin is probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure.	1a
In case of *U. urealyticum* infection the efficacy of doxycycline 100 mg twice for seven days is similar to azithromycin 1 g single dose treatment.	2a

Recommendations	**Strength rating**
Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis.	Strong
Perform a validated nucleic acid amplification test (NAAT) on a first-void urine sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections.	Strong
Delay treatment until the results of the NAATs are available to guide treatment choice in patients with mild symptoms.	Strong
Perform a urethral swab culture, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain.	Strong
Use a pathogen directed treatment based on local resistance data.	Strong
Sexual partners should be treated maintaining patient confidentiality.	Strong

Table 8: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Dosage & Duration of therapy	Alternative regimens
Gonococcal Infection	Ceftriaxone Azithromycin	1 g i.m. or i.v., SD 1 g p.o., SD	• Cefixime 400 mg p.o., SD plus Azithromycin 1 g p.o., SD In case of cephalosporin allergy: • Gentamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Gemifloxacin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2 g i.m., SD • Fosfomycin trometamol 3 g p.o., on days 1, 3 and 5 In case of azithromycin allergy, in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d, p.o., 7 days
Non-Gonococcal infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7-10 days	Azithromycin 500 mg p.o., day 1, 250 mg p.o., 4 days
Chlamydia trachomatis	Azithromycin Or Doxycycline	1.0-1.5 g p.o., SD 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days
Mycoplasma genitalium	Azithromycin	500 mg p.o., day 1, 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma urealyticum	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 1.0-1.5 g p.o., SD
Trichomonas vaginalis	Metronidazole Tinidazole	2 g p.o., SD 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis			
After first-line doxycycline	Azithromycin plus Metronidazole	500 mg p.o., day 1, 250 mg p.o., 4 days 400 mg b.i.d. p.o., 5 days	If macrolide resistant M. genitalium is detected moxifloxacin should be substituted for azithromycin
After first-line azithromycin	Moxifloxacin plus Metronidazole	400 mg p.o. q.d., 7–14 days 400 mg b.i.d. p.o., 5 days	

SD = single dose; b.i.d = twice daily; q.d = everyday; p.o. = orally; i.m. = intramuscular.

3.11 Bacterial Prostatitis

*3.11.1 **Introduction***

Bacterial prostatitis is a clinical condition caused by bacterial pathogens. It is recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis, with confirmed or suspected infection, is distinguished from chronic pelvic pain syndrome (CPPS) (Table 9) [261-263].

Table 9: Classification of prostatitis and CPPS according to NIDDK/NIH [261-263]

Type	Name and description
I	Acute bacterial prostatitis (ABP)
II	Chronic bacterial prostatitis (CBP)
III	Chronic non-bacterial prostatitis – CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion;
VB3 = voided bladder urine specimen 3 (urine following prostatic massage).

*3.11.2 **Evidence Question***

In men with NIDDK/NIH Category I or II prostatitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

*3.11.3 **Evidence Summary***

A systematic literature search from 1980 until June 2017 was performed. One systematic review [264], six RCTs [265-270], two narrative reviews [271, 272], one prospective cohort study [273], two prospective cross-sectional studies [274, 275], and one retrospective cohort study [267], were selected from 856 references.

A retrospective study [276], investigated the potential role of unusual pathogens in prostatitis syndrome in 1,442 patients over a four year period. An infectious aetiology was determined in 74.2% of patients; *C. trachomatis*, *T. vaginalis* and *U. urealyticum* infections were found in 37.2%, 10.5% and 5% of patients, respectively whilst *E. coli* infection was found in only 6.6% of cases. Cross sectional studies confirmed the validity of the Meares and Stamey test to determine the bacterial strain and targeted antibiotic therapies [274, 275]. The evidence levels were very good, in particular those regarding information on atypical strains, epidemiology and antibiotic treatments.

A systematic review on antimicrobial therapy for CBP [264] compared multiple antibiotic regimens from eighteen selected studies enrolling a total of 2,196 patients. The role of fluoroquinolones as first line agents was confirmed with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events. The efficacy of macrolides and tetracyclines on atypical pathogens was confirmed.

Randomised controlled trials on combined treatments [269, 270] indicated that the combination of plants/herbal extracts or PDE5Is with antibiotics may improve quality of life and symptoms in patients with CBP; however, the number of enrolled patients was inadequate to obtain definitive conclusions.

A review of treatment of bacterial prostatitis [271] indicated that the treatment of CBP is hampered by the lack of an active antibiotic transport mechanism into infected prostate tissue and fluids. The review underlined the potential effect of different compounds in the treatment of ABP and CBP on the basis of over 40 studies on the topic.

One RCT compared the effects of two different metronidazole regimens for the treatment of CBP caused by *T. vaginalis* [268]. Metronidazole 500 mg three times daily for fourteen days was found to be efficient for micro-organism eradication in 93.3% of patients with clinical failure in 3.33% of cases.

*3.11.4 **Epidemiology, aetiology and pathogenesis***

Prostatitis is a common diagnosis, but less than 10% of cases have proven bacterial infection [228]. Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in ABP [277]. In CBP, the spectrum of species is wider and may include atypical micro-organisms [271]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida* spp. and other rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum* [278]. The significance of identified intracellular bacteria, such as *C. trachomatis*, is uncertain [279]; however, two studies have highlighted its possible role as a causative pathogen in CBP [280, 281].

*3.11.5 **Diagnostic evaluation***

3.11.5.1 History and symptoms

Acute bacterial prostatitis usually presents abruptly with voiding symptoms and distressing but poorly localised pain. It is often associated with malaise and fever. Transrectal prostate biopsy increases the risk of ABP despite antibiotic prophylaxis and antiseptic prevention procedures [265]. Chronic bacterial prostatitis is defined by symptoms that persist for at least three months [282-284]. The predominant symptoms are pain at various locations including the perineum, scrotum, penis and inner part of the leg as well as LUTS [261-263].

3.11.5.2 Symptom questionnaires

In CBP symptoms appear to have a strong basis for use as a classification parameter [285]. Prostatitis symptom questionnaires have therefore been developed to assess severity and response to therapy [285, 286]. They include the validated Chronic Prostatitis Symptom Index (CPSI); however, its usefulness in clinical practice is uncertain [273].

3.11.5.3 Clinical findings

In ABP, the prostate may be swollen and tender on DRE. Prostatic massage should be avoided as it can induce bacteraemia and sepsis. Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% [287]. Blood culture and complete blood count are useful in ABP. Imaging studies can detect a suspected prostatic abscess [271].

In case of longer lasting symptoms CPPS as well as other urogenital and anorectal disorders must be taken into consideration. Symptoms of CBP or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should trigger investigation for urogenital tuberculosis.

3.11.5.4 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with ABP is mid-stream urine culture [271]. In CBP, quantitative bacteriological localisation cultures and microscopy of the segmented urine and expressed prostatic secretion (EPS), as described by Meares and Stamey [288], are still important investigations to categorise clinical prostatitis [274, 275]. Accurate microbiological analysis of samples from the Meares and Stamey test may also provide useful information on the presence of atypical pathogens such as *C. trachomatis*, *T. vaginalis* and *U. urealiticum* [276]. The two-glass test has been shown to offer similar diagnostic sensitivity to the four-glass test [289].

3.11.5.5 Prostate biopsy

Prostate biopsies cannot be recommended as routine work-up and are not advisable in patients with untreated bacterial prostatitis due to the increased risk of sepsis.

3.11.5.6 Other tests

Transrectal US may reveal endoprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles; however, it is unreliable as a diagnostic tool for prostatitis [290].

3.11.5.7 Additional investigations

3.11.5.7.1 Ejaculate analysis

Performing an ejaculated semen culture improves the diagnostic utility of the four glass test [274]; however, semen cultures are more often positive than EPS cultures in men with non-bacterial prostatitis [275]. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.5.7.2 First-void urine sample

First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs, since it is non-invasive and yet allows the detection of infected epithelial cells and associated *C. trachomatis* particles [291].

3.11.5.7.3 Prostate specific antigen (PSA)

Prostate specific antigen is increased in about 60% and 20% of men with ABP and CBP, respectively [272]. The PSA level decreases after antibiotic therapy (which occurs in approximately 40% of patients) and correlates with clinical and microbiological improvement [266]. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [292].

3.11.5.8 Summary of evidence and recommendations for the diagnosis of bacterial prostatitis

Summary of evidence	LE
Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% in patients with ABP.	3
The four-glass Meares and Stamey test is the optimum test for diagnosis of CBP. The two-glass test has been shown to offer similar diagnostic sensitivity in a comparison study.	2b
First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs.	2b
Transrectal ultrasound is unreliable and cannot be used as a diagnostic tool in prostatitis.	3
Semen culture sensitivity is reported to be approximately 50%; therefore, it is not routinely part of the diagnostic assessment of CBP.	3
Prostate specific antigen levels may be elevated during active prostatitis; therefore, PSA testing should be avoided as it offers no practical diagnostic information for prostatitis.	3

Recommendations	Strength rating
Do not perform prostatic massage in acute bacterial prostatitis (ABP).	Strong
Take a mid-stream urine dipstick to check nitrite and leukocytes in patients with clinical suspicion of ABP.	Weak
Take a mid-stream urine culture in patients with ABP symptoms to guide diagnosis and tailor antibiotic treatment.	Weak
Take a blood culture and a total blood count in patients presenting with ABP.	Weak
Perform accurate microbiological evaluation for atypical pathogens such as *Chlamydia trachomatis* or Mycoplasmata in patients with chronic bacterial prostatitis (CBP).	Weak
Perform the Meares and Stamey 2- or 4-glass test in patients with CBP.	Strong
Perform transrectal ultrasound in selected cases to rule out the presence of prostatic abscess.	Weak
Do not routinely perform microbiological analysis of the ejaculate alone to diagnose CBP.	Weak

*3.11.6 **Disease management***

3.11.6.1 Antimicrobials

Antimicrobials are life-saving in ABP and recommended in CBP. Culture-guided antibiotic treatments are the optimum standard; however, empirical therapies should be considered in all patients with ABP.

In ABP parenteral administration of high doses of bactericidal antimicrobials, such as broad-spectrum penicillins, a third-generation cephalosporin or fluoroquinolones, is recommended [293]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [277-286, 293-297]. Ancillary measures include adequate fluid intake and urine drainage [228]. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks [298].

Fluoroquinolones, despite the high resistance rates of uropathogens, are recommended as first-line agents in the empirical treatment of CBP because of their favourable pharmacokinetic properties [299], their generally good safety profile and antibacterial activity against Gram-negative pathogens including *P. aeruginosa* and C. trachomatis [264, 300]. However, increasing bacterial resistance is a concern. Azithromycin and doxycycline are active against atypical pathogens such as *C. trachomatis* and genital mycoplasmata [267, 276]. Levofloxacin did not demonstrate significant clearance of *C. trachomatis* in patients with CBP [301]. Metronidazole treatment is indicated in patients with *T. vaginalis* infections [268].

Duration of fluoroquinolone treatment must be at least fourteen days while azithromycin and doxycycline treatments should be extended to at least three to four weeks [267, 276]. In CBP antimicrobials should be given for four to six weeks after initial diagnosis [271]. If intracellular bacteria have been detected macrolides or tetracyclines should be given [264, 299, 302].

3.11.6.2 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [303, 304].

3.11.6.3 Combined treatments

A combination of fluoroquinolones with various herbal extracts may attenuate clinical symptoms without increasing the rate of adverse events [269]. However, a combination of fluoroquinolones with vardenafil neither improved microbiological eradication rates or attenuated pain or voiding symptoms in comparison with fluoroquinolone treatment alone [270].

3.11.6.4 Drainage and surgery

Approximately 10% of men with ABP will experience urinary retention [305] which can be managed by uretheral or suprapubic catheterisation. However, recent evidence suggests that suprapubic catheterisation can reduce the risk of development of CBP [306].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [307]; however, the abscess size may matter. In one study, conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [308].

3.11.6.5 Summary of evidence and recommendations for the disease management of bacterial prostatitis

Summary of evidence	**LE**
The treatment regimen for ABP is based on clinical experience and a number of uncontrolled clinical studies. For systemically ill patients with ABP, parenteral antibiotic therapy is preferable. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks.	3
The role of fluoroquinolones as first-line agents for antimicrobial therapy for CBP was confirmed in a systematic review, with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events.	1a
Metronidazole 500 mg three times daily for fourteen days was found to be efficient for eradication in 93.3% of patients with *T. vaginalis* CBP.	1b
In patients with CBP caused by obligate intracellular pathogens, macrolides showed higher microbiological and clinical cure rates compared to fluoroquinolones.	1a
Clinicians should consider local drug-resistance patterns when choosing antibiotics.	3

Recommendations	**Strength rating**
Acute bacterial prostatitis	
Treat acute bacterial prostatitis according to the recommendations for complicated UTIs (see section 3.7.5).	Strong
Chronic bacterial prostatitis (CBP)	
Prescribe a fluoroquinolone (e.g. ciprofloxacin, levofloxacin) as first-line treatment for CBP.	Strong
Prescribe a macrolide (e.g. azithromycin) or a tetracycline (e.g. doxycycline) if intracellular bacteria have been identified as the causative agent of CBP.	Strong
Prescribe metronidazole in patients with *Trichomonas vaginalis* CBP.	Strong

Table 10: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**
Floroquinolone	Optimal oral daily dose	4-6 weeks	
Doxycycline	100 mg b.i.d	10 days	Only for *C. trachomatis* or mycoplasma infections
Azithromycin	500 mg once daily	3 weeks	Only for *C. trachomatis* infections
Metronidazole	500 mg t.i.d.	14 days	Only for *T. vaginalis* infections

b.i.d = twice daily; t.i.d = three times daily.

3.11.7 ***Follow-up***

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory as there are no validated tests of cure for bacterial prostatitis except for cessation of symptoms [271]. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patient's partner/s is recommended. Antibiotic treatments may be repeated with a more prolonged course, higher dosage and/or different compounds [271].

3.12 Acute Infective Epididymitis

3.12.1 ***Evidence question***

In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen in:

1. men at low risk of gonorrhoea infection;
2. men at high risk of gonorrhoea infection?

3.12.2 ***Epidemiology, Aetiology and Pathophysiology***

Epididymitis is a common condition with incidence ranging from 25 to 65 cases per 10,000 adult males per year and can be acute, chronic or recurrent [309]. Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *C. trachomatis*, Enterobacteriaceae (typically *E. coli*) and *N. gonorrhoeae* [310]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by Enterobacteriaceae. The mumps virus should be considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur, typically as chronic epididymitis, in high-risk groups such as men with immunodeficiency and those from high prevalence countries, it frequently results in a discharging scrotal sinus. *Brucella* or *Candida* spp. are rare possible pathogens.

3.12.3 ***Diagnostic Evaluation***

Culture of a mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infection with *C. trachomatis* or *N. gonorrhoeae* should be detected by NAAT on first voided urine. A urethral swab or smear should be performed for Gram staining and culture if *N. gonorrhoeae* is likely [311]. Detection of these pathogens should be reported according to local procedures. All patients with probable sexually transmitted infections (STIs) should be advised to attend an appropriate clinic to be screened for other STIs. Men with Enterobacteriaceae may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA [312]. If appropriate prostate secretion, ejaculate, discharge from a draining scrotal fistula, as well as fine needle aspiration and biopsy specimens should be investigated using microscopy, AFB culture and NAAT.

3.12.4 ***Disease Management***

Men with suspected STI should be informed of the risks to others and advised not to have sex until free of infection. Empirical antimicrobial therapy has to be chosen with consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *C. trachomatis* and Enterobacteriaceae should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *C. trachomatis* or *M. genitalium* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *C. trachomatis* but not tested in epididymitis. Fluoroquinolones remain effective for oral treatment of Enterobacteriaceae although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third generation cephalosporin is effective against *N. gonorrhoeae*; current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after approximately three days. Men with likely or proven STI should be assessed at fourteen days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

3.12.5 ***Evidence Summary***

Relating to this chapter, three guidelines based on systematic reviews were identified [311, 313, 314] with search dates of December 2009, March 2012 and April 2013, respectively. No evidence quality assessments were detailed. A structured search of the literature from January 2010 to May 2017 identified 1,108 titles of which 46 were selected for full text review and six were included [315-320]. In addition, a high quality RCT outside the search dates was identified which demonstrated that a ten-day course of ciprofloxacin was superior to pivampicillin for clinical cure (80% vs. 60%) in men aged > 40 years [321]. Data from a large comparative case series suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [319].

Empiric antibiotic regimens from existing guidelines [311, 313, 314] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and Enterobacteriaceae should be used. Appropriate options are:

   A. A fluoroquinolone active against C. trachomatis orally once daily for ten to fourteen days*

   OR

   B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days* **plus** an antibiotic active against Enterobacteriaceae** for ten to fourteen days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against Gonococcus and *C. trachomatis* must be used such as:

   A. Ceftriaxone 500 mg intramuscularly single dose **plus** doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days*

3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate Enterobacteriaceae should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days*

*Depending upon pathogen identification and clinical response.
** A parenteral option will be required for men with severe infection requiring hospitalisation.

Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study found that lack of separation of epididymis and testis on palpation and the presence of abscess on US may predict requirement for surgery following initial antibiotic treatment [315].

A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [318]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [316] and by primary care physicians [317].

*3.12.6 **Screening***

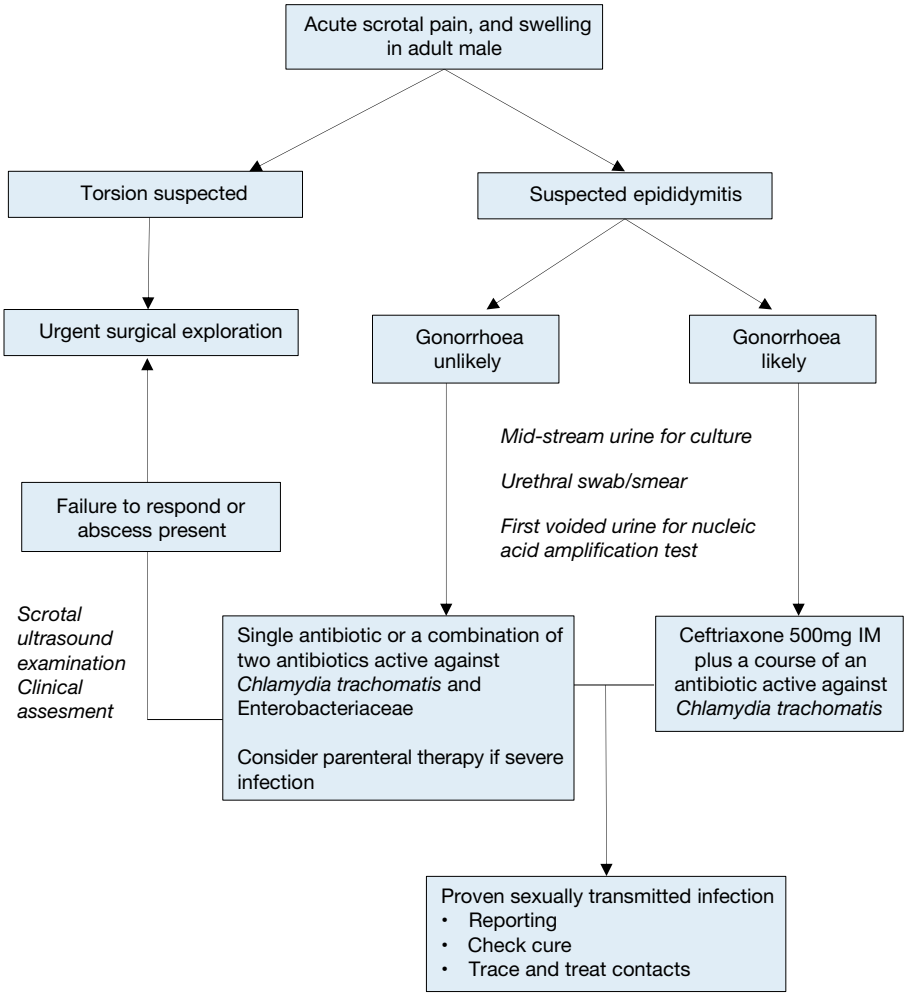
A large cohort screening study for carriage of *C. trachomatis* including a randomly selected group of 5,000 men of whom 1,033 were tested showed no benefit in terms of reduction in risk of epididymitis over nine years of observation [320].

*3.12.7 **Summary of evidence and recommendations for the diagnosis and treatment of acute infective epididymitis***

Summary of evidence	**LE**
In young sexually active patients both STIs and Enterobacteriaceae have to be considered as aetiological agents.	3
In patients > 40 years antibiotic therapy with ciprofloxacin is superior to pivmecillinam.	1b
A negative sexual risk history does not exclude STIs in sexually active men.	3

Recommendations	**Strength rating**
Obtain a mid-stream urine and a first voided urine for pathogen identification by culture and nucleic acid amplification test.	Strong
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	Strong
If gonorrhoeal infection is likely give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against *Chlamydia trachomatis*.	Strong
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	Weak
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	Strong

Figure 2: Diagnostic and treatment algorithm for adult men with acute epididymitis



3.13 Fournier's Gangrene (Necrotising fasciitis of the perineum and external genitalia)

3.13.1 Evidence questions

1. What is the best antimicrobial treatment strategy to reduce mortality?
2. What is the best debridement and reconstruction strategy to reduce mortality and aid recovery?
3. Are there any effective adjuvant treatments that improve outcome?

3.13.2 Epidemiology, Aetiology and Pathophysiology

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [322]. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway.

3.13.3 Diagnostic Evaluation

Typically, there is painful swelling of the scrotum or perineum with sepsis [322]. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Patient risk factors for occurrence and mortality include being immunocompromised, most commonly diabetes or malnutrition, recent urethral or perineal surgery, and high body mass index (BMI). In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment [323]. A high index of suspicion and careful examination, particularly of obese patients, is required. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for bowel diversion [322].

3.13.4 Disease Management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement with urinary diversion by suprapubic catheter is necessary to reduce

mortality [322]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery may result in higher mortality [322]. Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue. A suggested regime would comprise a broad-spectrum penicillin or third-generation cephalosporin, gentamicin and metronidazole or clindamycin [322]. This can then be refined, guided by microbiological culture.

*3.13.5 **Evidence Summary***

A systematic literature search from 1980 to July 2017 was performed. From 640 references one RCT [324], two systematic reviews [325, 326], one narrative review [322], three registry studies [327-329], one prospective cohort study [330] and two retrospective comparative cohort studies with at least 25 patients [331, 332] were selected. The three registry studies from the United States [327-329], found mortality rates of 10%, 7.5% and 5% from 650, 1,641 and 9,249 cases, respectively. Older age, diabetes and high BMI were associated with higher risk. A prospective cohort study showed that disease-specific severity scores did predict outcome, but were not superior to generic scoring systems for critical care [330]. Concerning the evidence questions:

1. A low quality retrospective case series [331] with 168 patients found no significant difference in mortality between patients given ≤ 10 days of parenteral antibiotics (80 patients) and those given > 10 days (88 patients).
2. A systematic review of wound closure techniques [326] found low-quality evidence from 16 case series involving 425 male patients. They recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.
3. A systematic review on the use of hyperbaric oxygen therapy [325] included three comparative case series and four other case series. All were retrospective and published prior to 2000. No consistent evidence of benefit was found; an RCT was advised. A more recent comparative case series [332] suggested benefit for use of hyperbaric oxygen therapy in 16 patients compared to 12 cases without use of such therapy in terms of reduced mortality and fewer debridements (low quality evidence). A low-quality RCT [324] with 30 patients found that use of honey soaked dressings resulted in a shorter hospital stay (28 vs. 32 days) than dressing soaked with Edinburgh solution of lime (EUSOL). We found no evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene.

*3.13.6 **Summary of evidence and recommendations for the disease management of Fournier's Gangrene***

Summary of evidence	**LE**
Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue.	3
A systematic review of wound closure techniques recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.	3
No consistent evidence of benefit for hyperbaric oxygen therapy was found.	3
A low quality RCT found that dressings soaked in honey resulted in a shorter hospital stay than dressing soaked with EUSOL.	3
No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.	4

Recommendations	**Strength rating**
Start treatment for Fournier's gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	Strong
Commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.	Strong
Do not use adjunctive treatments for Fournier's gangrene except in the context of clinical trials.	Weak

Table 11: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology adapted from [333]**.**

Antimicrobial	Dosage
Piperacillin-tazobactam plus Vancomycin	4.5 g every 6-8 h IV 15 mg/kg every 12 h
Imipenem-cilastatin	1 g every 6-8 h IV
Meropenem	1 g every 8 h IV
Ertapenem	1 g once daily
Gentamicin	5 mg/kg daily
Cefotaxime plus metronidazole or clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600-900 mg every 8 h IV
Cefotaxime plus fosfomycin plus metronidazole	2 g every 6 h IV 5 g every 8 h IV 500 mg every 6 h IV

IV = intravenous

3.14 Peri-Procedural Antibiotic Prophylaxis

3.14.1 ***General Principles***

3.14.1.1 Definition of infectious complications

The European Centre for Disease Prevention and Control (ECDC) and the CDC have both presented similar definitions recommended for the evaluation of infectious complications [334, 335].

3.14.1.2 Non-antibiotic measures for asepsis

There are a number of non-antibiotic measures designed to reduce the risk of surgical site infection (SSI), many are historically part of the routine of surgery. The effectiveness of measures tested by RCTs are summarised in systematic reviews conducted by the Cochrane Wounds Group (http://wounds.cochrane.org/news/reviews). Urological surgeons and the institutions in which they work should consider and monitor maintenance of an aseptic environment to reduce risk of infection from pathogens within patients (microbiome) and from outside the patient (nosocomial/healthcare-associated). This should include use of correct methods of instrument cleaning and sterilisation, frequent and thorough cleaning of operating rooms and recovery areas and thorough disinfection of any contamination. The surgical team should prepare to perform surgery by effective hand washing [336], donning of appropriate protective clothing and maintenance of asepsis. These measures should continue as required in recovery and ward areas.

Patients should be encouraged to shower pre-operatively, but use of chlorhexidine soap does not appear to be beneficial [337]. Although evidence quality is low, any required hair removal appears best done by clipping, rather than shaving, just prior to incision [338]. Mechanical bowel preparation should not be used as evidence review suggests harm not benefit [339, 340]. There is some weak evidence that skin preparation using alcoholic solutions or chlorhexidine result in a lower rate of SSI than iodine solutions [341]. Studies on the use of plastic adherent drapes showed no evidence of benefit in reducing SSI [342].

3.14.1.3 Detection of bacteriuria prior to urological procedures

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimise antimicrobial coverage in conjunction with the procedure. A systematic review of the evidence identified eighteen studies comparing the diagnostic accuracy of different index tests (dipstick, automated microscopy, dipslide culture and flow cytometry), with urine culture as the reference standard [343]. The systematic review concluded that none of the alternative urinary investigations for the diagnosis of bacteriuria in adult patients prior to urological interventions can currently be recommended as an alternative to urine culture [343].

3.14.1.4 Choice of agent

Urologists should have knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence in order to establish written local guidelines. These guidelines should cover the five modalities identified by the ECDC following a systematic review of the literature [344]. The agent should ideally not be one that may be required for treatment of infection. When risk of skin wound infection is low or absent, an aminoglycoside (gentamicin) should provide cover against likely uropathogens provided the eGFR is > 20 mL/min; second generation cephalosporins are an alternative [345]. Recent urine culture results including presence of any multi-resistant organisms, drug allergy, history of *C. difficile* associated diarrhoea,

recent antibiotic exposure, evidence of symptomatic infection pre-procedure and serum creatinine should be checked. The panel have decided not to make recommendations for specific agents for particular procedures as there is considerable variation in Europe and worldwide regarding bacterial pathogens, their susceptibility and availability of antibiotic agents.

3.14.2 ***Specific procedures and evidence question***

A literature search from 1980 to February 2017 identified RCTs, systematic reviews and meta-analyses that investigated the benefits and harms of using antibiotic prophylaxis prior to specific urological procedures. The available evidence enabled the panel to make recommendations concerning urodynamics, cystoscopy, stone procedures (extracorporeal shockwave lithotripsy [ESWL], ureteroscopy and percutaneous nephrolithotomy [PCNL]), transurethral resection of the prostate (TURP) and transurethral resection of the bladder (TURB). For nephrectomy and prostatectomy the scientific evidence was too weak to allow the panel to make recommendations either for or against antibiotic prophylaxis. The general evidence question was: Does antibiotic prophylaxis reduce the rate of post-operative symptomatic UTI in patients undergoing each named procedure?

3.14.2.1 Urodynamics

The literature search identified one Cochrane review with search date of December 2009 [346] and two later RCTs [347, 348]. Foon *et al.*, identified nine RCTs enrolling 973 patients with overall low quality and high or unclear risks of bias. The outcome of clinical UTI was reported in four trials with no benefit found for antibiotic prophylaxis versus placebo [RR (95%CI) 0.73 (0.52-1.03)]. A meta-analysis of nine trials showed that use of antibiotics reduced the rate of post-procedural bacteriuria [RR (95%CI) 0.35 (0.22-0.56)] [346]. Neither Hirakauva *et al.*, or Gurburz *et al.*, reported a clinical UTI outcome and had conflicting findings for reduction in risk of bacteriuria [347, 348].

3.14.2.2 Cystoscopy

The literature search identified two systematic reviews and meta-analyses with search dates of April 2014 and December 2013, respectively [349, 350]. No additional RCTs subsequent to these dates were found. Garcia-Perdomo *et al.*, included seven RCTs with a total of 3,038 participants. The outcome of symptomatic UTI was measured by five trials of moderate overall quality and meta-analysis showed a benefit for using antibiotic prophylaxis [RR (95%CI) 0.53 (0.31 – 0.90)]; ARR 1.3% (from 2.8% to 1.5%) with a NNT of 74 [350]. This benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis. Carey *et al.*, included seven RCTs with 5,107 participants. Six trials were included in meta-analysis of the outcome of symptomatic bacteriuria which found benefit for use of antibiotic prophylaxis [RR (95%CI) 0.34 (0.27 – 0.47)]; ARR 3.4% (from 6% to 2.6%) with NNT of 28 [349]. Given the low absolute risk of post-procedural UTI in well-resourced countries, the high number of procedures being performed, and the high risk of contributing to increasing antimicrobial resistance the panel consensus was to strongly recommend not to use antibiotic prophylaxis in patients undergoing urethrocystoscopy (flexible or rigid).

3.14.2.3 Interventions for urinary stone treatment

3.14.2.3.1 Extracorporeal shockwave lithotripsy

For patients without bacteriuria undergoing ESWL two systematic reviews and meta-analyses were identified with latest search dates of November 2011 and October 2012, respectively [351, 352]. The literature search to February 2017 identified one further trial [353]. Lu *et al.*, included nine RCTs with a total of 1,364 patients and found no evidence of benefit in terms of reducing the rate of post-procedural fever or bacteriuria [351]. Mrkobrada *et al.*, included eight RCTs with a total of 940 participants and found no evidence of benefit for antibiotic prophylaxis to reduce rate of fever or trial-defined infection [352]. The RCT reported by Hsieh *et al.*, with 274 patients had a severe risk of bias. It found no reduction in fever at up to one week post-procedure using a single dose of levofloxacin 500 mg and no difference in the rate of bacteriuria [353].

For patients with bacteriuria or deemed at high risk of complications one RCT comparing the use of ofloxacin or trimethoprim-sulphamethoxazole for three days prior and four days subsequent to ESWL in 56 patients with ureteric stents was identified [354]. They found no difference in rate of clinical UTI at seven days (no events) and no difference in post-ESWL bacteriuria.

3.14.2.3.2 Ureteroscopy

A single systematic review [355] and two meta-analyses [356, 357] with latest search date of December 2013 were identified. Bootsma *et al.*, and Dahm *et al.*, included two low quality RCTs with a total of 233 participants and showed low-grade evidence that antibiotic prophylaxis reduced risk of bacteriuria but not of clinical UTI [355, 356]. Lo *et al.*, included four RCTs with a total of 386 patients and found no evidence of benefit in reducing rate of clinical UTI [357]. The rate of bacteruria was reduced using antibiotic prophylaxis. Panel

discussion considered that despite low quality evidence suggesting no benefit in reducing risk of clinical UTI, clinicians and patients would prefer to use prophylaxis to prevent kidney infection or sepsis. Ideally this should be examined in a robustly designed clinical study.

3.14.2.3.3 Percutaneous neprolithotomy (PNL)

A single systematic review and meta-analysis with latest search date of October 2012 was identified which addressed whether or not antibiotic prophylaxis reduce the rate of clinical urinary infection following PNL [352]. The update search to February 2017 identified no further trials. Mrkobrada *et al.*, included five RCTs with 448 participants and pooled patients undergoing PNL or ureteroscopy. They showed a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI.

Two RCTs with overall low risk of bias comparing different antibiotic regimes in PNL were identified [358, 359]. Seyrek *et al.*, compared the rate of SIRS following PNL in 191 patients receiving either a combination of sulbactam/ampicillin or cefuroxime. There was no difference in SIRS or urosepsis rates [358]. Tuzel *et al.*, investigated single dose ceftriaxone versus ceftriaxone and subsequently an oral third-generation cephalosporin until after nephrostomy catheter withdrawal at mean (SD) of 3 (1) days in 73 participants undergoing PNL. They found no difference in rate of infectious complications between the two antibiotic regimens [359]. These two studies give moderate evidence that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.

3.14.2.4 Transurethral resection of the prostate

A systematic review of 39 RCTs with search date up to 2009 was identified [356]. The update search to February 2017 did not reveal any further relevant studies. Of the 39 RCTs reviewed by Dahm *et al.*, six trials involving 1,666 men addressed the risk of septic episodes, 17 trials reported procedure related fever and 39 investigated bacteriuria. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction (95% CI) for septic episode of 0.51 (0.27-0.96) with ARR of 2% (3.4%-1.4%) and a NNT of 50. The risk reduction (95% CI) for fever was 0.64 (0.55-0.75) and 0.37 (0.32-0.41) for bacteriuria.

3.14.2.5 Transurethral resection of the bladder

A literature search to February 2017 found one systematic review [355] which included two trials with a total of 152 participants. No more recent RCTs were identified. The two trials found no difference in rate of bacteriuria and either had no clinical UTI events, or did not report any. The review did not attempt sub-group analysis according to presence of risk factors for post-operative infection such as tumour size. Panel discussion concluded that a weak recommendation to use antibiotic prophylaxis for patients undergoing TURB who had a high risk of suffering post-operative sepsis would be appropriate.

3.14.2.6 Transrectal prostate biopsy

3.14.2.6.1 Non-antimicrobial interventions

A meta-analysis of four studies including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% CIs) 0.96 (0.64 to 1.54)] [360-362].

Meta-analysis of eight trials including 1,717 men showed that use of a rectal povidone-iodine preparation before biopsy in addition to antimicrobial prophylaxis resulted in a lower rate of infectious complications [RR (95% CIs) 0.55 (0.41 to 0.72)] [363-368]. Single RCTs showed no evidence of benefit for perineal skin disinfection [369], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [370].

No evidence was found that extended biopsy templates or use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than standard templates or no injection, respectively [371].

A total of seven studies including 1,330 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (37 events among 657 men) compared to transperineal biopsy (22 events among 673 men), [RR (95% CIs) 1.81 (1.09 to 3.00)] [372-378].

3.14.2.6.2 Antimicrobial prophylaxis

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using antimicrobial prophylaxis as compared to placebo/control [RR (95% CIs) 0.56 (0.40 to 0.77)] [360, 366, 368, 379-385]; therefore, antimicrobial prophylaxis is strongly recommended.

Fluoroquinolones have been traditionally used for antibiotic prophylaxis; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European

Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones for antibiotic prophylaxis in urological treatment and diagnostic interventions due to their disabling and potentially long-lasting side effects [121].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, is recommended [386]. In countries where fluoroquinolones are prohibited cephalosporins, aminoglycosides or fosfomycin can be used as individual agents. In the available RCTs, fosfomycin was superior to fluoroquinolones, but routine general use should be critically assessed due to the relevant infectious complications reported in non-randomised studies [387]. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date.

*3.14.3 **Summary of evidence and recommendations for peri-procedural antibiotic prophylaxis***

Summary of evidence	**LE**
The outcome of clinical UTI was reported in four out of eleven RCTs with no benefit found for antibiotic prophylaxis vs. placebo in patients following filling and voiding cystometry.	1b
A meta-analysis of five trials of moderate quality showed a benefit for using antibiotic prophylaxis for the reduction of symptomatic UTI in patients undergoing cystoscopy. However, this benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis.	1a
Two meta-analyses found no benefit for antibiotic prophylaxis following ESWL in terms of reducing the rate of post-procedural fever and bacteriuria or trial-defined infection in patients without bacteriuria.	1a
Two meta-analyses found no evidence of benefit for antibiotic prophylaxis prior to ureteroscopy in reducing the rate of clinical UTI; however, the rate of bacteriuria was reduced.	1a
A meta-analysis of five RCTs demonstrated a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI following PNL.	1a
Two RCTs concluded that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.	1b
A systematic review of 39 RCTs concluded that antibiotic prophylaxis reduced the rate of infectious complications in men undergoing TURP.	1b
A systematic review of two RCTs found no benefit for antibiotic prophylaxis in patients undergoing TURB.	1b
Meta-analysis of six trials showed that use of a rectal povidone-iodine preparation before biopsy in addition to antimicrobial prophylaxis resulted in a lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a
A meta-analysis of seven studies including 1,330 patients showed significantly reduced infectious in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a

Recommendations	**Strength rating**
Do not use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following: • urodynamics; • cystoscopy; • extracorporeal shockwave lithotripsy.	Strong
Use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following ureteroscopy.	Weak
Use single dose antibiotic prophylaxis to reduce the rate of clinical urinary infection following percutaneous nephrolithotomy.	Strong
Use antibiotic prophylaxis to reduce infectious complications in men undergoing transurethral resection of the prostate.	Strong
Use antibiotic prophylaxis to reduce infectious complications in high-risk patients undergoing transurethral resection of the bladder.	Weak
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Use antimicrobial prophylaxis in men prior to transrectal prostate biopsy.	Strong

Table 12: Suggested regimens for antimicrobial prophylaxis prior to urological procedures.
As stated in section 3.14.1.4 the panel have decided not to make recommendations for specific agents for particular procedures, those listed below represent possible choices only. Urologists should choose a specific antimicrobial based on their knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence.

Procedure	Prophylaxis recommended	Antimicrobial
Urodynamics	No	N/A
Cystoscopy	No	
Extracorporeal shockwave lithotripsy	No	
Ureteroscopy	Yes	Trimethoprim Trimethoprim-sulphamethoxazole Cephalosporin group 2 or 3 Aminopenicillin plus a beta-lactamase inhibitor
Percutaneous nephrolithotomy	Yes (single dose)	
Transurethral resection of the prostate	Yes	
Transurethral resection of the bladder	Yes, in patients who have a high risk of suffering post-operative sepsis.	
Transrectal prostate biopsy	Yes	Fluoroquinolones if permitted Cephalosporins, fosfomycin, aminoglycosides, if fluoroquinolones are not permitted

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5. CONFLICT OF INTEREST

All members of the EAU Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam the Netherlands 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Urolithiasis

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European
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of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel has prepared these guidelines to help urologists assess evidence-based management of stones/calculi in the urinary tract and incorporate recommendations into clinical practice. This document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision. Management of bladder stones are dealt with in a separate guideline authored by the same guideline group.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU, website Uroweb: http://uroweb.org/guideline/urolithiasis/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text versions. Also a number of scientific publications are available [1-3]. All documents can be accessed through the EAU website: http://uroweb.org/guideline/urolithiasis/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Urolithiasis Guidelines were first published in 2000. This 2020 document presents a limited update of the 2019 version.

*1.4.2 **Summary of changes***

The literature for the entire document has been checked and, wherever relevant, updated (see Methods section 2.1).

For 2020, conclusions and recommendations have been rephrased and strength ratings reassessed across a number of sections. Updated recommendations include the following:

3.3.2.3 Guidelines for laboratory examinations and stone analysis

Recommendations	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Weak

3.4.10.5 Summary of evidence and guidelines for the management of renal stones

Recommendations	Strength rating
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced computed tomography (CT). Stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	Strong

2. METHODS

2.1 Data identification

For the 2020 Urolithiasis Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the guideline was performed. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis (MA), randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between 1st May 2018 and 2nd May 2019. Databases covered by the search included Medline, EMBASE, Ovid and the Cochrane Libraries. A total of 887 unique records were identified, and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/urolithiasis/?type=appendices-publications.

A total of 30 new papers have been added, and 28 outdated references removed from the Urolithiasis 2020 Guidelines publication.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [4, 5]. Each strength-rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2015 Urolithiasis Guidelines were subjected to peer-review prior to publication.

2.3 Future goals

For the 2021 text update the Urolithiasis Guidelines Panel aim to perform extended literature searches and systematic reviews on how best to conduct follow-up in stones patients, where current evidence is poor.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence

*3.1.1 **Introduction***

Stone incidence depends on geographical, climatic, ethnic, dietary and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 20% [8]. In countries with a high standard of life such as Sweden, Canada or the USA, renal stone prevalence is notably high (> 10%). For some areas an increase of more than 37% over the last 20 years has been reported [9-11]. There is emerging evidence linking nephrolithiasis to the risk of chronic kidney disease [12].

Stones can be stratified into those caused by: infection, or non-infectious causes, genetic defects [13]; or adverse drug effects (drug stones) (Table 3.1). See also section 3.2.

Table 3.1: Stones classified by aetiology*

Non-infection stones
Calcium oxalate
Calcium phosphate
Uric acid
Infection stones
Magnesium ammonium phosphate
Carbonate apatite
Ammonium urate
Genetic causes
Cystine
Xanthine
2,8-Dihydroxyadenine
Drug stones

**See Section 4.4.2*

*3.1.2 **Stone composition***

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 3.2 lists the most clinically relevant substances and their mineral components.

Table 3.2: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonate apatite	$Ca_5(PO_4)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate dihydrate	Brushite	$CaHPO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate		$Ca_8H_2(PO_4)_6.5H_2O$
Uric acid	Uricite	$C_5H_4N_4O_3$
Uric acid dihydrate	Uricite	$C_5H_4O_3.2H_20$
Ammonium urate		$NH_4C_5H_3N_4O_3$
Sodium acid urate monohydrate		$NaC_5H_3N_4O_3.H_2O$
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	$MgHPO_4.3H_2O$
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4(PO_4).H_2O$
Cystine		$[SCH_2CH(NH_2)COOH]_2$
Xanthine		
2,8-Dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		
Melamine		
Matrix		
Drug stones	• Active compounds crystallising in urine • Substances impairing urine composition (Section 4.11)	
Foreign body calculi		

*3.1.3 **Risk groups for stone formation***

The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence [10, 14]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high risk of recurrence (Table 3.3) [15, 16].

Table 3.3: High-risk stone formers [15-31]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones ($CaHPO_4.2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e. jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
Increased levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation (see Table 4.11)
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental factors
High ambient temperatures
Chronic lead and cadmium exposure

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [10, 32-34].

*3.2.1 **Stone size***

Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

*3.2.2 **Stone location***

Stones can be classified according to anatomical position: upper, middle or lower calyx; renal pelvis; upper, middle or distal ureter; and urinary bladder. Treatment of bladder stones is not discussed in these guidelines.

*3.2.3 **X-ray characteristics***

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.4), which varies according to mineral composition [34]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 3.3) [32, 34].

Table 3.4: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dehydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

3.3 Diagnostic evaluation

*3.3.1 **Diagnostic imaging***

The most appropriate imaging modality will be determined by the clinical situation, which will differ depending on if a ureteral or a renal stone is suspected.

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic [35]. Immediate evaluation is indicated in patients with solitary kidney, fever or when there is doubt regarding a diagnosis of renal colic. Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures, should not be delayed by imaging assessments. Ultrasound is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calyces, pelvis, and pyeloureteric and vesico-ureteral junctions (US with filled bladder), as well as in patients with upper urinary tract (UUT) dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteral stones and a sensitivity of 45% and specificity of 88% for renal stones [36, 37].

The sensitivity and specificity of KUB is 44-77% [38]. Kidney-ureter-bladder radiography should not be performed if NCCT is being considered [39]; however, it is helpful in differentiating between radiolucent and radiopaque stones and should be used for comparison during follow-up.

3.3.1.1 Evaluation of patients with acute flank pain/suspected ureteral stones

Non-contrast-enhanced computed tomography has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU). Non-contrast-enhanced CT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT is significantly more accurate than IVU [40].

Non-contrast-enhanced CT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [41]. Non-contrast-enhanced CT can determine stone density, inner structure of the stone, skin-to-stone distance and surrounding anatomy; all of which affect selection of treatment modality [34, 42-44]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [45-48].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [49-51]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteral stones < 3 mm and 100% for calculi > 3 mm [52]. A MA of prospective studies [51] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 93.1% (95% CI: 91.5-94.4), and a specificity of 96.6% (95% CI: 95.1-97.7%). Dual-energy CT can differentiate uric acid containing stones from calcium-containing stones [53].

3.3.1.2 Radiological evaluation of patients with renal stones

Intravenous urography (IVU) can provide information about renal function, the anatomy of the collecting system and the level of an obstruction, while CT allows for rapid 3D data acquisition including information on stone size and density, skin-to-stone distance and surrounding anatomy, but at the cost of increased radiation exposure. Low-dose and ultra-low-dose protocols seem to yield comparable results to standard-dose protocols with the exception of detection of very small stones or stones in obese patients [51, 52, 54, 55].

A small randomised study showed that in supine percutaneous antegrade ureteroscopy (PNL), pre-operative planning using CT, compared to IVU, resulted in easier access and shorter operating times [56].

In case stone removal is planned and the renal collecting system needs to be assessed, a contrast study should be performed [57].

3.3.1.3 Summary of evidence and guidelines for diagnostic imaging

Summary of evidence	LE
Non-contrast-enhanced CT is used to confirm stone diagnosis in patients with acute flank pain, as it is superior to IVU.	1a
Enhanced CT enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance.	2a

Recommendations	Strength rating
Immediate imaging is indicated with fever or solitary kidney, and when diagnosis is doubtful.	Strong
Use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain following initial ultrasound assessment.	Strong
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	Strong

3.3.2 ***Diagnostics - metabolism-related***

Besides imaging, each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood besides imaging. At this point, no distinction is made between high- and low-risk patients for stone formation.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients. However, if no intervention is planned, examination of sodium, potassium, C-reactive protein (CRP), and blood coagulation time can be omitted.

Only patients at high risk for stone recurrence should undergo a more specific analytical programme [16]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest method for diagnosing stones is by analysis of a passed stone using a validated method as listed in section 3.3.2.3. Once the mineral composition is known, a potential metabolic disorder can be identified.

3.3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.

In clinical practice, repeat stone analysis is needed in the case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period [58, 59].

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of normal renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [60-62]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [60, 63].

3.3.2.3 Guidelines for laboratory examinations and stone analysis [16, 22, 57, 64]

Recommendations: basic laboratory analysis - emergency urolithiasis patients	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Weak
Perform a coagulation test (partial thromboplastin time and international normalised ratio) if intervention is likely or planned.	Strong
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong
Repeat stone analysis in patients presenting with: • recurrent stones despite drug therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone-free period because stone composition may change.	Strong

*3.3.3 **Diagnosis in special groups and conditions***

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women radiation exposure may cause non-stohastic (teratogenesis) or stohastic (carcinogenesis, mutagenesis) effects. Teratogenic effects are cumulative with increasing dose, and require a threshold dose (< 50 mGy are considered as safe) and depend on the gestation age (minimum risk prior to 8th week and after the 23rd week). Carcinogenesis (dose even < 10 mGy present a risk) and mutagenesis (500-1000 mGy doses are required, far in excess of the doses in common radiographic studies) get worse with increasing dose but they do not require a dose threshold and are not dependent on the gestational age [65].

There is no imaging modality that should be routinely repeated in pregnant women. Scientific societies and organisations agree on the safety of the diagnostic evaluation when US [66], X-ray imaging [67, 68], and MRI [69, 70] are used as and when indicated [71-77]. A radiographic procedure should not be withheld from a pregnant woman if the procedure is clearly indicated and doing so will affect her medical care.

It is generally recommended that an investigation resulting in an absorbed dose to the foetus of greater than 0.5 mGy requires justification.

Ultrasound (when necessary, using changes in renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic. However, normal physiological changes in pregnancy can mimic ureteral obstruction [73-75].

Magnetic resonance imaging can be used, as a second-line procedure [71], to define the level of urinary tract obstruction, and to visualise stones as a filling defect [69]. As 3 Tesla (T) MRI has not been evaluated in pregnancy, the use of 1.5T is currently recommended [72, 77]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects to the embryo [73].

For the detection of urolithiasis during pregnancy, low-dose CT is associated with a higher positive predictive value (95.8%), compared to MRI (80%) and US (77%). As per White *et al.* low-dose CT offers improved diagnostic accuracy that can avoid negative interventions such as ureteroscopy [78]. Although low-dose CT protocols reduce the radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [73].

3.3.3.1.1 Summary of evidence and guidelines for diagnostic imaging during pregnancy

Summary of evidence	LE
Only low-level data exist for imaging in pregnant women supporting US and MRI.	3

Recommendations	Strength rating
Use ultrasound as the preferred method of imaging in pregnant women.	Strong
In pregnant women, use magnetic resonance imaging as a second-line imaging modality.	Strong
In pregnant women, use low-dose computed tomography as a last-line option.	Strong

3.3.3.2 Diagnostic imaging in children

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply, including a valid stone analysis (Section 3.1.3 and Chapter 4). The most common non-metabolic disorders facilitating stone formation are vesico-ureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [79].

When selecting diagnostic procedures to identify urolithiasis in children, it should be remembered that these patients might be uncooperative, require anaesthesia, and may be sensitive to ionising radiation. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed [80-82].

Ultrasound

Ultrasound is the primary imaging technique [83] in children. Its advantages are absence of radiation and no need for anaesthesia. Imaging should include both the fluid-filled bladder with adjoining portion of the ureters, as well as the upper ureter [84-88]. Colour Doppler US shows differences in the ureteral jet [85] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [86]. Nevertheless, US fails to identify stones in > 40% of children [87-90] and provides limited information on renal function.

Plain films (KUB radiography)

Kidney-ureter-bladder radiography can help to identify stones and their radiopacity, and facilitate follow-up.

Intravenous urography

The radiation dose for IVU is comparable to that for voiding cysto-urethrography (0.33 mSV) [91]. However, the need for contrast medium injection is a major drawback.

Helical computed tomography

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [48, 55, 92]. In children, only 5% of stones escape detection by NCCT [85, 92, 93]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

Magnetic resonance urography

Magnetic resonance urography (MRU) cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [94].

3.3.3.2.1 Summary of evidence and guidelines for diagnostic imaging in children

Summary of evidence	LE
Ultrasound is the first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder and the ureter next to the kidney and the (filled) bladder.	2b
A kidney-ureter-bladder radiography (or low-dose NCCT) is an alternative investigation if US will not provide the required information.	2b

Recommendations	Strength rating
Complete a metabolic evaluation based on stone analysis in all children.	Strong
Collect stone material for analysis to classify the stone type.	Strong
Perform ultrasound as first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder and the ureter.	Strong
Perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if ultrasound will not provide the required information.	Strong

3.4 Disease Management

3.4.1 Renal colic

Pain relief

Non-steroidal anti-inflammatory drugs (NSAIDs) (including metamizoledipyrone), and paracetamol are effective in patients with acute stone colic [95-97], and have better analgesic efficacy than opioids [98]. The addition of antispasmodics to NSAIDs does not result in better pain control. Patients receiving NSAIDs are less likely to require further analgesia in the short term. It should be taken into consideration that the use of diclofenac and ibuprofen increased major coronary events [99, 100]. Diclofenac is contraindicated in patients with congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease and peripheral arterial- and cerebrovascular disease. Patients with significant risk factors for cardiovascular events should be treated with diclofenac only after careful consideration. As risks increase with dose and duration, the lowest effective dose should be used for the shortest duration [99, 100].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed [97, 101] (see below). If an opioid is used, it is recommended that it is not pethidine. Data on other types of non-opioid and non-NSAID medication is increasing. Ketamine in combination with morphine, compared to morphine alone, leads to morphine consumption reduction, less pain, nausea and vomiting [102, 103]. Patients receiving ketamine and NSAIDs attained greater reduction in pain scores with less side effects, and better functional state, as well as less further analgesia requirement than those administered pethidine [104]. However, when comparing ketamine vs. NSAID (ketolorac) alone, equal efficacy but higher rates of dizziness, agitation and hypertension with ketamine were observed [105]. Conflicting results have been reported regarding the utility of intravenous lidocaine. Acupuncture seems to be effective in renal colic alone or in combination, but there is limited data [106, 107].

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.9. For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain [108, 109]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [110].

The systematic review and MA by Hollingsworth *et al.* [111] addressed pain reduction as a secondary outcome and concluded that medical expulsive therapy (MET) seems efficacious in reducing pain episodes of patients with ureteral stones.

If analgesia cannot be achieved medically, drainage, using stenting, percutaneous nephrostomy or stone removal, is indicated [112].

3.4.1.1 Summary of evidence and guidelines for the management of renal colic

Summary of evidence	LE
Non-steroidal anti-inflammatory drugs are very effective in treating renal colic and are superior to opioids.	1b
For symptomatic ureteral stones, stone removal as first-line treatment is a feasible option in selected patients.	1b

Recommendations	Strength rating
Offer a non-steroidal anti-inflammatory as the first drug of choice; e.g. metamizol*** (dipyrone); alternatively paracetamol or, depending on cardiovascular risk factors, diclofenac*, indomethacin or ibuprofen**.	Strong
Offer opiates (hydromorphine, pentazocine or tramadol) as a second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesic refractory colic pain.	Strong

* *Affects glomerular filtration rate (GFR) in patients with reduced renal function.*

** *Recommended to counteract recurrent pain after ureteral colic.*

*** *Maximum single oral dose recommended 1000 mg, total daily dose up to 5000 mg, not recommended in the last three months of pregnancy [113].*

*3.4.2 **Management of sepsis and/or anuria in obstructed kidney***

The obstructed kidney with all signs of urinary tract infection (UTI) and/or anuria is a urological emergency. Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to stone-induced, unilateral or bilateral, renal obstruction.

Decompression

Currently, there are two options for urgent decompression of obstructed collecting systems:

- placement of an indwelling ureteral stent;
- percutaneous placement of a nephrostomy tube.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good quality evidence to suggest that ureteral stenting has more complications than percutaneous nephrostomy [114, 115].

Only one RCT [116] compared different modalities of decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteral stent insertion are less well described [114]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy. A small RCT showed the feasibility of immediate ureteroscopic stone removal combined with an appropriate antibiotic regimen; however, at the cost of longer hospital stay and higher analgesic requirements [117].

Further measures

Following urgent decompression of the obstructed and infected urinary collecting system, both urine- and blood samples should be sent for culture-antibiogram sensitivity testing and antibiotics should be initiated immediately thereafter or continued, if initiated prior to testing. The regimen should be re-evaluated in the light of the culture-antibiogram results. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated. Intensive care might become necessary [118].

3.4.2.1 Summary of evidence and guidelines for the management of sepsis and anuria

Summary of evidence	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	Strength rating
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	Strong
Delay definitive treatment of the stone until sepsis is resolved.	Strong
Collect (again) urine for antibiogram test following decompression.	Strong
Start antibiotics immediately (+ intensive care, if necessary).	Strong
Re-evaluate antibiotic regimen following antibiogram findings.	Strong

*3.4.3 **Medical expulsive therapy***

Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). Several drug classes are used for MET [119-122]. When using α-blockers for MET, possible side effects include retrograde ejaculation and hypotension [109].

Patients treated with α-blockers, calcium-channel inhibitors (nifedipine) and phosphodiesterase type 5 inhibitors (PDEI-5) (tadalafil) are more likely to pass stones with fewer colic episodes than those not receiving such therapy [109, 123, 124]. Based on studies with a limited number of patients [122, 124-126], no recommendation for the use of PDEI-5 or corticosteroids in combination with α-blockers in MET can be made.

Tamsulosin showed an overall superiority to nifedipine for distal ureteral calculi [127]. A class effect of α-blockers has been demonstrated in MAs [126, 128, 129]. However, there is contradictory evidence between these studies and several well-designed, multicentre, placebo-controlled, double-blinded randomised studies showing limited, or no, benefit using α-blockers, besides some advantage for distal ureteral stones > 5 mm [130-132]. A published MA, including 55 trials with a data search cut-off of July 1st 2015, including the publications addressed above, assessed stone passage as primary outcome [111]. Based on the well-designed sensitivity analyses of this MA, α-blockers promote spontaneous stone expulsion of large stones located in any part of the ureter. There are small trials of uncertain quality suggesting tadalafil alone or in combination with tamsulosin may be beneficial for ureteric stone passage [124]. A large double-blind, placebo-controlled study of 3,296 patients with distal ureteral stones, across 30 centres, evaluated the efficacy and safety of tamsulosin. Participants were randomly assigned (1:1) to tamsulosin (0.4 mg) or placebo groups for 4 weeks. Tamsulosin benefits from a higher stone expulsion rate than the placebo (86% vs. 79%; $p < 0.001$) for distal ureteral stones. Subgroup analysis identified a significant benefit of tamsulosin for the treatment of large distal ureteral stones (> 5 mm) but no benefit for smaller stones (≤ 5 mm). Considering the secondary end points, tamsulosin-treated patients reported a shorter time to expulsion ($p < 0.001$), required lower use of analgesics compared with placebo ($p < 0.001$), and significantly relieved renal colic ($p < 0.001$). No differences in the incidence of adverse events were identified between the two groups [133].

The primary outcome of most trials assessing MET was stone passage, or follow up, up to four weeks. No data are currently available to support other time-intervals.

The Panel concludes that MET seems efficacious in the treatment of patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm distal stones [134].

Medical expulsive therapy in special situations is addressed in the relevant chapters.

3.4.3.1 Summary of evidence and guideline for MET

Summary of evidence	**LE**
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) ureteral stones.	1a
Insufficient data exist to support the use of PDEI-5 or corticosteroids in combination with α-blockers as an accelerating adjunct.	2a
α-blockers increase stone expulsion rates in distal ureteral stones > 5 mm.	1a
A class effect of α-blockers has been demonstrated.	1a

Recommendation	**Strength rating**
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong

*3.4.4 **Chemolysis***

Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays, for practical reasons. Percutaneous irrigation chemolysis may be an option for infection-stones and theoretically also for uric acid stones. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used. The method has been described in case series and literature reviews [135-137].

Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate stones, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics can provide information on the type of stone.

Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate. The pH should be adjusted to 7.0-7.2. Chemolysis is more effective at a higher pH, which might, however, promote calcium phosphate stone formation. Patients will need to adjust the dosage of alkalising medication by self-monitoring the pH of their urine. No RCTs are available for this therapy, which has been in use for decades. Rodman, *et al.* [138] reviewed the principles and provided guidance to its clinical use, which was supported by Becker, *et al.* in 2007 [139]. Monitoring of radiolucent stones during therapy is the domain of US; however, repeat-NCCT might be necessary [138, 139].

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [140]. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones as shown in one RCT for stones > 5 mm [140].

3.4.4.1 Summary of evidence and guidelines for chemolysis

Summary of evidence	**LE**
Irrigation chemolysis has been in limited clinical use to dissolve struvite stones.	3
Uric acid stones > 5mm can be dissolved based on oral alkalinisation of the urine above 7.0.	3
For obstructing uric acid stones, a combination of oral chemolysis with tamsulosin is more effective than each substance alone, particularly in stones > 8 mm.	1b

Recommendations (oral chemolysis of uric acid stones)	**Strength rating**
Inform the patient how to monitor urine-pH by dipstick and to modify the dosage of alkalising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during/after oral chemolysis of uric acid stones.	Strong
Combine oral chemolysis with tamsulosin in case of (larger) ureteral stones (if active intervention is not indicated).	Weak

*3.4.5 **Extracorporeal shock wave lithotripsy (SWL)***

The success of SWL depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Section 3.4.9.3);
- patient's habitus (Section 3.4.10.3);
- performance of SWL (best practice, see below).

Each of these factors significantly influences the retreatment rate and final outcome of SWL.

Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve stone free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce formation of steinstrasse [141-144].

Pacemaker

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken. Patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters [145].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [146-154]. Tissue damage increases with shock wave frequency [155-157].

Number of shock waves, energy setting and repeat treatment sessions

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves [158]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [155], which prevents renal injury [159-161]. Animal studies [162] and a prospective randomised study [163]

have shown better SFRs (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used [164].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within 1 day for ureteral stones).

Improvement of acoustic coupling

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defects (air pockets) in the coupling gel deflect 99% of shock waves [165]. Ultrasound gel is probably the most widely-used agent available as a lithotripsy coupling agent [166].

Procedural control

Results of treatment are operator dependent, and experienced clinicians obtain better results. During the procedure, careful imaging control of localisation contributes to outcome quality [167].

Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [168-171].

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [64, 172, 173].

Medical therapy after extracorporeal shock wave lithotripsy

In spite of conflicting results, most RCTs and several MAs support MET after SWL for ureteral or renal stones as adjunct to expedite expulsion and to increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [174-182].

Post treatment management

Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [183-185].

Complications of extracorporeal shock wave lithotripsy

Compared to PNL and ureteroscopy (URS), there are fewer overall complications with SWL [186, 187] (Table 3.5).

Table 3.5: Shock wave lithotripsy-related complications [188-202]

Complications			**%**	**Reference**
Related to stone fragments	Steinstrasse		4 – 7	[200-202]
	Regrowth of residual fragments		21 – 59	[189, 190]
	Renal colic		2 – 4	[191]
Infectious	Bacteriuria in non-infection stones		7.7 – 23	[189, 192]
	Sepsis		1 – 2.7	[189, 192]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[193]
		Haematoma, asymptomatic	4 – 19	[193]
	Cardiovascular	Dysrhythmia	11 – 59	[189, 194]
		Morbid cardiac events	Case reports	[189, 194]
	Gastrointestinal	Bowel perforation	Case reports	[195-197]
		Liver, spleen haematoma	Case reports	[188, 197-199]

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory; however, no evidence exists supporting the hypothesis that SWL may cause long-term adverse effects [203-209].

3.4.5.1 Summary of evidence and guidelines for SWL

Summary of evidence	LE
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0 to 1.5 Hz.	1a
Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important.	2
Careful imaging control of localisation of stone contributes to outcome of treatment.	2a
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions.	1a
Antibiotic prophylaxis is recommended in the case of internal stent placement, infected stones or bacteriuria.	1a

Recommendations	Strength rating
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	Strong
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy (SWL).	Strong
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	Strong
Prescribe antibiotics prior to SWL in the case of infected stones or bacteriuria.	Strong

*3.4.6 **Ureteroscopy (URS) (retrograde and antegrade, RIRS)***

The current standard for rigid ureteroscopes is a tip diameter of < 8 French (F). Rigid URS can be used for the whole ureter [203]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [210].

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large (> 15 mm), impacted proximal ureteral calculi in a dilated renal collecting system [211-213], or when the ureter is not amenable to retrograde manipulation [213-217].

Ureteroscopy for renal stones (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both renal and ureteral stones. Major technological progress has been achieved for RIRS. A recent systematic review addressing renal stones > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were > Clavien 3 [210, 218, 219]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [218].

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones within the lower renal pole that need disintegration; it may help to displace them into a more accessible calyx [220].

Best clinical practice in ureteroscopy

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Intravenous sedation is suitable for female patients with distal ureteral stones [221]. Antegrade URS is an option for large, impacted, proximal ureteral calculi [211-213, 222].

Safety aspects

Fluoroscopic equipment must be available in the operating room. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [223-225]. Balloon and plastic dilators should be available, if necessary.

Prior rigid URS can be helpful for optical dilatation followed by flexible URS, if necessary. If ureteral access is not possible, insertion of a JJ stent followed by URS after seven to fourteen days offers an alternative [226]. Bilateral URS during the same session is feasible resulting in equivalent-to-lower SFRs, but slightly higher overall complication rates (mostly minor, Clavien I and II) [227, 228].

Ureteral access sheaths

Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted (via a guide wire) with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy, multiple, access to the UUT and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreases intra-renal pressure, and potentially reduces operating time [229, 230].

The insertion of ureteral access sheaths may lead to ureteral damage, the risk is lowest in pre-stented systems [231]. No data on long-term side effects are available [231, 232]. Whilst larger cohort series showed no difference in SFRs and ureteral damage, they did show lower post-operative infectious complications [233]. Use of ureteral access sheaths depends on the surgeon's preference.

Stone extraction

The aim of URS is complete stone removal. "Dust and go" strategies should be limited to the treatment of large (renal) stones [234]. Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [235].

Intracorporeal lithotripsy

The most effective lithotripsy system is the holmium:yttrium-aluminium-garnet (Ho:YAG) laser, which is currently the optimum standard for URS and flexible nephroscopy (Section 3.4.6), because it is effective in all stone types [236, 237]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [238, 239]. However, stone migration into the kidney is a common problem, which can be prevented by placement of special anti-migration tools proximal of the stone [240]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [241].

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces intra-operative complications [242, 243].

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher post-operative morbidity and costs [244-247]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [248].

Stents should be inserted in patients who are at increased risk of complications (e.g., ureteral trauma, residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [249, 250].

Medical expulsive therapy after ureteroscopy

Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [241].

Complications of ureteroscopy

The overall complication rate after URS is 9-25% [203, 251, 252]. Most complications are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.6.1 Summary of evidence and guidelines for retrograde URS, RIRS and antegrade ureteroscopy

Summary of evidence	**LE**
In uncomplicated URS, a stent need not be inserted.	1a
In URS (in particular for renal stones), pre-stenting has been shown to improve outcomes.	1b
An α-blocker can reduce stent-related symptoms and colic episodes.	1a
Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic.	1b
The most effective lithotripsy system for flexible ureteroscopy is the Ho:YAG laser.	2a
Pneumatic and US systems can be used with high disintegration efficacy in rigid URS.	2a
Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes.	1b
Percutaneous antegrade removal of proximal ureter stones, or laparoscopic ureterolithotomy are feasible alternatives to retrograde ureteroscopy, in selected cases.	1a

Recommendations	Strength rating
Use holmium: yttrium-aluminium-garnet (Ho:YAG) laser lithotripsy for (flexible) ureteroscopy (URS).	Strong
Perform stone extraction only under direct endoscopic visualisation of the stone.	Strong
Do not insert a stent in uncomplicated cases.	Strong
Pre-stenting facilitates URS and improves outcomes of URS (in particular for renal stones).	Strong
Offer medical expulsive therapy for patients suffering from stent-related symptoms and after Ho:YAG laser lithotripsy to facilitate the passage of fragments.	Strong
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy (SWL) is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	Strong
Use flexible URS in cases where percutaneous nephrolithotomy or SWL are not an option (even for stones > 2 cm). However, in this case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong

*3.4.7 **Percutaneous nephrolithotomy***

Percutaneous nephrolithotomy remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available and the selection is mainly based on the surgeon's own preference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 F, were initially introduced for paediatric use, but are now increasingly utilised in the adult population [253].

Contraindications

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [254].

Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy during PNL are available. Ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy, whilst laser is increasingly used for miniaturised instruments [255]. Flexible endoscopes also require laser lithotripsy to maintain tip deflection, with the Ho:YAG laser having become the standard.

Pre-operative imaging

Pre-procedural imaging evaluations are summarised in Section 3.3.1. In particular, US or CT of the kidney and the surrounding structures can provide information regarding interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).

Positioning of the patient

Both prone and supine positions are equally safe, although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple accesses [256, 257]. On the other hand, supine position allows simultaneous retrograde access to the collecting system, using flexible ureteroscope [258, 259].

Puncture

Although fluoroscopy is the most common intra-operative imaging method, the (additional) use of US reduces radiation exposure [260, 261].

Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of visceral injury. The calyceal puncture may be done under direct visualisation using simultaneous flexible URS [259, 261, 262].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. Although there are papers demonstrating that single step dilation is equally effective as other methods, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [263].

Choice of instruments

The Urolithiasis Panel performed a systematic review assessing the outcomes of PNL using smaller tract sizes (< 22 F, mini-PNL) for removing renal calculi [253]. Stone-free rates were comparable in miniaturised and standard PNL procedures. Procedures performed with small instruments tend to be associated with significantly lower blood loss, but the duration of procedure tends to be significantly longer. There were no significant differences in any other complications. However, the quality of the evidence was poor with only two RCTs and the majority of the remaining studies were single-arm case series only. Furthermore, the tract sizes used, and types of stones treated, were heterogeneous; therefore, the risk of bias and confounding were high.

Nephrostomy and stents

The decision on whether, or not, to place a nephrostomy tube at the conclusion of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intra-operative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Small-bore nephrostomies seem to have advantages in terms of post-operative pain [253, 264, 265]. Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL [266]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [267].

Complications of percutaneous nephrolithotomy

A systematic review of almost 12,000 patients shows the incidence of complications associated with PNL; fever 10.8%, transfusion 7%, thoracic complication 1.5%, sepsis 0.5%, organ injury 0.4%, embolisation 0.4%, urinoma 0.2%, and death 0.05% [268].

Peri-operative fever can occur, even with a sterile pre-operative urinary culture and peri-operative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. Intra-operative renal stone culture may therefore help to select post-operative antibiotics [269]. Intra-operative irrigation pressure < 30 mmHg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis [270]. Bleeding after PNL may be treated by briefly clamping of the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

3.4.7.1 Summary of evidence and guidelines for endourology techniques for renal stone removal

Summary of evidence	**LE**
Imaging of the kidney with US or CT can provide information regarding inter-positioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).	1a
Both prone and supine positions are equally safe, but neither has a proven advantage in operating time or SFR.	1a
Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of procedure tended to be significantly longer. There are no significant differences in SFR or any other complications.	1a
In uncomplicated cases, a totally tubeless PNL results in a shorter hospital stay, with no increase in complication rate.	1a

Recommendations	Strength rating
Perform pre-procedural imaging, including contrast medium where possible or retrograde study when starting the procedure, to assess stone comprehensiveness and anatomy of the collecting system to ensure safe access to the renal stone.	Strong
Perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy procedure, in uncomplicated cases.	Strong

*3.4.8 **General recommendations and precautions for stone removal***

3.4.8.1 Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days before starting stone removal. A urine culture or urinary microscopy should be performed before treatment [271].

Peri-operative antibiotic prophylaxis

For prevention of infection following URS and percutaneous stone removal, no clear-cut evidence exists [272]. In a review of a large database of patients undergoing PNL, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [273]. Single dose administration was found to be sufficient [274].

Recommendations	Strength rating
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	Strong
Exclude or treat urinary tract infections prior to stone removal.	Strong
Offer peri-operative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong

3.4.8.2 Antithrombotic therapy and stone treatment

Patients with a bleeding diathesis, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [275-279]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anti-coagulant/anti-platelet medication [280-282]);
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [275].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [283-287]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [288-290]. Despite appropriate cessation of anti-platelet agents, following standardised protocols, prolonged haematuria in tube drainage after PNL has been reported [291]. Only data on flexible URS are available which support the superiority of URS in the treatment of proximal ureteral stones [292, 293].

Table 3.6: Risk stratification for bleeding [277-279, 294]

Low-risk bleeding procedures	Cystoscopy Flexible cystoscopy Ureteral catheterisation Extraction of ureteral stent Ureteroscopy
High-risk bleeding procedures	Shock wave lithotripsy Percutaneous nephrostomy Percutaneous nephrolithotomy

Table 3.7: Suggested strategy for antithrombotic therapy in stone removal [277-279]
(In collaboration with a cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. delaying elective surgical procedures).

	Bleeding risk of planned procedure	**Risk of thromboembolism**		
		Low risk	**Intermediate risk**	**High risk**
Warfarin Dabigatran Rivaroxaban Apixaban	Low-risk procedure	May be continued	Bridging therapy	Bridging therapy
	High-risk procedure	May be temporarily discontinued at appropriate interval. Bridging therapy is strongly recommended.	Bridging therapy	Bridging therapy
Aspirin	Low-risk procedure	Continue	Continue	Elective surgery: postpone. Non deferrable surgery: continue.
	High-risk procedure	Discontinue	Elective surgery: postpone. Non-deferrable surgery: continue, if is possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue five days before intervention. Resume within 24-72 hours with a loading dose.	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue five days before intervention and resume within 24-72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors if aspirin is discontinued.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours, with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors.

3.4.8.2.1 Summary of evidence and guidelines for antithrombotic therapy and stone treatment

Summary of evidence	**LE**
Active surveillance is indicated in patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4
The temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be discussed with the internist.	3
Retrograde (flexible) URS stone removal is associated with less morbidity in patients when antithrombotic therapy cannot be discontinued.	2a

Recommendations	Strength rating
Offer active surveillance to patients at high risk of thrombotic complications in the presence of an asymptomatic calyceal stone.	Weak
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	Strong
Retrograde (flexible) URS is the preferred intervention if stone removal is essential and antithrombotic therapy cannot be discontinued, since it is associated with less morbidity.	Strong

3.4.8.3 Obesity

A high BMI can pose a higher anaesthetic risk and a lower success rate after SWL [295] and PNL, and may influence the choice of treatment.

3.4.8.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard, as well as homogeneous stones with a high density on NCCT [42, 296]. Percutaneous nephrolithotomy or RIRS and URS are alternatives for removal of large SWL-resistant stones.

3.4.8.4.1 Guidelines for stone composition

Recommendations	Strength rating
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit on unenhanced computed tomography.	Strong
Attempt to dissolve radiolucent stones.	Strong

3.4.8.5 Contraindications of procedures

Contraindications of extracorporeal SWL

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [297];
- bleeding diatheses, which should be compensated for at least 24 hours before and 48 hours after treatment [298];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [299];
- anatomical obstruction distal to the stone.

Contraindications of URS

Apart from general problems, for example with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

Contraindications of PNL

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [290]. Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

3.4.9 ***Specific stone management of ureteral stones***

3.4.9.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [300]. It is estimated that 95% of stones up to 4 mm pass within 40 days [203].

Based on an analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided; < 10 mm may be considered a best estimate [203]. Therefore, the Panel decided not to include stone size but rather recommend “small”, suggesting < 6 mm. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

Sexual intercourse has been reported to be beneficial in facilitating stone expulsion in men with ureteral stones, in one meta-analysis consisting of three RCTs [301].

3.4.9.2 Pharmacological treatment, medical expulsive therapy

Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). In case of known uric acid stones in the distal ureter, a combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage. For details see Sections 3.4.3 and 3.4.4.

3.4.9.3 Indications for active removal of ureteral stones

Indications for active removal of ureteral stones are [203, 300, 302]:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate analgesic medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, or single kidney).

3.4.9.4 Selection of procedure for active removal of ureteral stones

Overall, SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS. Although URS is effective for ureteral calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of URS has been significantly reduced [303]. It has been demonstrated that URS is a safe option in obese patients (BMI > 30 kg/m2) with comparable SFRs and complication rates. However, in morbidly obese patients (BMI > 35 kg/m2) the overall complication rates double [304].

The Panel performed a systematic review to assess the benefits and harms of URS compared to SWL [305]. Compared with SWL, URS was associated with a significantly greater SFR of up to four weeks, but the difference was not significant at three months in the included studies. Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with lower morbidity. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL.

Bleeding disorder

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.8.2) [290].

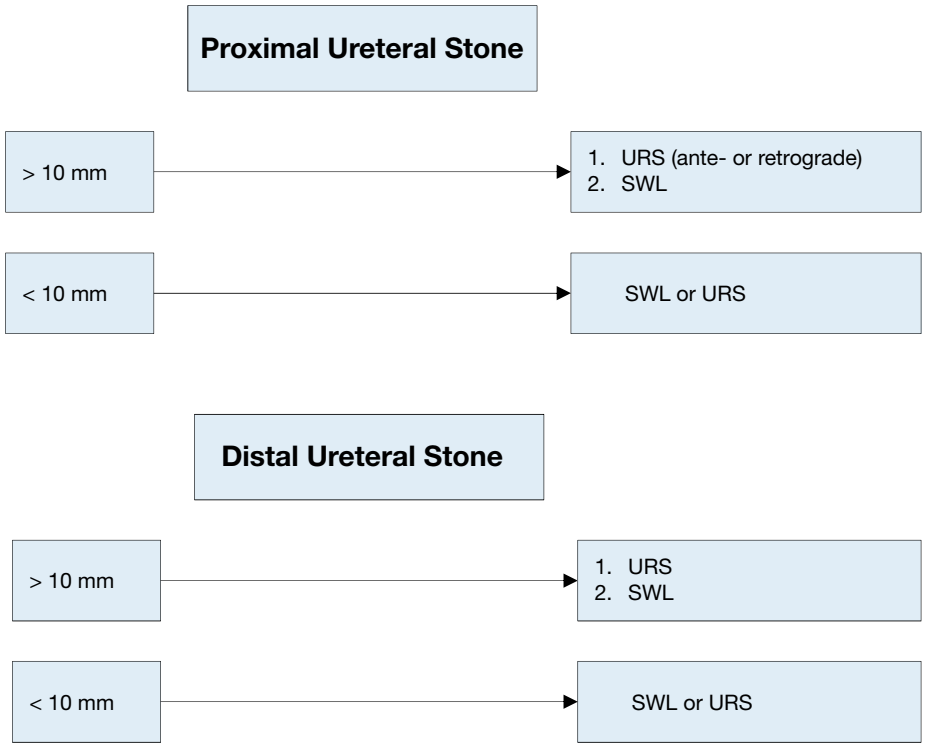
3.4.9.4.1 Summary of evidence and guidelines for selection of procedure for active removal of ureteral stones

Summary of evidence	**LE**
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	1a
Medical expulsive therapy seems to be efficacious treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) stones.	1a
Compared with SWL, URS was associated with significantly greater SFRs up to four weeks, but the difference was not significant at three months in the included studies.	1a
Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay.	1a
In the case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

Recommendations	**Strength rating**
In patients with newly diagnosed small* ureteral stones, if active removal is not indicated (Section 3.4.9.3), observe patient initially with periodic evaluation.	Strong
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong
Inform patients that ureteroscopy (URS) has a better chance of achieving stone-free status with a single procedure.	Strong
Inform patients that URS has higher complication rates when compared to shock wave lithotripsy.	Strong
In cases of severe obesity use URS as first-line therapy for ureteral (and renal) stones.	Strong

**See stratification data [203].*

Figure 3.1: Treatment algorithm for ureteral stones (if active stone removal is indicated)



SWL = shock wave lithotripsy; URS = Ureteroscopy.

*3.4.10 **Specific stone management of renal stones***

The natural history of small, non-obstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, timing and type of intervention. Treatment options are chemolysis or active stone removal.

3.4.10.1 Conservative treatment (observation)

Observation of renal stones, especially in calyces, depends on their natural history (Section 3.4.10.3). The recommendations provided are not supported by high-level literature. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones, < 10 mm. In case stone growth is detected, the follow-up interval should be lowered. Intervention is advised for growing stones > 5 mm [306].

3.4.10.2 Pharmacological treatment of renal stones

Dissolution of stones through pharmacological treatment is an option for uric acid stones only, but information on the composition of the stone will need to guide the type of treatment selected. See sections 3.4.4. and 3.4.8.4.

3.4.10.3 Indications for active stone removal of renal stones

Indications for the removal of renal stones, include:

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain or haematuria) [307];
- stones > 15 mm;
- stones < 15 mm if observation is not the option of choice;
- patient preference;
- comorbidity;
- social situation of the patient (e.g., profession or travelling);
- choice of treatment.

The risk of a symptomatic episode, or need for intervention in patients with asymptomatic renal stones seems to be ~10-25% per year, with a cumulative five-year event probability of 48.5% [306, 308, 309]. A

prospective RCT with more than 2 years clinical follow-up reported no significant difference between SWL and observation when comparing asymptomatic calyceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life (QoL), renal function, or hospital admission [310]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [309, 311, 312]. In a follow-up period of almost five years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [190, 313]. Although the question of whether calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment [307, 314, 315].

3.4.10.4 Selection of procedure for active removal of renal stones

For general recommendations and precautions see Section 3.4.8.

3.4.10.4.1 Stones in renal pelvis or upper/middle calyces

Shock wave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [316-319]. Shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [318, 320, 321]. Endourology is considered an alternative because of the reduced need for repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and is associated with an increased risk of ureteral obstruction (colic or steinstrasse) with a need for adjunctive procedures (Figure 3.2) [186]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [322-324]. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.10.4.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intra-renal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-95%. The preferential use of endoscopic procedures is supported by some current reports, even for stones < 1 cm [186, 316, 317, 319, 320, 324-332].

The following can impair successful stone treatment by SWL [327, 333-337]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum;
- Shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance (See 3.4.5 Extracorporeal shock wave lithotripsy (SWL)) [184, 338].

If there are negative predictors for SWL, PNL and RIRS might be reasonable alternatives, even for smaller calculi [325]. Retrograde renal surgery seems to have comparable efficacy to SWL [186, 317, 320, 339]. Recent clinical experience has suggested a higher SFR of RIRS compared to SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated by RIRS [219, 340-342]. However, staged procedures are frequently required.

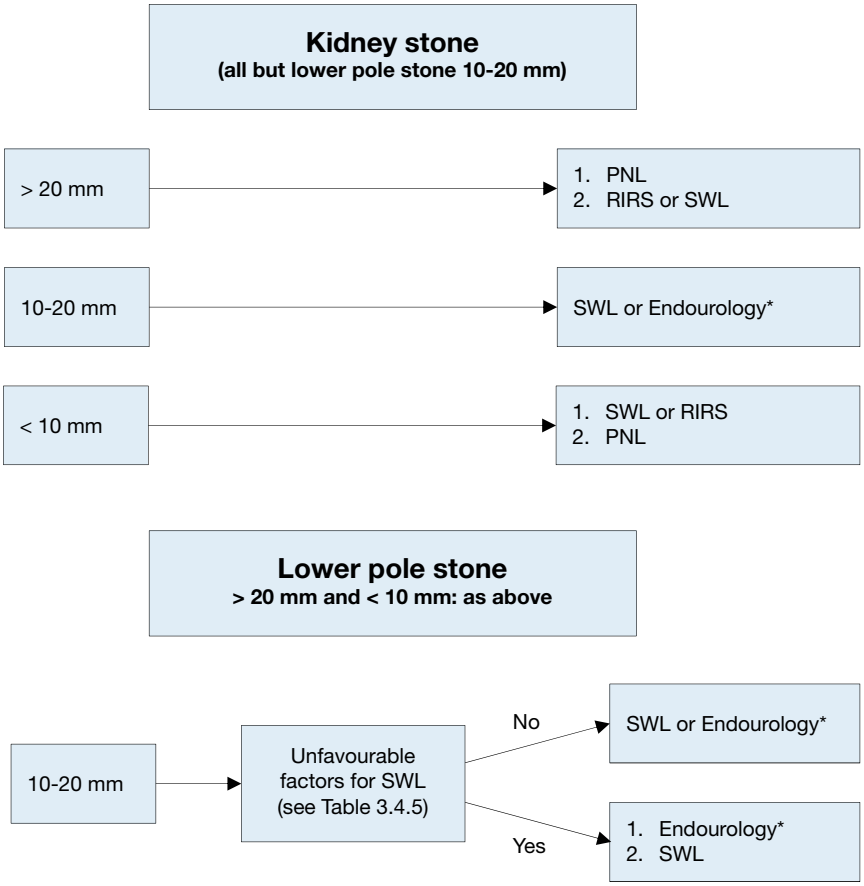
In complex stone cases, open or laparoscopic approaches are possible alternatives.

3.4.10.5 Summary of evidence and guidelines for the management of renal stones

Summary of evidence	**LE**
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.	4
Although the question of whether asymptomatic calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	3
Percutaneous nephrolithotomy is indicated in renal stones > 2 cm as primary option.	1a

Recommendations	Strength rating
Follow-up periodically in cases where renal stones are not treated (initially after six months then yearly, evaluating symptoms and stone status [either by ultrasound, kidney-ureter bladder radiography or computed tomography]).	Strong
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	Weak
Evaluate stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced computed tomography (CT). Stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	Strong
Perform PNL as first-line treatment of larger stones > 2 cm.	Strong
Treat larger stones (> 2 cm) with flexible ureteroscopy or SWL, in cases where PNL is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong
Perform PNL or RIRS for the lower pole, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong

Figure 3.2: Treatment algorithm for renal stones (if/when active treatment is indicated)



**The term 'Endourology' encompasses all PNL and URS interventions.*
PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureteroscopy.

*3.4.11 **Laparoscopy and open surgery***

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [343-348]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL and RIRS may also be an appropriate alternative. However, if percutaneous approaches are not likely to be successful, or if multiple endourological approaches have been performed unsuccessfully; open or laparoscopic surgery may be a valid treatment option [349-355].

Few studies have reported laparoscopic stone removal. These procedures are usually reserved for special cases. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal

ureteral stones as an alternative to URS or SWL [356, 357]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [211, 212, 222, 358]. A recent systematic review showed no difference in the post-operative phase for stented or unstented laparoscopic ureterolithotomy [358]. A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [359]. Open surgery should be considered as the last treatment option, after all other possibilities have been explored.

3.4.11.1 Summary of evidence and guideline for laparoscopy and open surgery

Recommendation	Strength rating
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	Strong

*3.4.12 **Steinstrasse***

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter and may interfere with the passage of urine [360]. Steinstrasse occurs in 4-7% cases of SWL [200], and the major factor in the development of steinstrasse formation is stone size [361].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A MA including eight RCTs (n = 876) suggests a benefit of stenting before SWL in terms of steinstrasse formation, but does not result in a benefit on SFRs or less auxiliary treatments [142].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [362, 363]. Ureteroscopy and SWL are effective in treatment of steinstrasse [202, 364]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [115, 117].

3.4.12.1 Summary of evidence and guidelines for steinstrasse

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse.	1b
Ureteroscopy is effective for the treatment of steinstrasse.	3
Only low-level evidence is available, supporting SWL or URS for the treatment of steinstrasse.	4

Recommendations	Strength rating
Treat steinstrasse associated with urinary tract infection (UTI)/fever preferably with percutaneous nephrostomy.	Weak
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureteroscopy (in absence of signs of UTI).	Weak

*3.4.13 **Management of patients with residual stones***

Following initial treatment with SWL, URS or PNL residual fragments may remain and require additional intervention [313, 365, 366]. Most of the studies indicate that initial imaging is performed on the first day or the first week after treatment. However, false positive results from dust or residual fragments, that will pass spontaneously without causing any stone-related event, might lead to over-treatment. As a consequence, imaging at four weeks seems most appropriate [367-369]. Compared to US, KUB and IVU, NCCT scan has a higher sensitivity to detect small residual fragments after definitive treatment of ureteral or kidney stones [370, 371]. However, more than half of the patients with a residual fragment on NCCT images may not experience a stone-related event [372].

It is clear that NCCT has the highest sensitivity to detect residual fragments; however, this must be balanced against the increased detection of clinically insignificant fragments and the exposure to ionising radiation when compared with KUB and US. In the absence of high level supporting evidence, the timing of follow-up imaging studies and need for secondary intervention is left to the discretion of the treating physician. Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [373]. For all stone compositions, 21-59% of patients with residual stones required treatment within five years. Fragments > 5 mm are more likely than smaller ones to require intervention [190, 374, 375]. There is evidence that

fragments > 2 mm are more likely to grow, although this is not associated with increased re-intervention rates at one year follow up [365].

3.4.13.1 Summary of evidence and guideline for management of patients with residual stones

Summary of evidence	LE
To detect residual fragments after SWL, URS or PNL, deferred imaging is more appropriate than immediate imaging post intervention.	3

Recommendation	Strength rating
Perform imaging after shock wave lithotripsy, ureteroscopy or percutaneous antegrade ureteroscopy to determine presence of residual fragments.	Strong

3.4.14 ***Management of specific patient groups***

3.4.14.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician and urologist. For diagnostic imaging see Section 3.3.1.

If spontaneous passage does not occur, or if complications develop (e.g., intractable symptoms, severe hydronephrosis or induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary as it is more effective than conservative treatment for symptom relief [376, 377].

Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation [378].

Ureteroscopy has become a reasonable alternative in these situations [369, 379]. When compared to temporary ureteral JJ stenting until after delivery, ureteroscopy resulted in fewer needs for stent exchanges, less irritative LUTS and better patient satisfaction [380].

Non-urgent ureteroscopy in pregnant women is best performed during the second trimester, by an experienced urologist. Counselling of the patient should include access to neonatal and obstetric services [73].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres. Pregnancy remains an absolute contraindication for SWL.

3.4.14.1.1 Summary of evidence and guideline for the management of urinary stones and related problems during pregnancy

Summary of evidence	LE
Stent insertion seems to be more effective than conservative treatment in the management of symptomatic moderate-to-severe hydronephrosis during pregnancy.	1b
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1a
There is a higher tendency for stent encrustation during pregnancy.	3

Recommendation	Strength rating
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except when there are clinical indications for intervention).	Strong

3.4.14.2 Management of stones in patients with urinary diversion

Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [381, 382]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [383] (section 3.1.3). One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PNL was 63% at five years [384].

Management

Smaller upper-tract stones can be treated effectively with SWL [217, 385]. In the majority of cases, endourological techniques are necessary to achieve stone-free status [214]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible.

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [386].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of overlying bowel, which could make this approach unsafe [387], and if present, an open surgical approach should be considered.

Prevention

Recurrence risk is high in these patients [384]. Metabolic evaluation and close follow-up are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyperdiuresis or regular irrigation of continent reservoirs [388].

3.4.14.2.1 Summary of evidence and guideline for the management of stones in patients with urinary diversion

Summary of evidence	**LE**
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade ureteroscopy is the alternative.	4

Recommendation	**Strength rating**
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	Strong

3.4.14.3 Management of stones in patients with neurogenic bladder

Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, hydronephrosis, VUR, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [389]. The most common causes are urinary stasis and infection (Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [390, 391].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesico-urethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.

Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3.3. In myelomeningocele patients, latex allergy is common; therefore, appropriate measures need to be taken regardless of the treatment [392]. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table [393]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [388].

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control, and restoration of normal storing/voiding function of the bladder are needed.

3.4.14.3.1 Summary of evidence and guideline for the management of stones in patients with neurogenic bladder

Summary of evidence	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3

Recommendation	Strength rating
Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common.	Strong

3.4.14.4 Management of stones in patients with transplanted kidneys

Stones in transplanted kidneys can either be transplanted or present *de novo* allograft stones. Usually they are detected by routine US examination, followed by NCCT in cases of unclear diagnosis [394].

Aetiology

Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Risk factors for *de novo* stone formation in these patients are multi-fold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyper-filtration, excessively alkaline urine, renal tubular acidosis (RTA), and increased serum calcium caused by persistent tertiary hyperparathyroidism [395] are biochemical risk factors.

Stones in kidney allografts have an incidence of 1% [396].

Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are similar to those applied in other single renal units [397-399]. Additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made URS a valid treatment option for transplant calculi; however, one must be aware of potential injury to adjacent organs [399-401]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [402-404]. Treatment of donor stones may be needed pre-transplant and increases the pool available for renal transplants. Post-transplant stone disease may also need treatment to maintain the allograft function. A systematic review evaluating the outcomes of pre- vs. post-transplant URS demonstrated a 100% SFR with an overall 7.5% complication rate, compared to SFR of 60-100% with an overall complication rate of 12.9% for post-transplant URS; most complications were Clavien 1 [405].

3.4.14.4.1 Summary of evidence and guideline for the management of stones in patients with transplanted kidneys

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	3
Shock wave lithotripsy for small calyceal stones is an option with minimal risk of complication, but localisation of the stone can be challenging and SFRs are poor.	4

Recommendation	Strength rating
Offer patients with transplanted kidneys, any of the contemporary management options, including shock wave lithotripsy, flexible ureteroscopy and percutaneous nephrolithotomy.	Weak

3.4.14.5 Special problems in stone removal

Table 3.8: Special problems in stone removal

Calyceal diverticulum stones	• SWL, PNL [406] (if possible) or RIRS [406, 407]. • Can also be removed using laparoscopic retroperitoneal surgery [408, 409]. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above [410]. • Passage of fragments after SWL might be poor. • Acceptable SFRs can be achieved with flexible ureteroscopy.
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery. • In obese patients, the options are RIRS, PNL or open surgery.
Stones formed in a continent reservoir	• Each stone must be considered and treated individually.
Patients with obstruction of the UPJ	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG laser. • Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvic-ureteral incision [411-414]. • Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option [415].

*3.4.15 **Management of stones in children***

The true incidence of nephrolithiasis in children remains unclear due to the global lack of large epidemiological studies. Data derived from nation-wide epidemiological studies, studies performed in different counties worldwide [416, 417], and large-scale databases [418, 419] indicate that the incidence and prevalence of paediatric urinary stone disease has increased over the last few decades. Although boys are most commonly affected in the first decade of life [420] the greatest increase in incidence has been seen in older female adolescences [416, 417, 421].

Stone composition is similar in children as in adults, with a predominance of calcium oxalate stones. Compared to historical data, metabolic abnormalities responsible for stone formation are less commonly identified in children nowadays [422-424]. Hypocitraturia, low urine volume and hypercalciuria predominate [82, 422-424]. Age may affect the predominant metabolic abnormality with hypercalciuria and hypocitraturia being the most common disorder present in children < 10 and > 10 years old, respectively [424]. Genetic or systemic diseases (e.g. cystinuria or nephrocalcinosis) contributing to stone formation are rare in children accounting for less than 17% of the identifying causes [422, 425]. The role of diet remains unclear in children, although there is some evidence that children are drinking less water and taking greater daily amounts of sodium than is recommended [426-428].

For diagnostic procedures see Section 3.3.3.2, for acute decompression see Section 3.4.2. and for metabolic evaluation see Chapter 4.

3.4.15.1 Clinical presentation

Children with urinary stones can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis. Symptoms are age-dependent with infants presenting with crying, irritability and vomiting in 40% of cases [429] while in older children flank pain, micro or gross haematuria and recurrent UTIs are more common [430].

3.4.15.2 Conservative management

There is a lack of evidence on conservative management of paediatric stones with evidence for ureteric calculi coming from the placebo arms of medical expulsive trials, while evidence for renal stones comes from small cohort studies, either on primary stones [431, 432] or residual fragments remained after SWL, RIRS or PNL [433]. Expectant management for single, asymptomatic lower-pole renal stones could be the initial approach with increased odds of stone passage, especially in patients with non-struvite, non-cystine stones < 7 mm,

with no anatomic abnormalities [431]. Intervention may be needed for stones located elsewhere independently of their size [431-433].

3.4.15.3 Medical expulsive therapy in children

There are limited studies on MET as off-label expulsive therapy for children with stones which show conflicting outcomes. A recent MA of five trials showed that adrenergic α-antagonists (tamsulosin 0.2-0.4 mg/day and doxazosin 0.03 mg/kg/day) are effective for MET increasing SFR compared to control (OR = 2.7, p = 0.001) without significantly increasing the treatment-emergent adverse events (OR = 2.01, p = 0.17) [434]. Similarly, an updated systematic review of six placebo-controlled studies showed that α-blockers might increase SFR of distal ureteric stones (RR: 1.34, 95% CI: 1.16 - 1.54) [435]. Due to study limitations and very serious imprecision, no conclusion could be drawn regarding the effect of MET on hospital stay, pain episodes or secondary procedures for residual fragments after definitive stone treatment [435].

3.4.15.4 Extracorporeal shock wave lithotripsy

Shock wave lithotripsy is still the first-line treatment for most ureteral stones in children. However, it is less likely to be successful for stones > 10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [436].

Studies on extracorporeal SWL in children suggest an overall SFR of 70-90%, retreatment rate of 4-50% and need for auxiliary procedures in 4-12.5% of cases [437-441]. A MA of 14 studies reporting on 1,842 paediatric patients treated with SWL found significantly higher SFR for stones < 10 mm than for stones > 10 mm and higher retreatment rates as the stone size increased [436]. For best clinical practice see Section 3.4.5. A recent MA on slow SWL vs. rapid SWL for renal stones revealed very low-quality evidence about the effects of SWL on SFRs, serious adverse events or complications of treatment and secondary procedures for residual fragments [435]. Shock wave lithotripsy is well tolerated; however, good treatment outcomes are more likely to require the administration of general anaesthesia to children. With improvements in modern (second and third generation) lithotripters, successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children [442].

Based on the results of a recent MA which compared SWL to dissolution therapy for intra-renal stones, and SWL to ureteroscopy with holmium laser or pneumatic lithotripsy for renal and distal ureteric stones, no firm conclusions can be drawn about the effects of SWL on SFR, serious adverse events or complications of treatment and secondary procedures for residual fragments [435].

When SWL was compared to mini-percutaneous nephrolithotomy for lower pole renal stones 1-2 cm in size SWL resulted in lower SFRs (RR: 0.88, 95% CI: 0.80 - 0.97; moderate quality evidence) and higher rates of secondary procedures (RR: 2.50, 95% CI: 1.01 - 6.20; low-quality evidence); however, SWL showed less severe adverse events (RR: 0.13, 95% CI: 0.02 - 0.98; low quality evidence) [443].

3.4.15.5 Endourological procedures

Rigid/semi-rigid ureteroscopy

In recent years ureteroscopy is increasingly used in children with ureteral stones [444]. Ureteroscopy proved to be effective with SFR of 81-98% [445-447], retreatment rates of 6.3%-10% [448] and complication rates of 1.9-23% [445-447, 449]. Similar to adults, routine stenting is not necessary before URS. However, pre-stenting may facilitate URS, increase SFR and decrease complication rates [450]. Stenting after URS is a strong indicator for retreatment requiring anaesthesia in children [451].

Flexible ureteroscopy/retrograde intrarenal surgery

Retrograde intra-renal surgery with flexible ureteroscopes (FURS) has become an efficacious treatment modality for paediatric renal stones. Recent studies report SFRs of 76-100%, retreatment rates of 0-19% and complication rates of 0-28% [452-455]. Younger age, cystine composition [456], large stone diameter [455] and lack of pre-stenting predispose to FURS failure in children [450].

Although high-level evidence is lacking to support a strong recommendation [435], FURS may be a particularly effective treatment option for lower calceal stones in the presence of unfavourable factors for SWL [447, 453, 457].

For large and complex kidney stones RIRS has a significantly lower SFR compared to PNL (71% vs. 95%), but is associated with less radiation exposure, lower complication rates and a shorter hospital stay [458]. Similarly, retrospectively data indicate that RIRS may achieve lower SFRs compared to minor micro-percutaneous surgery in favour of shorter operative time, shorter fluoroscopy time, and less hospitalisation time [459, 460]. A recently published MA confirmed the aforementioned results [461].

Percutaneous nephrolithotomy

Indications for PNL in children are similar to those in adults, and include renal stones > 2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PNL are 71.4-95% after a single session [458-460, 462, 463] with an overall complication rate of 20% [464]. High degree of hydronephrosis, increased number of tracts and operative time [465] and large tract size [463, 466-468] are associated with increased blood loss. Child age [467] and stone burden [463] predispose to the use of larger instruments during PNL in children. Miniaturisation of equipment increases the opportunity to perform tubeless PNL in appropriately selected children, which can reduce the length of hospital stay and post-operative pain [469, 470].

Concerns have been raised regarding possible adverse effects of PNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [471]. Using pre- and post-PNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al.* demonstrated that PNL tracts between 12-24 Charrière in size did not cause significant harm to paediatric kidneys [462].

3.4.15.6 Open and laparoscopic/robot-assisted stone surgery

With the advances in ESWL, PNL and RIRS, very few cases of paediatric urolithiasis require open surgery. Data extracted from the National Inpatient Sample (NIS) databases for 2001-2014 showed that in the USA incisional procedures (mainly nephrolithotomy, pyelolithotomy and ureterotomy) were performed in 2.6% of hospitalised patients (52% aged 15-17 years) who required surgical intervention for urinary stones [472]. Laparoscopy for the management of paediatric renal and ureteric stones is a safe and effective procedure when specific indications are followed. Stone free rates of 100% were reported when laparoscopic pyelolithotomy was applied for a ≥1cm single stone located in an extra-renal pelvis [473], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones ≥1.5 cm, or to ureteric stones that were refractory to SWL or URS [474]. There are extremely limited data available on efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [475].

3.4.15.7 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. Children are in the high-risk group for stone recurrence (See Chapter 4).

3.4.15.8 Summary of evidence and guidelines for the management of stones in children

Summary of evidence	**LE**
In children, the indications for SWL, URS and PNL are similar to those in adults.	1b

Recommendations	**Strength rating**
Offer children with single ureteral stones less than 10 mm shock wave lithotripsy (SWL) if localisation is possible as first line option.	Strong
Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong
Offer children with renal stones with a diameter of up to 20 mm (~300 mm^2) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2) percutaneous nephrolithotomy.	Strong
Retrograde renal surgery is a feasible alternative for renal stones smaller than 20 mm in all locations.	Weak

4. FOLLOW UP: METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

4.1.1 ***Evaluation of patient risk***

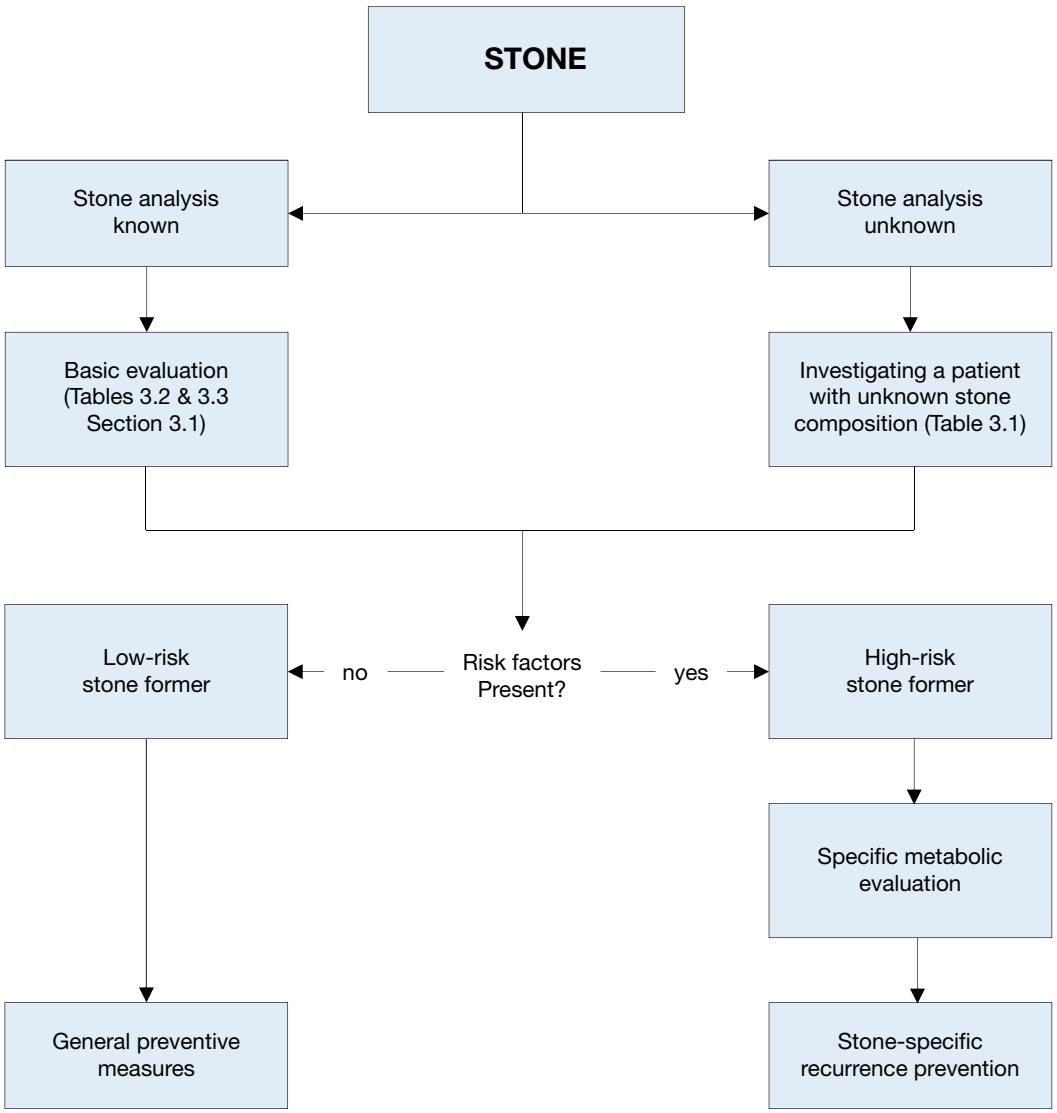
After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 4.1). For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.3.2).

Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones;
- stones of unknown composition.

Figure 4.1: Assignment of patients to low- or high-risk groups for stone formation



4.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-hour urine samples [476, 477]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at < 8°C during collection to prevent the risk of spontaneous crystallisation in the urine. Pre-analytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively, boric acid (10 g powder per urine container) can also be used. The collecting method should be chosen in close cooperation with the particular laboratory. Urine pH should be assessed during collection of freshly voided urine four times daily using sensitive pH-dipsticks or a pH-meter [22, 478].

Spot urine samples are an alternative method of sampling, particularly when 24-hour's urine collection is difficult, for example, in non-toilet trained children [479]. Spot urine studies normally link the excretion rates to creatinine [480], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

4.1.3 Timing of specific metabolic work-up

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone free for at least twenty days [481]. Follow-up studies are necessary in patients taking medication for recurrence prevention [482]. The first follow-up 24-hour urine measurement is suggested eight to twelve weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-hour urine measurements, if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-hour urine evaluation every twelve months. The Panel realise that on this issue there is only very limited published evidence, and aim to set up a systematic review on the ideal timing of the 24-hour urine collection.

4.1.4 Reference ranges of laboratory values

Tables 4.1-4.4 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 4.1: Normal laboratory values for blood parameters in adults [482, 483]

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 µmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO_2	80-90 mmHg
	pCO_2	35-45 mmHg
	HCO_3	22-26 mmol/L
	BE	BE ± 2 mmol/L

BE = base excess (loss of buffer base to neutralise acid); HCO = bicarbonate; PCO = partial pressure of carbon dioxide; PO = partial pressure of oxygen.

4.1.5 Risk indices and additional diagnostic tools

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine [484-487]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of renal tubular acidosis)
	Constantly > 7.0 (suspicious of infection)
	Constantly < 5.8 (suspicious of acidic arrest)
Specific weight	Specific weight > 1.010
Creatinine	7-13 mmol/day (females), 13-18 mmol/day (males)
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	> 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	> 1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (females), 5 mmol/day (males)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children [488]

Parameter/Patient age	Ratio of solute to creatinine	Units
Calcium	**mol/mol**	**mg/mg**
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	**mol/mol**	**mg/mg**
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	**mol/mol**	**g/g**
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium	**mol/mol**	**g/g**
	> 0.63	> 0.13
Uric acid		
> 2 years	< 0.56 mg/dL (33 imol/L) per GFR (ratio x plasma creatinine)	

Table 4.4: Solute excretion in 24-hour urine samples in children [490, 491]*****

Calcium/24 hour	Citrate/24 hour		Cystine/24 hour		Oxalate/24 hour		Urate/24 hour	
All age groups	Boys	Girls	< 10 years	> 10 years	All age groups	< 1 year	1-5 years	> 5 years
< 0.1 mmol/kg/ 24 h < 4 mg/kg/24 h	> 1.9 mmol/ 1.73 m^2/24 h > 365 mg/ 1.73 m^2/24 h	> 1.6 mmol/ 1.73 m^2/24 h > 310 mg/ 1.73 m^2/24 h	< 55 µmol/ 1.73 m^2/24 h < 13 mg/ 1.73 m^2/24 h	< 200 µmol/ 1.73 m^2/24 h < 48 mg/ 1.73 m^2/24 h	< 0.5 mmol/ 1.73 m^2/24 h < 45 mg / 1.73 m^2/24 h	< 70 µmol/ kg/24 h < 13 mg/ kg/24 h	< 65 mµmol/ kg/24 h < 11 mg/ kg/24 h	< 55 µmol/ kg/24 h < 9.3 mg/ kg/24 h

**24 h urine parameters are diet and gender dependent and may vary geographically.*

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment based on stone analysis.

Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Circadian drinking
	Neutral pH beverages
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1010 g/day
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1-1.2 g/day
	Limited NaCl content: 4-5 g/day
	Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: Retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss

*Caution: Protein requirements are age dependent; therefore, protein restriction in childhood should be handled carefully. * Avoid excessive consumption of vitamin supplements.*

*4.2.1 **Fluid intake***

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [489-492]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [493]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [494, 495]. One large moderate quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption of at least 160 mL/day to reduced soft drink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR: 0.83; CI: 0.71-0.98), the level of evidence for this outcome is low because results were from only one trial [496].

*4.2.2 **Diet***

A common sense approach to diet should be taken, that is, a mixed, balanced diet with contributions from all food groups, without any excesses [497-499].

Fruits, vegetables and fibre: Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [500-503]. The alkaline content of a vegetarian diet also increases urinary pH.

Oxalate: Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [504], particularly in patients who have high oxalate excretion.

Vitamin C: Although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial [505]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: Animal protein should not be consumed in excess [491, 506] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake: Calcium should not be restricted, unless there are strong reasons for doing so, due to the inverse relationship between dietary calcium and stone formation [501, 507]. The daily requirement for calcium is 1,000 to 1,200 mg [22]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [491, 497, 504, 508]. Older adults who do not have a history of renal stones but who take calcium supplements should ensure adequate fluid intake since it may prevent increases in urine calcium concentration, and thereby reduce or eliminate any increased risk of renal stones formation associated with calcium supplement use [509].

Sodium: Daily sodium (NaCl) intake should not exceed 3-5 g [22]. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein [491, 506]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [507]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: Intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [510, 511] and uric acid stones. Intake should not exceed 500 mg/day [22].

*4.2.3 **Lifestyle***

Lifestyle factors may influence the risk of stone formation, for example, obesity [512] and arterial hypertension [513, 514].

*4.2.4 **Summary of evidence and guideline for recurrence prevention***

Summary of evidence	**LE**
Increasing fluid intake reduces the risk of stone recurrence.	1a

Recommendation	**Strength rating**
Advise patients that a generous fluid intake is to be maintained, allowing for a 24-hour urine volume > 2.5 L.	Strong

4.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

*4.3.1 **Introduction***

Pharmacological treatment is necessary in patients at high risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 4.6 highlights the most important characteristics of commonly used medication.

Table 4.6: Pharmacological substances used for stone prevention - characteristics, specifics and dosage

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine	[515-520]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[497, 521-524]
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate	[491, 507, 508]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[525, 526]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[527, 528]
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy	Infection stones Ammonium urate Calcium phosphate	[515, 529]
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia	Calcium oxalate	[530, 531] (Low level of evidence)
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	N/A	Calcium oxalate Uric acid, Cystine	[532]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[533]
Thiazide (Hydrochlorothiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia	Calcium oxalate Calcium phosphate	[515, 530, 534-541]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria	Cystine	[542-545]

4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Chapter 3.1.2.

*4.4.1 **Diagnosis***

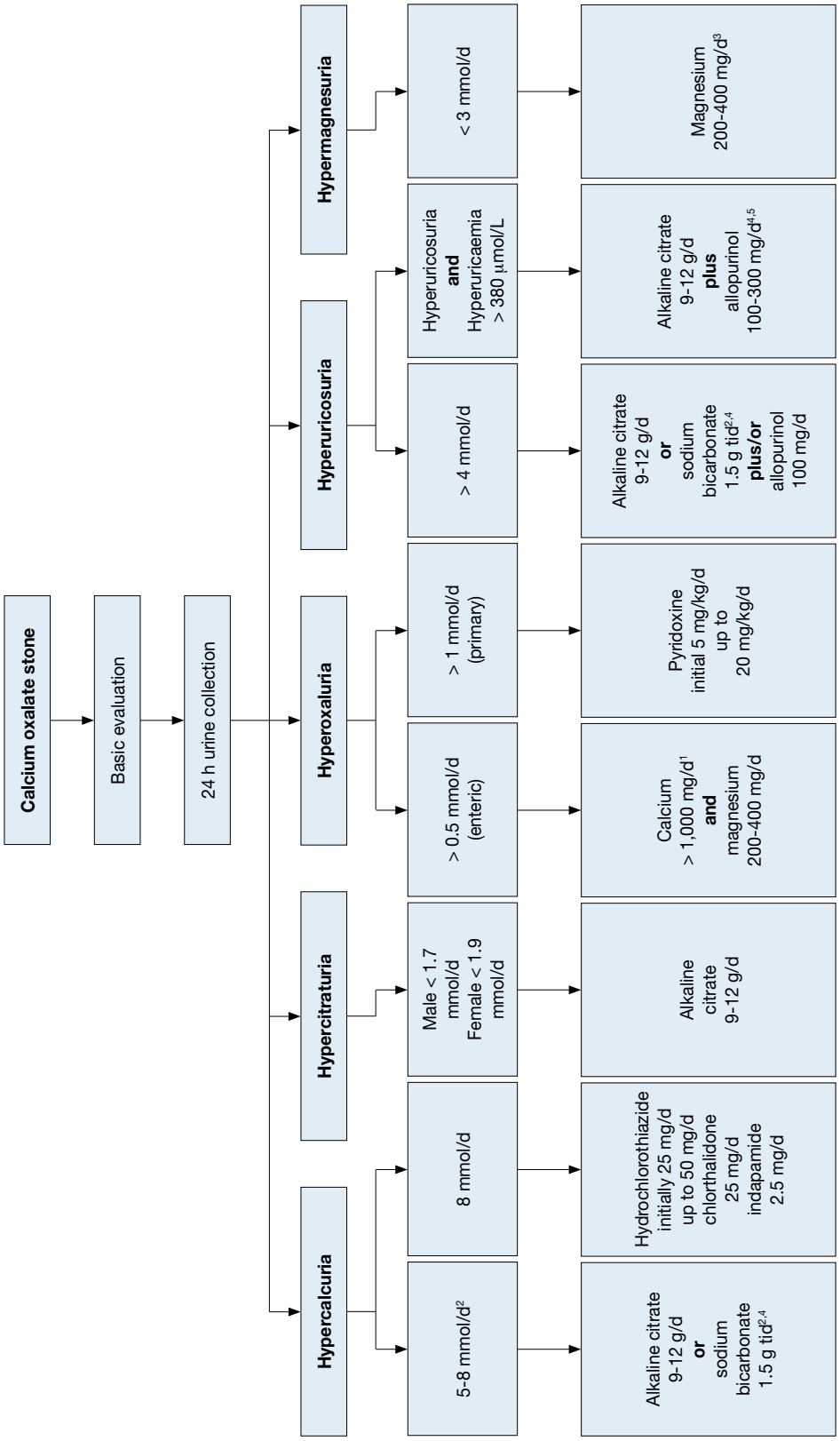
Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) (and vitamin D) in the case of increased calcium levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

*4.4.2 **Interpretation of results and aetiology***

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesiuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [546].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- "Acidic arrest" (urine pH constantly < 5.8) may promote co-crystallisation of uric acid and calcium oxalate.
- Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile indicate RTA, provided UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (male < 1.7 mmol/d, female < 1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m^2/day in children) confirms hyperoxaluria.
    - o primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
    - o secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesiuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic and therapeutic algorithm for calcium oxalate stones



[1] Be aware of excess calcium excretion.

[2] tid = three times/day (24h).

[3] No magnesium therapy for patients with renal insufficiency.

[4] There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone [516, 550].

[5] Febuxostat 80 mg/d.

4.4.3 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.2 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones [495, 497, 515-518, 521, 522, 524, 527, 530-532, 534-541, 546-549]. There is only low level evidence on the efficacy of preventing stone recurrence through pre-treatment stone composition examination and biochemistry measures, or on-treatment biochemistry measures [497].

4.4.4 ***Summary of evidence and guidelines for pharmacological treatments for patients with specific abnormalities in urine composition (based on 24-hour urine samples)***

Summary of evidence	**LE**
Thiazide + alkaline citrates can reduce stone formation.	1a
Oxalate restriction is beneficial if hyperoxaluria is present.	2b
Alkaline citrates can reduce stone formation in enteric hyperoxaluria.	4
Calcium supplement can reduce stone formation in enteric hyperoxaluria.	2
A diet reduced in fat and oxalate can be beneficial in reducing stone formation.	3
Alkaline citrates and sodium bicarbonate can be used to if hypocitraturia is present.	1b
Allopurinol is first-line treatment of hyperuricosuria.	1a
Febuxostat is second-line treatment of hyperuricosuria.	1b
Avoid excessive intake of animal protein in hyperuricosuria.	1b
Restricted intake of salt is beneficial if there is high urinary sodium excretion.	1b

Recommendations	**Strength rating**
Prescribe thiazide + alkaline citrates in case of hypercalcuria.	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplement in enteric hyperoxaluria.	Weak
Advise reduced dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates and sodium bicarbonate in case of hypocitraturia.	Strong
Prescribe allopurinol in case of hyperuricosuria.	Strong
Offer febuxostat as second-line treatment of hypericosuria.	Strong
Avoid excessive intake of animal protein in hypericosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

4.5 Calcium phosphate stones [497, 515, 524, 534, 535, 539, 551]

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in Section 3.1.2.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH > 6.8 and may be associated with infection.
Brushite crystallises at an optimum pH of 6.5-6.8 at high urinary concentrations of calcium
(> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI. Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

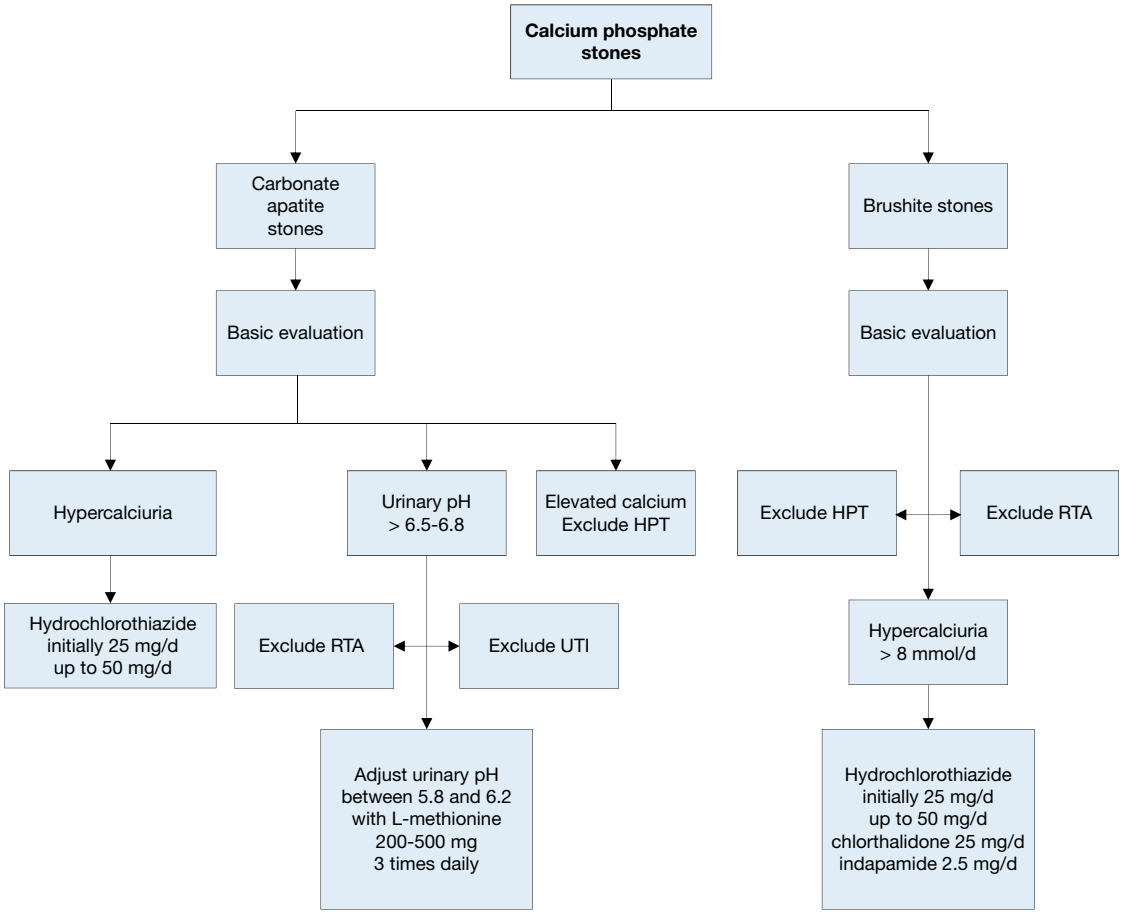
4.5.1 ***Diagnosis***

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), and PTH (in the case of increased calcium levels). Urinalysis includes measurement of: volume, urine pH profile, specific weight, calcium, phosphate and citrate.

4.5.2 ***Interpretation of results and aetiology***

General preventative measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.3.

Figure 4.3: Diagnostic and therapeutic algorithm for calcium phosphate stones



HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

4.5.3 ***Pharmacological therapy*** [497, 515, 524, 534, 535, 539, 551]

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be beneficial; however, it is not commonly used and needs monitoring for systemic acidosis development. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

4.5.4 ***Summary of evidence and guidelines for the management of calcium phosphate stones***

Summary of evidence	LE
Thiazide is beneficial in case of hypercalciuria.	1a
Acidification of urine can be beneficial in case of high urine pH.	3-4

Recommendations	Strength rating
Prescribe thiazide in case of hypercalciuria.	Strong
Advise patients to acidify their urine in case of high urine pH.	Weak

4.6 Disorders and diseases related to calcium stones

4.6.1 ***Hyperparathyroidism*** [552-554*]*

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover,

leading to hypercalcaemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits and, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of HPT patients may contain both calcium oxalate and calcium phosphate.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

*4.6.2 **Granulomatous diseases** [555]*

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria secondary to increased calcitriol production. The latter is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focuses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for a specialist.

*4.6.3 **Primary hyperoxaluria** [533]*

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, as successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m2 body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates and magnesium. However, in end-stage renal failure, PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 9-12 g/day in adults, 0.1-0.15 mq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).

4.6.3.1 Summary of evidence and guideline for the management of primary hyperoxaluria

Summary of evidence	**LE**
Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria.	3

Recommendation	**Strength rating**
Prescribe pyridoxine for primary hyperoxaluria.	Strong

*4.6.4 **Enteric hyperoxaluria** [504, 508, 556-558]*

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgery, as well as in Crohn's disease and pancreas insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, and stone formation. Specific preventive measures are:

- restricted intake of oxalate-rich foods [504];
- restricted fat intake [504];
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [508, 556-558];
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

4.6.4.1 Summary of evidence and guidelines for the management of enteric hyperoxaluria

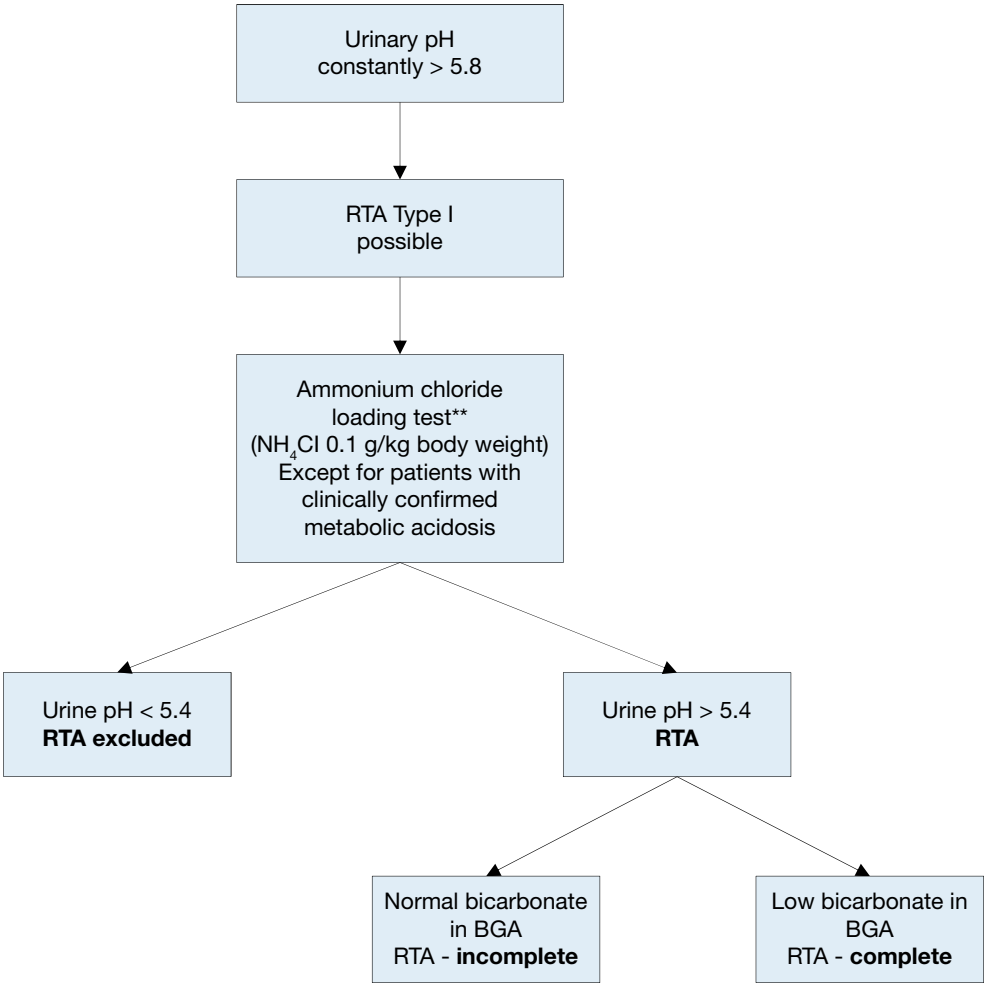
Summary of evidence	LE
Alkaline citrates can be beneficial to replace citrate loss and raise urine pH.	3
Calcium supplements with meals can enable calcium oxalate complex formation in the intestine.	2
Reduction in dietary fat and oxalate can be beneficial in intestinal malabsorption.	3

Recommendations	Strength rating
Prescribe alkaline citrates for enteric hyperoxaluria.	Weak
Advise patients to take calcium supplements with meals.	Weak
Advise patients to follow a diet with a low fat and oxalate content.	Weak

*4.6.5 **Renal tubular acidosis*** [497, 524, 559, 560]

Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4.4 outlines the diagnosis of RTA. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.4: Diagnosis of renal tubular acidosis



BGA = blood gas analysis; RTA = renal tubular acidosis.

*** An alternative ammonium chloride loading test using NH_4Cl load with 0.05 g/kg body weight over three days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide acidification test.*

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria, and primary parathyroidism; it may also be drug-induced (e.g. zonisamide).

Table 4.7: Inherited causes of renal tubular acidosis

Type - inheritance	Gene/gene product/function	Phenotype
Autosomal dominant	*SLC4A1/AE1/Cl*-bicarbonate exchanger	Hypercalciuria, hypokalaemia, osteomalacia
Autosomal recessive with hearing loss	*ATP6V1B1/B1* sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets
Autosomal recessive	*ATP6V0A4/A4* sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets

The main therapeutic aim of RTA treatment is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is important for normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 4.8: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day divided in three doses OR Sodium bicarbonate, 1.5 g, three times daily

4.6.5.1 Summary of evidence and guidelines for the management of tubular acidosis

Summary of evidence	LE
Alkaline citrates can be beneficial in distal renal tubular acidosis to correct the intracellular acidosis.	2b
Thiazide and alkaline citrates are beneficial for hypercalciuria.	1a

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Weak
Prescribe thiazide and alkaline citrates for hypercalciuria.	Strong

4.6.6 ***Nephrocalcinosis*** *[561]*

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with renal stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease, Bartter's syndrome and medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimising the biochemical risk factors.

4.6.6.1 Diagnosis

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate urine pH profile (minimum four times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

4.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [22]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [562] and associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism [563]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [563].

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), potassium deficiency, hypokalaemia and malnutrition. Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence.

*4.7.1 **Diagnosis***

Figure 4.5 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in the case of ammonium urate stones.

*4.7.2 **Interpretation of results***

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.

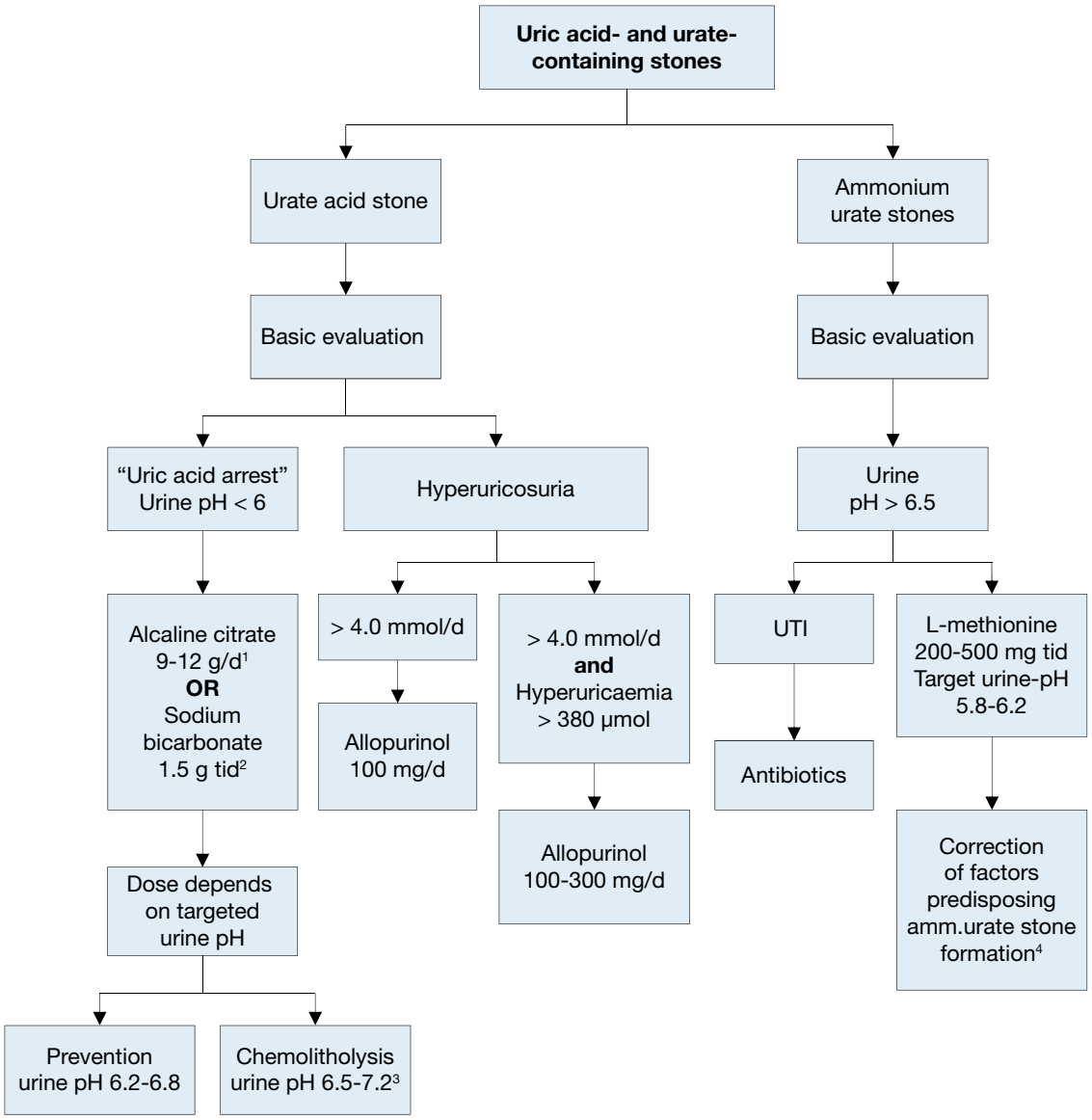
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [564].

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [565, 566]. Ammonium urate crystals form in urine at pH > 6.5, high uric acid concentration when ammonium is present serves as a cation [567-569].

*4.7.3 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.5 describes pharmacological treatment [22, 480, 562, 563, 565-574]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [575].

Figure 4.5: Diagnostic and therapeutic algorithm for uric acid- and ammonium urate stones



[1] *d: day.*
[2] *tid: three times a day.*
[3] *A higher pH may lead to calcium phosphate stone formation.*
[4] *In patients with high uric acid excretion, allopurinol may be helpful.*

4.7.4 *Summary of evidence and guidelines for the management of uric acid- and ammonium urate stones*

Summary of evidence	LE
Alkaline citrates can be beneficial to alkalinise the urine in urate stone formers.	3
Allopurinol can be beneficial in hyperuricosuric urate stone formers.	1b

Recommendations	Strength rating
Prescribe alkaline citrates to alkalinise the urine in urate stone formers.	Strong
Prescribe allopurinol in hyperuricosuric urate stone formers.	Strong

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence. Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate *de novo* or grow on pre-existing stones, which are infected with urea-splitting bacteria [576]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [577].

*4.8.1 **Diagnosis***

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

*4.8.2 **Interpretation***

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [578, 579]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [580, 581].

*4.8.3 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [577], short- or long-term antibiotic treatment [582], urinary acidification using methionine [529] or ammonium chloride [583], and advice to restrict intake of urease [584, 585]. For severe infections, acetohydroxamic acid may be an option [584, 585] (Figure 4.6); however, it is not licensed/available in all European countries.

Eradication of infection after complete stone removal is desirable. The evidence regarding the duration of post-operative antibiotic administration is inconclusive.

*4.8.4 **Summary of evidence and guidelines for the management of infection stones***

Summary of evidence	LE
Removing the stone material as completely as possible with surgery can reduce ongoing infection.	3
Antibiotics are beneficial after complete stone removal.	3
Ammonium chloride, 1 g, two or three times daily, can ensure urinary acidification to prevent recurrent infection.	3
Methionine, 200-500 mg, one to three times daily, can be used as an alternative to ammonium chloride, to ensure urinary acidification.	3
Urease inhibitors in case of severe infection are occasionally used (if licensed).	1b

Recommendations	Strength rating
Surgically remove the stone material as completely as possible.	Strong
Prescribe antibiotics in case of persistent bacteriuria.	Strong
Prescribe ammonium chloride, 1 g, two or three times daily to ensure urinary acidification.	Weak
Prescribe methionine, 200-500 mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

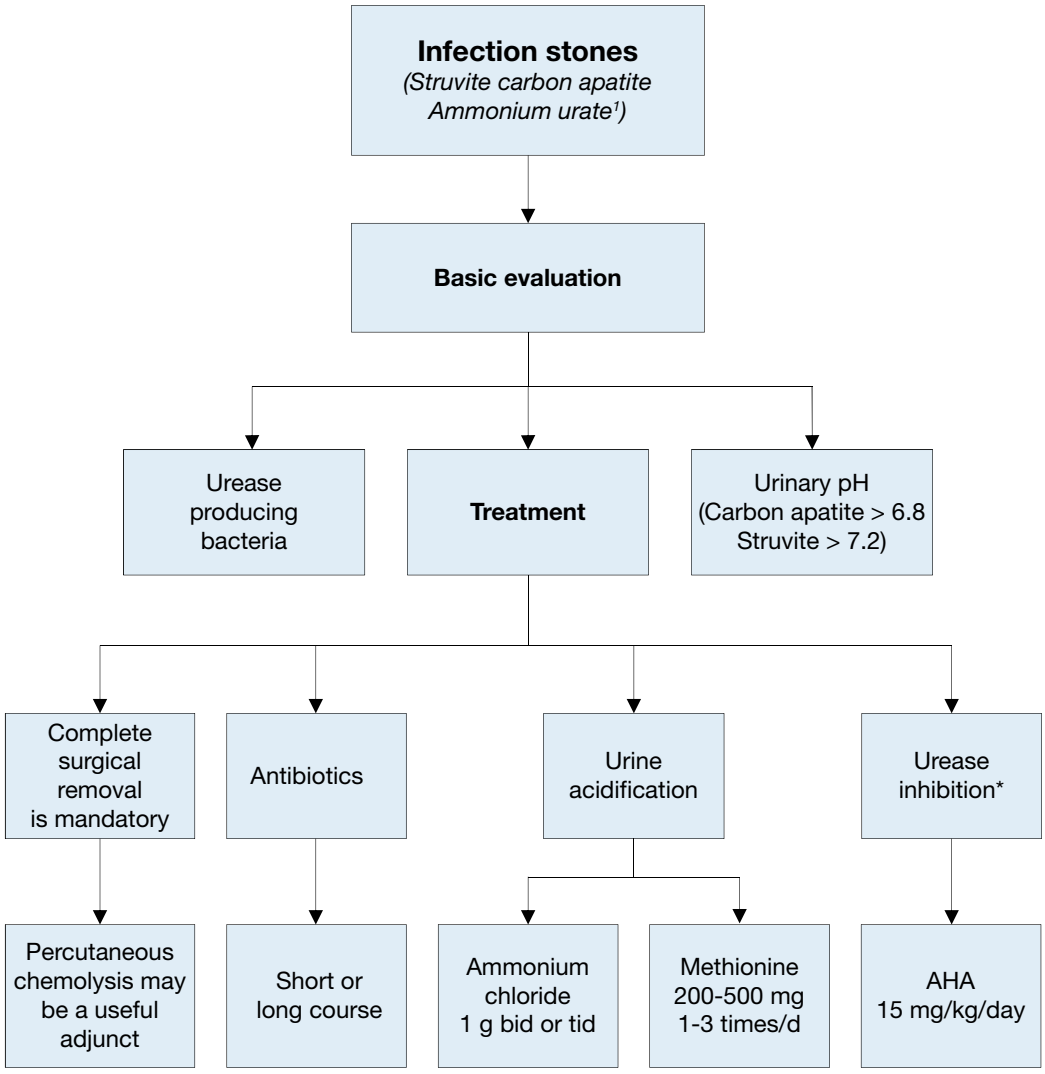
Table 4.9: Factors predisposing to struvite stone formation

• Neurogenic bladder • Spinal cord injury/paralysis • Continent urinary diversion • Ileal conduit • Foreign body • Stone disease • Indwelling urinary catheter	• Urethral stricture • Benign prostatic hyperplasia • Bladder diverticulum • Cystocele • Calyceal diverticulum • UPJ obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
• *Proteus spp.* • *Providencia rettgeri* • *Morganella morganii* • *Corynebacterium urealyticum* • *Ureaplasma urealyticum*
Facultative urease-producing bacteria
• *Enterobacter gergoviae* • *Klebsiella spp.* • *Providencia stuartii* • *Serratia marcescens* • *Staphylococcus spp.*
CAUTION: 0-5% of *Escherichia coli, Enterococcus spp*. and *Pseudomonas aeruginosa* strains may produce urease.

Figure 4.6: Diagnostic and therapeutic algorithm for infection stones



[1] Discussed with uric acid stones.

** When nationally available.*

bid = twice a day; tid = three times a day; AHA = acetohydroxamic acid.

4.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies [32, 586]. All cystine stone formers are deemed at high risk of recurrence.

4.9.1 ***Diagnosis***

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [587].
- There is no role for genotyping patients in the routine management of cystinuria [588, 589].
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [590].
- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including infection stones [591].
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 30 mg/day are considered abnormal [592, 593].

4.9.2 ***Specific treatment***

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day [594]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [587, 590, 594, 595]. A considerable fluid intake evenly distributed throughout the day is necessary.

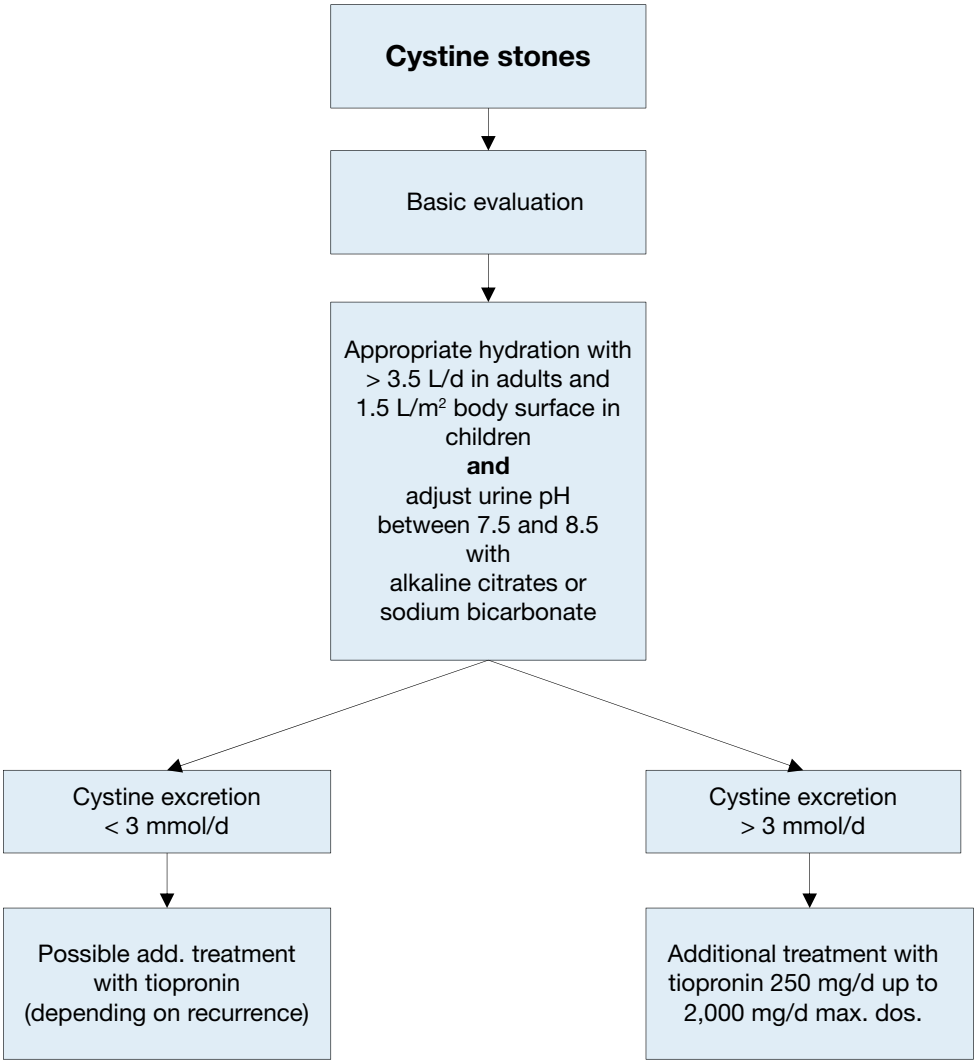
4.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cysteine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children [587, 590, 594, 595].

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cysteine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example when nephrotic syndrome develops or when there is poor compliance, especially with long-term use. After carefully considering the risk of early tachyphylaxis, put into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day or in the case of recurring stone formation, notwithstanding other preventive measures [587, 590, 594, 595].

Figure 4.7: Metabolic management of cystine stones



4.9.3 Summary of evidence and guidelines for the management of cystine stones

Summary of evidence	**LE**
Increasing fluid intake so that 24-hour urine volume exceeds 3 L is used to dilute the cystine.	3
Alkaline citrates 3-10 mmol two or three times daily can be used to achieve pH > 7.5.	3
Tiopronin, 250-2,000 mg/day can be used to reduce stone formation in patients with cysteine excretion, > 3 mmol/day, or when other measures are insufficient.	3

Recommendations	**Strength rating**
Therapeutic measures	
Urine dilution Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3 L.	Strong
Alkalinisation Prescribe potassium citrate 3-10 mmol two or three times daily, to achieve pH > 7.5 for patients with cystine excretion < 3 mmol/day.	Strong
Complex formation with cystine For patients with cystine excretion, > 3 mmol/day, or when other measures are insufficient: prescribe in addition to other measures tiopronin, 250-2,000 mg/day.	Strong

4.10 2,8-Dihydroxyandenine stones and xanthine stones [22]

All 2,8-Dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

*4.10.1 **2,8-Dihydroxyadenine stones***

A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-Dihydroxyadenine. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring [596].

*4.10.2 **Xanthine stones***

Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

*4.10.3 **Fluid intake and diet***

Recommendations for general preventive measures apply. Pharmacological intervention is difficult; therefore, high fluid intake ensures optimal specific weight levels of urine < 1.01. A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug stones [515]

Drug stones are induced by pharmacological treatment [597] (Table 4.10). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 4.11: Compounds that cause drug stones

Active compounds crystallising in urine	Substances impairing urine composition
• Allopurinol/oxypurinol	• Acetazolamide
• Amoxicillin/ampicillin	• Allopurinol
• Ceftriaxone	• Aluminium magnesium hydroxide
• Quinolones	• Ascorbic acid
• Ephedrine	• Calcium
• Indinavir	• Furosemide
• Magnesium trisilicate	• Laxatives
• Sulphonamides	• Methoxyflurane
• Triamterene	• Vitamin D
• Zonisamide	• Topiramate

4.12 Matrix Stones

Pure matrix stones are extremely rare with less than 70 cases described in the literature. They are more prevalent in females. The main risk factors are recurrent UTIs, especially due to *P. mirabilis or E. coli*, previous surgery for stone disease, chronic renal failure and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi a specific prophylactic regimen to minimise recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [598].

4.13 Unknown stone composition [16]

An accurate medical history is the first step towards identifying risk factors as summarised below (see Chapter 4.13.1).

Diagnostic imaging begins with US examination of both kidneys to establish whether the patient is stone free. Stone detection by US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia should additionally be screened for.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection. Constant urine pH < 5.8 in the daily profile indicates acidic arrest, which may promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded [559, 560].

Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-Dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi's syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication [591, 599].

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expulsed stone material is available, it should be analysed by diagnostic confirmation or correction.

4.13.1 ***Recommendations for investigations for the assessment of patients with stones of unknown composition*** [16, 22, 64, 515]

Investigation	Rationale for investigation	Strength rating
Take a medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart	Strong
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Un-enhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition	Strong
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid	Strong
Perform a urinalysis	• Urine pH profile (measurement after each voiding, minimum four times daily) • Dipstick test: leukocytes, erythrocytes, nitrites, protein, urine pH, specific weight • Urine cultures • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion) Further examinations depend on the results of the investigations listed above.	Strong

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6. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location are required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/.

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Bladder Stones

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European
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1. INTRODUCTION

1.1 Aims and Scope

The European Association of Urology (EAU) Bladder Stones Guidelines Panel, a sub-panel of the EAU Urolithiasis Guidelines Panel, has prepared these guidelines to help urologists assess evidence-based management of calculi in native urinary bladders and urinary tract reconstructions and to incorporate recommendations into clinical practice. The management of upper urinary tract stone is addressed in a separate document: the EAU Guidelines on Urolithiasis.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Bladder Stones Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/bladderstones/.

1.3 Available Publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text versions. The EAU Urolithiasis Panel has also published a number of scientific publications in the EAU journal European Urology [1-3]. All documents can be accessed through the EAU website: http://uroweb.org/guideline/bladderstones/.

1.4 Publication History and Summary of Changes

*1.4.1 **Publication History***

The EAU Bladder stones Guidelines were first published in 2019. This 2020 document presents a full update of the 2019 text.

*1.4.2 **Summary of Changes***

The literature throughout the entire document has been reassessed and updated (see Methods section below).

For 2020, the content of each chapter has been rephrased and reassessed; in particular the discussion of metabolic factors in section 3.1, Prevalence, aetiology and risk factors has seen significant revision. The summary of evidence and recommendations tables have been completely revised and updated.

2. METHODS

2.1 Data Identification

For the 2019 Bladder Stones guideline, a structured assessment of the literature including lower levels of evidence was performed to assess all aspects of bladder stones, examining publications from 1970 until December 2018. For the 2020 guideline the searches were updated to February 2019. A detailed search strategy is available online: http://uroweb.org/guideline/bladder-stones/?type=appendices-publications.

The chapters on the treatment of bladder stones in adults and children are based on a systematic review [4].

All methodological information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [5, 6, 7]. Each strength-rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

2.2 Review

This document was peer reviewed prior to its first publication in 2019.

3. GUIDELINES

3.1 Prevalence, aetiology and risk factors

Bladder stones constitute only approximately 5% of all urinary tract stones [9], yet are responsible for 8% of urolithiasis-related mortalities in developed nations [10]. The incidence is higher in developing countries [11]. The prevalence of bladder stones is higher in males, with a reported male:female ratio between 10:1 and 4:1 [12, 13]. The age distribution is bimodal: incidence peaks at three years in children in developing countries [12, 14], and 60 years in adulthood [13].

The aetiology of bladder stones is typically multi-factorial [13]. Bladder stones can be classified as primary, secondary or migratory [15]. Primary or endemic bladder stones occur in the absence of other urinary tract pathology, typically seen in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein [16].

Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include: bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies (including catheters), bladder diverticula and bladder augmentation or urinary diversion. In adults, BOO is the most common predisposing factor for bladder stone formation and accounts for 45-79% of vesical calculi [13, 17-20].

Migratory bladder stones are those which have passed from the upper urinary tract where they formed and may then serve as a nidus for bladder stone growth; patients with bladder calculi are more likely to have a history of upper tract stones and risk factors for their formation [21].

A wide range of metabolic urinary abnormalities can predispose to calculi anywhere in the urinary tract, which is covered in more detail in the EAU Urolithiasis Guideline [22]. There is a paucity of studies on the specific metabolic abnormalities which predispose to bladder stones.

Bladder stones will form in 3-4.7% of men undergoing surgery for benign prostatic obstruction BPO [23, 24], 15-36% of spinal cord injury patients [25-27], and 2.2% of patients with long-term catheters [28]. Of 57 men with chronic urinary retention secondary to BPO, the urine of the 30 men with bladder stones had a higher uric acid concentration (2.2 vs. 0.6 mmol/L, $p < 0.01$), lower magnesium (106 vs. 167 mmol/L, $p = 0.01$) and lower pH (5.9 vs. 6.4, $p = 0.02$) than the 27 men without bladder stones [21]. It is therefore likely that patients with these conditions who form bladder stones also have an abnormal urine composition which pre-disposes them to bladder stone formation.

The metabolic abnormalities which pre-dispose patients to form secondary bladder stones are poorly understood. Stone analysis of 86 men with a BPO-related bladder stone demonstrated 42% had calcium based stones (oxalate, phosphate), 33% had magnesium ammonium phosphate, 10% had mixed stones and 14% had urate stones [13]. Similar findings were reported in more recent studies [29-31] and it is therefore likely that multiple metabolic factors pre-dispose patients to secondary bladder stone formation.

The exact metabolic basis for primary bladder stones is poorly understood and likely multi-factorial. Low urine volume (poor hydration) is the most consistently demonstrable abnormality [32-34]. Twenty-four hour urine analysis in children with endemic bladder stones is reported in two studies. Of 57 children in Pakistan, 89.5% had hypocitraturia, 49% had a low urine volume, 44% had hyperoxaluria and 42% had hypokaluria [32]. Of 61 children in India, stone formers had higher urine calcium and uromucoid concentrations than controls [33]. One study from Thailand compared 24 hour urine analyses from children from a rural area with a high prevalence of bladder stones with those from an urban area: rural children had lower urine volumes and, despite equal calcium, oxalate and uric acid concentrations, crystalluria with uric acid and calcium oxalate crystals was more prevalent in rural children [34].

3.2 Presentation

The symptoms most commonly associated with bladder stones are urinary frequency, haematuria (which is typically terminal) and dysuria or suprapubic pain, which are worst towards the end of micturition. Sudden movement and exercise may exacerbate these symptoms. Detrusor over-activity is found in over two thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4 cm). However, recurrent urinary tract infections (UTIs) may be the only symptom [18, 19].

In children, symptoms may also include pulling of the penis, difficulties in micturition, urinary retention, enuresis and rectal prolapse (resulting from straining due to bladder spasms). Bladder stones may also be an incidental finding in 10% of cases [16, 35].

3.3 Diagnostic evaluation

*3.3.1 **Diagnostic investigations for bladder stones***

Plain X-ray of kidney ureter bladder (KUB) has a reported sensitivity of 21%-78% for cystoscopically detected bladder stones in adults [18, 36]. Larger (> 2.0 cm) stones are more likely to be radiopaque [36]. However, plain X-Ray provides information on radio-opacity which may guide treatment and follow-up [22].

Ultrasound (US) has a reported sensitivity and specificity of 20-83% and 98-100%, respectively for the detection of bladder stones in adults [37, 38]. Computer tomography (CT) and cystoscopy have a higher sensitivity for detecting bladder stones than US or X-Ray in adults [37, 38]. No study compares cystoscopy and CT for the diagnosis of bladder stones. Cystoscopy has the advantage of detecting other potential causes for a patient's symptoms (e.g. bladder cancer), whilst CT can also assess upper tract urolithiasis [22, 39].

There is a paucity of evidence for the investigation of bladder stones, particularly in children [40, 41]. See also EAU Guidelines on Urolithiasis, Section 3.3, for further information on diagnostic imaging for urolithiasis [22]. The principle of ALARA (As Low As Reasonably Achievable) should be applied, especially in children [42].

*3.3.2 **Diagnosing the cause of bladder stones***

The cause of the bladder stone should be considered prior to bladder stone treatment as eliminating the underlying cause will reduce recurrence rates [43]. The following should be performed where possible prior to (or at the time of) bladder stone treatment:

- physical examination of external genitalia, peripheral nervous system (including digital rectal examination, peri-anal tone and sensation in men);
- uroflowmetry and post-void residual urine assessment;
- urine dipstick to include pH ± culture;
- metabolic assessment (see also EAU Guideline on Urolithiasis section 3.3.2.3) including: serum (creatinine, (ionised) calcium, uric acid, sodium, potassium, blood cell count);
- urine pH;
- stone analysis: in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).

The following investigations should also be considered for selected patients:

- upper tract imaging (in patients with a history of urolithiasis or loin pain);
- cysto-urethroscopy or urethrogram.

3.4 Disease Management

*3.4.1 **Conservative treatment and Indications for active stone removal***

Migratory bladder stones in adults may typically be left untreated, especially asymptomatic small stones. Rates of spontaneous stone passage are unknown, but data on ureteric stones suggest stones < 1 cm are likely to pass in the absence of BOO, bladder dysfunction or long-term catheterisation [22].

Primary and secondary bladder stones are usually symptomatic and are unlikely to pass spontaneously: active treatment of such stones is usually indicated.

*3.4.2 **Medical management of bladder stones***

There is a paucity of evidence on chemolitholysis of bladder stones. However, guidance on the medical management of urinary tract stones in Chapter 3.4.9 of the EAU Urolithiasis Guidelines [22] can be applied to urinary stones in all locations. Uric acid stones can be dissolved by oral urinary alkalinisation when a pH > 6.5 is consistently achieved, typically using an alkaline citrate or sodium bicarbonate. Regular monitoring is required during therapy [22]. Irrigation chemolysis is also possible using a catheter; however, this is time consuming and may cause chemical cystitis and is therefore not commonly employed [44, 45].

*3.4.3 **Bladder stone interventions***

Minimally invasive techniques for the removal of bladder stones have been widely adopted to reduce the risk of complications and shorten hospital stay and convalescence. Bladder stones can be treated with open, laparoscopic, robotic assisted laparoscopic, endoscopic (transurethral or percutaneous) surgery or extracorporeal shock wave lithotripsy (ESWL) [4].

3.4.3.1 Suprapubic cystolithotomy

Open suprapubic cystolithotomy is very effective, but is associated with a need for catheterisation and longer hospital stay in both adults and children compared to all other stone removal modalities [4]. In children, a non-randomised study found that, if the bladder was closed meticulously in two layers, “tubeless” (drain-less and catheter-less) cystolithotomy was associated with a significantly shorter length of hospital stay compared with traditional cystolithotomy, without significant differences regarding late or intra-operative complications provided that children with prior UTI, recurrent stones, or with previous surgery for anorectal malformation (or other relevant surgery) were excluded [46].

3.4.3.2 Transurethral cystolithotripsy

In both adults and children, transurethral cystolithotripsy provides high stone-free rates (SFR) and appears to be safe, with a very low risk of unplanned procedures and major post-operative and late complications [4].

3.4.3.2.1 Transurethral cystolithotripsy in adults:

In adults, meta-analysis of four randomised controlled trials (RCTs) including 409 patients demonstrated that transurethral cystolithotripsy has a shorter hospital stay and convalescence with less pain, but equivalent SFR and complications compared to percutaneous cystolithotripsy [4]. Transurethral cystolithotripsy with a nephroscope was quicker than percutaneous cystolithotripsy in three RCTs, although transurethral cystolithotripsy with a cystoscope was slower than percutaneous cystolithotripsy [4].

One small RCT demonstrated a shorter duration of catheterisation, hospital stay and procedure with transurethral cystolithotripsy than open cystolithotomy with similar SFR [4]. Meta-analysis of four RCTs found shorter procedure duration for transurethral cystolithotripsy using a nephroscope vs. cystoscope with similar SFRs, hospital stay, convalescence, pain and complications [4, 29, 47-49]. A retrospective study (n=107) reported that using a resectoscope was associated with a shorter procedure duration ($p < 0.05$) than a cystoscope for transurethral cystolithotripsy [50]. This suggests that transurethral cystolithotripsy is quicker when using a continuous flow instrument.

3.4.3.2.1.1 Lithotripsy modalities used during transurethral cystolithotripsy in adults

When considering lithotripsy modalities for transurethral cystolithotripsy, our systematic review found very low quality evidence from five non-randomised studies (n=385) which found no difference in SFR between modalities (mechanical, laser, pneumatic, ultrasonic, electrohydraulic lithotripsy (EHL) or washout alone) [4]. Unplanned procedures and major postoperative complications were low rate events and were not significantly different between lithotripsy modalities, although one non-randomised study (NRS) suggested these might be higher with EHL or mechanical lithotripsy than pneumatic or ultrasonic lithotripsy [51]. All outcomes had very low quality of evidence (GRADE) [4].

While the laser power setting (30W vs. 100W) does not seem to influence lithotripsy time significantly [30], laser lithotripsy was faster than pneumatic lithotripsy (MD 16.6 minutes; CI 23.51-9.69, $p < 0.0001$) in one NRS (n=62); however, a laser was used with a resectoscope and the pneumatic device with a cystoscope [52]. Continuous vs. intermittent irrigating instrument may affect the operation time more significantly than the choice of lithotripsy device [4].

Transurethral cystolithotripsy in children:
In children, three NRS suggest that transurethral cystolithotripsy has a shorter hospital stay and catheterisation time than open cystolithotomy, but similar stone-free and complication rates [4, 53]. One small quasi RCT found a shorter procedure time using laser vs. pneumatic lithotripsy for < 1.5 cm bladder stones with no difference in SFR or other outcomes [4, 54].

3.4.3.3 Percutaneous cystolithotripsy

3.4.3.3.1 Percutaneous cystolithotripsy in adults:
One NRS found a shorter duration of procedure and catheterisation and less blood loss for percutaneous, compared with open surgery in adult male patients with urethral strictures; all patients in both groups were rendered stone-free [31].

Meta-analysis of four RCTs comparing transurethral and percutaneous cystolithotripsy found a shorter hospital stay for transurethral cystolithotripsy over percutaneous surgery. Transurethral cystolithotripsy was quicker when using a nephroscope. There were no significant differences in SFRs, major post-operative complications, urethral strictures or re-treatment [4].

3.4.3.3.2 Percutaneous cystolithotripsy in children:
In children, three NRS suggest that percutaneous cystolithotripsy has a shorter hospital stay and catheterisation time but a longer procedure duration and more peri-operative complications than open cystolithotripsy; SFRs were similar [4, 35, 53].

Two small NRS compared percutaneous and transurethral cystolithotripsy and both found similar SFRs, but that transurethral surgery offers a shorter duration of catheterisation and hospital stay [35, 53]. One small NRS found a non-significant increased risk of unplanned procedures (within 30 days of primary procedure) and major post-operative complications for percutaneous operations compared with transurethral procedures; however, age and stone size determined which intervention children underwent and all patients were rendered stone-free [35]. Urethral stricture rates were not robustly compared in either study.

3.4.3.4 Extracorporeal shock wave lithotripsy

Extracorporeal SWL is the least invasive therapeutic procedure [55].

3.4.3.4.1 Shock wave lithotripsy in adults
In adults, NRS found a lower SFR and higher rate of unplanned procedures for SWL vs. transurethral cystolithotripsy, despite continuous irrigation in all patients and fragment evacuation in 16% of cases [4, 56].

3.4.3.4.2 Shock wave lithotripsy in children
One large NRS found lower SFR for SWL than both transurethral cystolithotripsy and open cystolithotomy, despite treating smaller stones with SWL. However, the length of hospital stay favoured SWL over cystolithotomy, although this appeared to be comparable between SWL and transurethral cystolithotripsy [57].

3.4.3.5 Laparoscopic cystolithotomy

Laparoscopic cystolithotomy has been described in adults, and is typically performed in combination with simple prostatectomy using either traditional laparoscopy or with robotic-assistance [58, 59]. A SR found no studies comparing laparoscopic surgery with other procedures [4].

3.4.4 ***Treatment for bladder stones secondary to bladder outlet obstruction in adult men***

Bladder stones in men aged over 40 years are typically related to BPO, the management of which should also be considered. Bladder stones were traditionally an indication for a surgical intervention for BPO: a doctrine which has been questioned by recent studies. One NRS compared 64 men undergoing transurethral cystolithotripsy with either transurethral resection of prostate (TURP) or medical management for BPO (α-blocker with or without 5-alpha reductase inhibitor). After 28 months follow-up, no men on medication had had a recurrence, but 34% underwent TURP: a high post-void residual urine volume predicted the need for subsequent TURP [60]. Another observational study of 23 men undergoing cystolithotripsy and commencing

medical management for BPO found 22% developed a BPO related complication, including 17% who had recurrent stones [43].

Large studies support the safety of performing BPO and bladder stone procedures during the same operation with no difference in major complications compared to a BPO procedure alone [61, 62]. An observational study on 2,271 patients undergoing TURP found no difference in complications except UTIs, which occurred slightly more frequently in patients with simultaneously treated bladder stones: 0% vs. 0.6%, p = 0.044 [61]. An observational study of 321 men undergoing Holmium laser enucleation of the prostate (HoLEP) found a higher rate of early post-operative incontinence (26.8% vs. 12.5%, p = 0.03) in men having concomitant transurethral cystolithotripsy, but no difference in long-term continence rates [62].

*3.4.5 **Special situations***

3.4.5.1 Neurogenic bladder and stone formation

Patients with neurogenic bladder secondary to spinal cord injury or myelomeningocele are at increased risk of forming bladder stones. Within eight to ten years, 15-36% of patients with spinal cord injury will develop a bladder stone [25-27]. The absolute annual risk of stone formation in spinal cord injury patients with an indwelling catheter is 4% compared with 0.2% for those voiding with clean intermittent self-catheterisation (CISC) [63]. Bladder stones are no more likely to form in patients with suprapubic catheters compared to those with indwelling urethral catheters [63]. Spinal cord injury patients with an indwelling urethral catheter are approximately six times more likely to develop bladder stones than patients with normal micturition [27].

The risk of stone recurrence in these patients is 16% per year [63]. An RCT of 78 spinal cord injury patients who perform CISC found a significant reduction in bladder stone formation when twice weekly manual bladder irrigations were performed for 6 months (49% vs. 0%, p = <0.0001), as well as less symptomatic UTIs (41% vs. 8%; p = 0.001) [64]. However, this study excluded patients who developed autonomic dysreflexia during bladder irrigations.

3.4.5.2 Bladder Augmentation

The incidence of vesical calculus formation after bladder augmentation is 2-44% in adults [65-73], and 4-53% in children [74-86]. The reported cumulative incidence of bladder stone formation after ten years is 36% [87]. Following cystoplasty, stones form after 24-31 months in adults [66, 68, 73], and after 25-68 months in children [78, 80, 82, 86, 88-90].

Drainage by vesico-entero-cystostomy (Mitrofanoff or Monti) is associated with an increased risk of bladder stone formation [66, 71, 72, 77, 78, 80, 87, 91]. The risk of bladder stone formation is elevated in patients voiding by CISC compared with those voiding spontaneously [70]. Gastric segment augmentation confers a lower risk of bladder stones than ileal or colononic segment cystoplasty [74, 77, 78, 80].

In previous stone formers, the rate of recurrence is 15-44% in adults [66-68, 70, 73], and 19-56% in children [74, 77, 78, 80, 82-84, 90, 91]. The risk of recurrence is greatest during the first two years, at about 12% per patient per year, with the risk decreasing with time [90]. Daily bladder irrigation with 250 mL of saline solution significantly reduces the incidence of recurrent stone formation and bacterial colonisation compared to lower volume bladder irrigations [69]. A paediatric study reported that patients placed on an irrigation protocol using 240 mL saline solution twice a week and gentamicin sulphate solution once a week (240–480 mg gentamicin/L saline, at 120–240 mL per irrigation, depending on patient age and reservoir size), was associated with a significantly lower risk of vesical calculus formation [91].

3.4.5.3 Urinary diversion

The incidence of stone formation after urinary diversion with an ileal or colon conduit is 0-3% [92, 93]. The incidence of stone formation is 0-34% in orthotopic ileal neobladders (Hautmann, hemi-Kock, Studer, T-pouch or w-neobladder) [70, 92, 94-102], and 4-6% in orthotopic sigmoid neobladders (Reddy) [98, 103]. The risk of pouch stone formation is 4-43% in adults with an ileocaecal continent cutaneous urinary diversion (Indiana, modified Indiana, Kock or Mainz I) [70, 92, 93, 101, 104, 105]. The average interval from construction of the urinary diversion to stone detection is 71-99 months [97, 106]. In children, the incidence of neobladder stone formation is 30% after Mainz II diversion (rectosigmoid reservoir) [75], and 27% after Kock ileal reservoir construction [85].

3.4.5.4 Treatment of stones in patients with bladder augmentation or urinary diversion

Stones may be removed by open or endoscopic surgery in patients with bladder augmentation or diversion

[84]. However, often access cannot be obtained through a continent vesico-entero-cystostomy without damaging the continence apparatus; hence a percutaneous or open approach is typically preferred [84].

No studies comparing outcomes following procedures for stones in reconstructed or augmented bladders were found. Two observational studies indicate that percutaneous lithotomy can be safely performed with US or CT guidance in patients with reconstructed or augmented bladders [107, 108] and is proposed to offer similar advantages over open surgery to those for percutaneous native bladder surgery. Stone recurrence after successful removal has been reported to be 10-42% [107, 108], but appears to be unrelated to the modality used for stone removal [73, 77, 78, 80, 83, 90].

4. FOLLOW-UP

There are no studies examining the merits of differing follow-up modalities or frequencies following conservative, medical or operative treatment of bladder stones in adults or children. Identification and prevention of the cause of bladder stone formation will be crucial to prevent recurrence (see section 3.3.2).

In adults, there is a paucity of evidence on dietary modification or medical treatment for the prevention of bladder stone recurrence. Recommendations in the EAU Guideline on Urolithiasis, based on evidence from upper tract stones, constitutes the best available recommendations, especially for migratory bladder stones (see chapter 4 in the main EAU Urolithiasis guideline) [22].

Where it is possible to address the cause of secondary bladder stones (e.g. treatment of BPO), it is unclear whether metabolic intervention would offer any significant additional benefit in preventing stone recurrence. However, especially where the secondary cause cannot be addressed (e.g. indwelling catheter, neuropathic bladder, bladder augmentation or urinary diversion); metabolic interventions are likely to reduce bladder stone recurrence rates.

Regular bladder irrigation reduces the chances of bladder stone recurrence in adults and children with bladder augmentation or continent cutaneous urinary diversion and adults with spinal cord injury who perform CISC (see section 3.3.5) [64, 69, 91].

In children with primary (endemic) bladder stones maintenance of hydration, avoidance of diarrhoea and a mixed cereal diet with milk and Vitamins A and B supplements, with the addition of eggs, meat and boiled cows' milk after one year of age are recommended to prevent recurrence [32].

Finally, there are contradictory reports on a possible association between bladder calculi and future development of bladder cancer [109-111]. The need for follow-up with regular cystoscopy therefore remains controversial.

Summary of evidence	LE
The incidence of bladder stones peaks at three years in children (endemic/primary stones in developing countries) and 60 years in adults.	2c
The aetiology of bladder stones is typically multi-factorial. Bladder stones can be classified as primary (endemic), secondary (associated with lower urinary tract abnormalities e.g. BPO, neuropathic bladder, foreign body, chronic bactiuria) or migratory (having formed in the upper tract).	4
In adults, bladder outlet obstruction (BOO) is the most common predisposing factor for bladder stone formation.	2c
Metabolic abnormalities are also likely to contribute to bladder stone formation in patients with secondary bladder stones.	2b
In adults, US has a sensitivity of 20-83% for diagnosing bladder stones.	2b
In adults, X-Ray kidney ureter bladder (XR-KUB) has a sensitivity of 21-78%; sensitivity increases with stone size.	2b
Computer tomography has a higher sensitivity than US for the detection of bladder stones.	2b
Cystoscopy has a higher sensitivity than XR-KUB or US for the detection of bladder stones.	2b
Endoscopic bladder stone treatments are associated with comparable stone-free rates (SFRs) but a shorter length of hospital stay, duration of procedure and duration of catheterisation compared to open cystolithotomy in adults.	1a
Stone-free rates are lower in patients treated with shock wave lithotripsy (SWL) than those treated with open or endoscopic procedures in both adults and children.	2a
Transurethral cystolithotripsy is associated with a shorter length of hospital stay, less pain and a shorter convalescence period than percutaneous cystolithotripsy in adults.	1b
Transurethral cystolithotripsy with a nephroscope is quicker than when using a cystoscope with no difference in SFR in adults.	1a
Transurethral cystolithotripsy with a resectoscope is quicker than when using a cystoscope with no difference in SFR in adults.	2a
Mechanical, pneumatic and laser appear equivalent lithotripsy modalities for use in endoscopic bladder stone treatments in adults and children.	2a
Open cystolithotomy without a retropubic drain or urethral catheter (“tubeless”) is associated with a shorter length of hospital stay than traditional cystolithotomy and can be performed safely in children with primary stones and no prior bladder surgery or infections.	2b
Bladder stone removal with concomitant treatment for BOO is associated with no significant difference in major post-operative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term post-operative incontinence and urinary infection.	2b
The absolute annual risk of stone formation in spinal cord injury patients is significantly higher with an indwelling catheter compared to those voiding with CISC. Suprapubic and urethral catheters have equal rates of bladder stone formation in spinal cord injury patients.	2b
The incidence of bladder stone formation after bladder augmentation or vesico-entero-cystostomy is between 2-53% in adults and children.	2b
Urinary diversion including orthotopic ileal neobladders, ileocaecal continent cutaneous urinary diversion and rectosigmoid reservoirs is associated with stone formation in 0-43%.	2b
Primary (endemic) bladder stones typically occur in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein. The following measures are proposed to reduce their incidence: maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements; with the addition of eggs, meat and boiled cows’ milk after one year of age.	5

Recommendations	Strength rating
Use ultrasound (US) as first-line imaging in adults with symptoms suggestive of a bladder stone.	Strong
Use cystoscopy or computer tomography (CT) kidney ureter bladder (KUB) to investigate adults with persistent symptoms suggestive of a bladder stone if US is negative.	Strong
Use US as first-line imaging in children with symptoms suggestive of a bladder stone.	Strong
Use X-Ray KUB for adults with confirmed bladder stones to guide treatment options and follow-up.	Weak
All patients with bladder stones should be examined and investigated for the cause of bladder stone formation, including: • uroflowmetry and post-void residual; • urine dipstick, pH, ± culture • metabolic assessment and stone analysis (see sections 3.3.2.3 and 4.1 of the Urolithiasis guideline for further details). In selected patients, consider: • upper tract imaging (in patients with a history of urolithiasis or loin pain); • cysto-urethroscopy or urethrogram.	Weak
Offer oral chemolitholysis for radio-lucent or known uric acid bladder stones in adults.	Weak
Offer adults with bladder stones transurethral cystolithotripsy where possible.	Strong
Perform transurethral cystolithotripsy with a continuous flow instrument in adults (e.g. nephroscope or resectoscope) where possible.	Weak
Offer adults percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or advisable.	Strong
Suggest open cystolithotomy as an option for very large bladder stones in adults and children.	Weak
Offer children with bladder stones transurethral cystolithotripsy where possible.	Weak
Offer children percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or is associated with a high risk of urethral stricture (e.g. young children, previous urethral reconstruction and spinal cord injury).	Weak
Open, laparoscopic and extracorporeal shock wave lithotripsies are alternative treatments where endoscopic treatment is not possible in adults and children.	Weak
Prefer “tubeless” procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery or bladder dysfunction where open cystolithotomy is indicated.	Weak
Perform procedures for the stone and underlying BOO simultaneously in adults with bladder stones secondary to bladder outlet obstruction (BOO), where possible.	Strong
Individualise imaging follow up for each patient as there is a paucity of evidence. Factors affecting follow up will include : • whether the underlying functional predisposition to stone formation can be treated (e.g. TURP); • metabolic risk.	Weak
Recommend regular irrigation therapy with saline solution to adults and children with bladder augmentation, continent cutaneous urinary reservoir or neuropathic bladder dysfunction, and no history of autonomic dysreflexia, to reduce the risk of recurrence.	Weak

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6. CONFLICT OF INTEREST

All members of the Bladder Stones Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Paediatric Urology

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European Society for Paediatric Urology

European Association of Urology

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1. INTRODUCTION

1.1 Aim

A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document is limited to a number of common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of urological clinical problems in children are specialised and in many ways differ to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological conditions. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary team is available.

Over time, paediatric urology has developed and matured, establishing its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of children and their caregivers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU-ESPU Paediatric Urology Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website: http://uroweb.org/guideline/paediatric-urology/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications are also available [1-7]. All documents can be viewed through the EAU website: http://uroweb.org/guideline/paediatric-urology/.

1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001 [8]. This 2020 publication includes a number of updated chapters and sections as detailed below.

1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2020 publication:

- Section 3.1 – Phimosis: Both the literature and the text have been updated;
- Section 3.3 – Hydrocele: Both the literature and the text have been updated;
- Section 3.14 – Urinary stone disease: The literature has been updated resulting in minor amendments to the text;
- Section 3.17 - Congenital lower urinary tract obstruction (CLUTO): The former text on PUV has been revised extensively to form this new section;
- Section 3.18 – Paediatric urological trauma: Both the literature and the text have been updated;
- Section 3.19 – Post-operative fluid management: Both the literature and the text have been updated;
- Section 3.20 – Post-operative pain management: general information: Both the literature and the text have been updated
- Section 3.21 - Basic principles of laparoscopic surgery in children: This is a new section in the Guideline.

1.5.1 New recommendations

3.21.3 Recommendations for laparoscopy in children

Recommendations	Strength rating
Use lower intra-abdominal pressure (6-8 mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

2. METHODS

2.1 Introduction

These Guidelines were compiled based on current literature following a structured review. Databases covered by the searches included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [9, 10]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [11];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation.
The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [12]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

All chapters of the Paediatric Urology Guidelines were peer-reviewed in 2015.

2.3 Future goals

The Paediatric Urology Guidelines Panel aim to systematically address the following key clinical topic in a future update of the Guidelines:

- Does using an inlay graft during primary hypospadias repair affect the outcomes?
- Is there any prognostic importance of diagnosing testicular microlithiasis in the paediatric population in predicting the risk of testicular malignancy and infertility?

3. THE GUIDELINE

3.1 Phimosis

This chapter does not deal with neonatal circumcision as practised in the USA, nor mass circumcision as practised in many African countries as part of a national program to prevent HIV. Also “religious and cultural” circumcision is not discussed. At present in some European countries the professional organisations do not support circumcision for these reasons and it is no longer covered by insurance in these countries. Special centres have been set up, where well-trained doctors perform circumcisions under sedation and local anaesthetics at a lower cost. In all circumstances facilities have to comply with national regulations regarding hygiene, special equipment, pain protocols and follow-up. Usually these clinics have an agreement with a nearby hospital for the immediate treatment of possible complications. It is estimated that 37-39% of men worldwide are circumcised [13].

*3.1.1 **Epidemiology, aetiology and pathophysiology***

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in approximately 50% of boys; this increases to approximately 89% by the age of three years. The incidence of phimosis is 8% in six to seven year olds and in just 1% in males aged sixteen to eighteen years [14].

*3.1.2 **Classification systems***

Phimosis is either primary with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans (BXO) [14]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found in 35% of circumcised prepuce in children and adolescents and in 17% of boys younger than ten years presenting with phimosis. The clinical appearance of BXO in children may be confusing and does not always correlate with the final histopathological results. Lymphocyte-mediated chronic inflammatory disease was the most common finding [15, 16] (LE: 2b).

Phimosis has to be distinguished from normal agglutination (adhesion) of the foreskin to the glans, which is a more or less lasting physiological phenomenon with clearly-visible meatus and partial retraction [17]. Separation of the prepuce from the glans is based on accumulated epithelial debris (smegma) and penile erections. Forceful preputial retraction should be discouraged to avoid cicatrix formation [18].

Paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glanular sulcus may constrict the shaft and lead to oedema of the glans and retracted foreskin. It interferes with perfusion distally from the constrictive ring and brings a risk of preputial necrosis.

*3.1.3 **Diagnostic evaluation***

The diagnosis of phimosis and paraphimosis is made by physical examination. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenulum breve. Paraphimosis is characterised by a retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

*3.1.4 **Management***

Conservative treatment is an option for primary phimosis. The class 4 therapies were more effective over placebo and manual stretching [19]. A corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 4-8 weeks with a success rate of > 80% [20-23] (LE: 1b). A recurrence rate of up to 17% can be expected [24]. This treatment has no side effects and the mean bloodcortisol levels are not significantly different from an untreated group of patients [25] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [26]. Adhesion of the foreskin to the glans does not respond to steroid treatment [20] (LE: 2).

Operative treatment of phimosis in children is dependent on the caregivers’ preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [27]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision, trident preputial plasty, combining 2 Z-plasties a Y plasty) [28, 29]. However, this procedure carries the potential for recurrence of the phimosis [30]. In the same session, adhesions are released and an associated fraenulum breve is corrected by fraenulotomy. Meatoplasty is added if necessary. In all cases meticulous haemostasis is mandatory and absorbable interrupted sutures are most often used.

An absolute indication for circumcision is secondary phimosis. In primary phimosis (including those not responding to medical treatment), recurrent balanoposthitis and recurrent urinary tract infections (UTIs) in patients with urinary tract abnormalities are indications for surgical intervention [31-34] (LE: 2b). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [35] (LE: 2b). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [36]. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, as the foreskin may be required for a reconstructive procedure [37, 38]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic blade are used [39, 40]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [41-45] (LE: 1b). Balanitis xerotica obliterans is associated with meatal pathology (stenosis) after circumcision in up to 20% of boys and adjuvant local steroid treatment is advised [16, 46].

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band or 20% mannitol may be helpful to release the foreskin [47, 48] (LE: 3-4). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

*3.1.5 **Complications***

Complications following circumcision vary and have been reported between 0% and 30% [45]. In a recent study Hung *et al* found during a 5-year follow-up period 2.9% complications in non-neonates of which 2.2% were early (within 30 days after circumcision). Non-healing wounds, haemorrhage, wound infection, meatal stenosis, redundant skin and non-satisfying cosmetic appearance as well as cicatrix formation and trapped penis all may occur [49].

*3.1.6 **Follow-up***

Any surgery done on the prepuce requires an early follow-up of four to six weeks after surgery.

*3.1.7 **Summary of evidence and recommendations for the management of phimosis***

Summary of evidence	**LE**
Treatment for phimosis usually starts after two years of age or according to caregivers' preference.	3
In primary phimosis, conservative treatment with a third generation corticoid ointment or cream is a first-line treatment with a success rate of more than 80%.	1b

Recommendations	**LE**	**Strength rating**
Offer corticoid ointment or cream to treat primary symptomatic phimosis. Circumcision will also solve the problem.	1b	Strong
Treat primary phimosis in patients with recurrent urinary tract infection and/or with urinary tract abnormalities.	2b	Strong
Circumcise in case of lichen sclerosus or scarred phimosis.	2b	Strong
Treat paraphimosis by manual reposition and proceed to surgery if it fails.	3	Strong
Avoid retraction of asymptomatic praeputial adhesions.	2b	Weak

3.2 Management of undescended testes

*3.2.1 **Background***

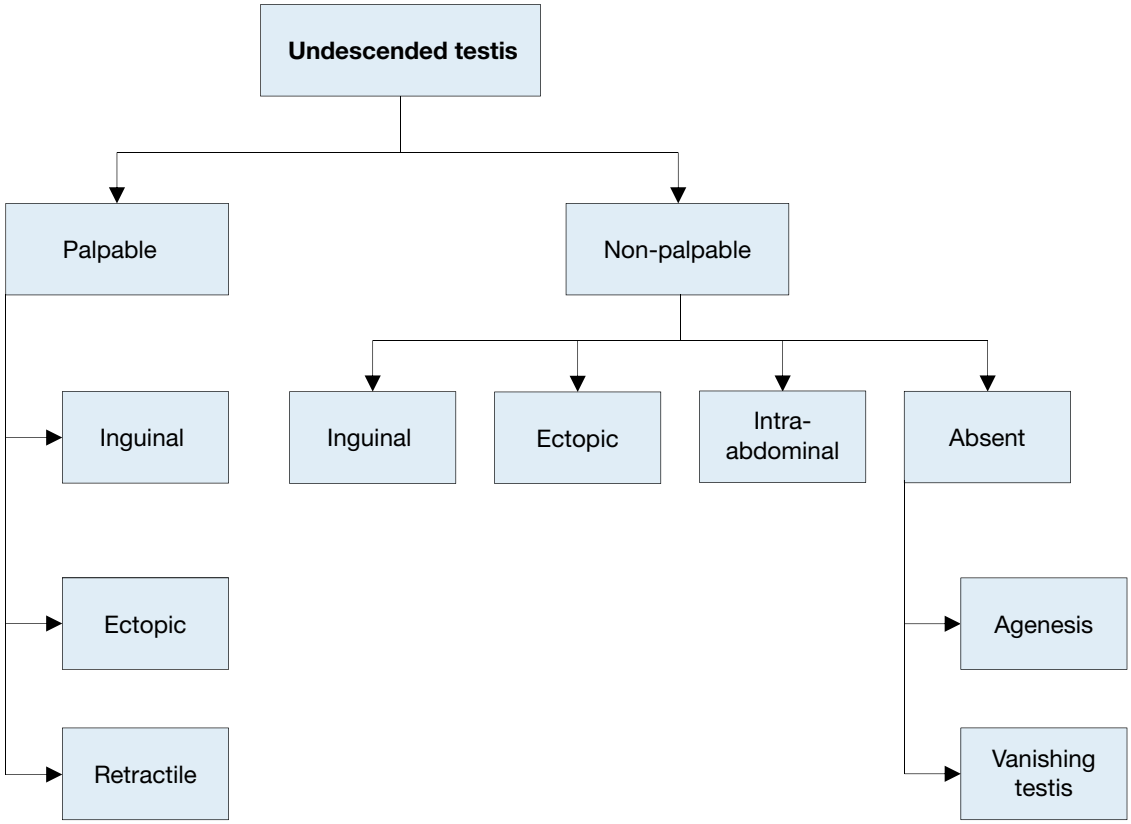
Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [50]. This congenital malformation may affect both sides in up to 30% of cases [51]. In newborn cases with non-palpable or undescended testes on both sides and any sign of disorders of sex development (DSDs) like concomitant hypospadias, urgent endocrinological and genetic evaluation is required [52].

3.2.2 ***Classification***

The term cryptorchidism is most often used synonymously for undescended testes. The most useful classification of undescended testes is distinguishing into palpable and non-palpable testes, and clinical management is decided by the location and presence of the testes (see Figure 1). Approximately 80% of all undescended testes are palpable [53]. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as this is the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes



3.2.2.1 *Palpable testes*

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position.

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex [54]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily.

They are typically normal in size and consistency. However, they may not be normal and should be monitored carefully since up to one-third can ascend and become undescended [55].

3.2.2.2 Non-palpable testes

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be located in different positions, with most of them being found close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall, and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of boys with undescended testes, and anorchidism (bilateral absence) in < 1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion with the latter one most probably due to an *in utero* infarction of a normal testis by gonadal vessel torsion. The term “vanishing testis” is commonly used for this condition [56].

3.2.3 ***Diagnostic evaluation***

History taking and physical examination are key in evaluating boys with undescended testes. Localisation studies using different imaging modalities are usually without any additional benefit.

3.2.3.1 History

Caregivers should be asked for maternal and paternal risk factors, including hormonal exposure and genetic or hormonal disorders. If the child has a history of previously descended testes this might be suggestive of testicular ascent [57]. Prior inguinal surgery is indicative of secondary undescended testes due to entrapment.

3.2.3.2 Physical examination

An undescended testis is pursued by carefully advancing the examining fingers along the inguinal canal towards the pubis region, perhaps with the help of lubricant. A possible inguinal testis can be felt to bounce under the fingers [58]. A non-palpable testis in the supine position may become palpable once the child is in a sitting or squatting position. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In the event of unilateral non-palpable testis, the contralateral testis needs to be examined. Its size and location can have important prognostic implications. Any compensatory hypertrophy suggests testicular absence or atrophy [59]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [60].

In the event of bilateral undescended testes and any evidence or sign of DSDs, such as genital ambiguity, or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [61].

3.2.3.3 Imaging studies

Imaging studies cannot determine with certainty that a testis is present or not [62]. Ultrasound (US) lacks the diagnostic sensitivity to detect the testis confidently or establish the absence of an intra-abdominal testis [63].

Consequently, the use of different imaging modalities, such as US or Magnetic resonance imaging (MRI) [64], for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g. identification of Müllerian structures in cases with suspicion of DSDs) [63].

3.2.4 ***Management***

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [65]. Any kind of treatment leading to a scrotally positioned testis should be finished by twelve months, or eighteen months at the latest, because histological examination of undescended testes at that age has already revealed a progressive loss of germ cells and Leydig cells [66]. The early timing of treatment is also driven by the final adult results on spermatogenesis and hormone production, as well as on the risk of tumour development [67].

3.2.4.1 Medical therapy

Unfortunately, most of the studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking.

Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation,

and induction of pubic hair and penile growth. Some boys experience pain after intramuscular injection of human chorionic gonadotropin (hCG). All of these tend to regress after treatment cessation [68, 69].

3.2.4.1.1 Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotropin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, but has a limited success rate of only 20% [70]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [71]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [68]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [72]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

Human chorionic gonadotropin

Human chorionic gonadotropin stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules are reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for fourteen days [73]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [74]. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for five weeks seem to be superior to one higher dose every seven to ten days for three weeks with regard to testicular descent [75].

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone analogues (e.g., buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations [76].

3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [76, 77] and therefore serve as an additional tool to orchidopexy. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [78]. It is still unknown whether this effect on testicular histology persists into adulthood but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment [76].

It is reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood [79].

Identification of specific subgroups of boys with undescended testes who would benefit from such an approach using hormones is difficult. Since these important data on specific groups as well as additional support on the long-term effects are still lacking, the Nordic consensus does not recommend hormonal therapy [80]. The consensus of the Panel is to recommend endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4).

3.2.4.2 Surgical therapy

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and since spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year, and by age eighteen months at the latest [67]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [78]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [65].

3.2.4.2.1 Palpable testes

Surgery for palpable testes includes orchidofunicolysis and orchidopexy, either via an inguinal or scrotal approach. The latter approach is mainly reserved for low-positioned, undescended testes, with the pros and cons of each method being weighed against each other [81].

3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [82]. Important steps include mobilisation of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum

testis. The patent processus vaginalis needs to be ligated proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy [83]. Any additional pathology has to be taken care of, such as removal of an appendix testis (hydatid of Morgagni). At this moment the size of the testis can be measured and the connection of the epididimis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. In case the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially, in order to provide a straight course to the scrotum, might be an option [84]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [85]. Lymph drainage of a testis that has undergone surgery for orchidopexy may have changed from high retroperitoneal drainage to iliac and inguinal drainage, which might become important in the event of later malignancy [86].

3.2.4.2.1.2 Scrotal orchidopexy

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency [87]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia [88]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates ranged from 88 to 100%, with rates of recurrence and post-operative testicular atrophy or hypotrophy < 1% [81].

3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [89]. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. An important step in surgery is a thorough re-examination once the boy is under general anaesthesia, since a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy, as described above. Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic laparoscopy [90]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [91]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [92]. If an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option avoiding the need for laparoscopy [93].

During laparoscopy for non-palpable testes, possible anatomical findings include spermatic vessels entering the inguinal canal (40%), an intra-abdominal (40%) or peeping (10%) testis, or blind-ending spermatic vessels confirming vanishing testis (10%) [94].

In case of a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, one may find an atrophic testis upon inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [95]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [96]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying > 2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels [97]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [98] (see Figure 2).

Proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels comprise the key features of the Fowler-Stephens procedure. Recently, a modification with low spermatic vessel ligation has gained popularity, allowing blood supply from the testicular artery to the deferential artery. An additional advantage is the position of the peritoneal incision, leading to a longer structure, to ease later scrotal placement [99]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [100]. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 60%, with success rates increasing up to 90% for the two-stage procedure [101]. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [102]. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy [103]. An alternative might be microsurgical auto-transplantation, which has a success rate of up to 90%. However, this approach requires skilled and experienced surgeons and is performed in a limited number of centres [104].

3.2.4.2.3 Complications of surgical therapy

Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic

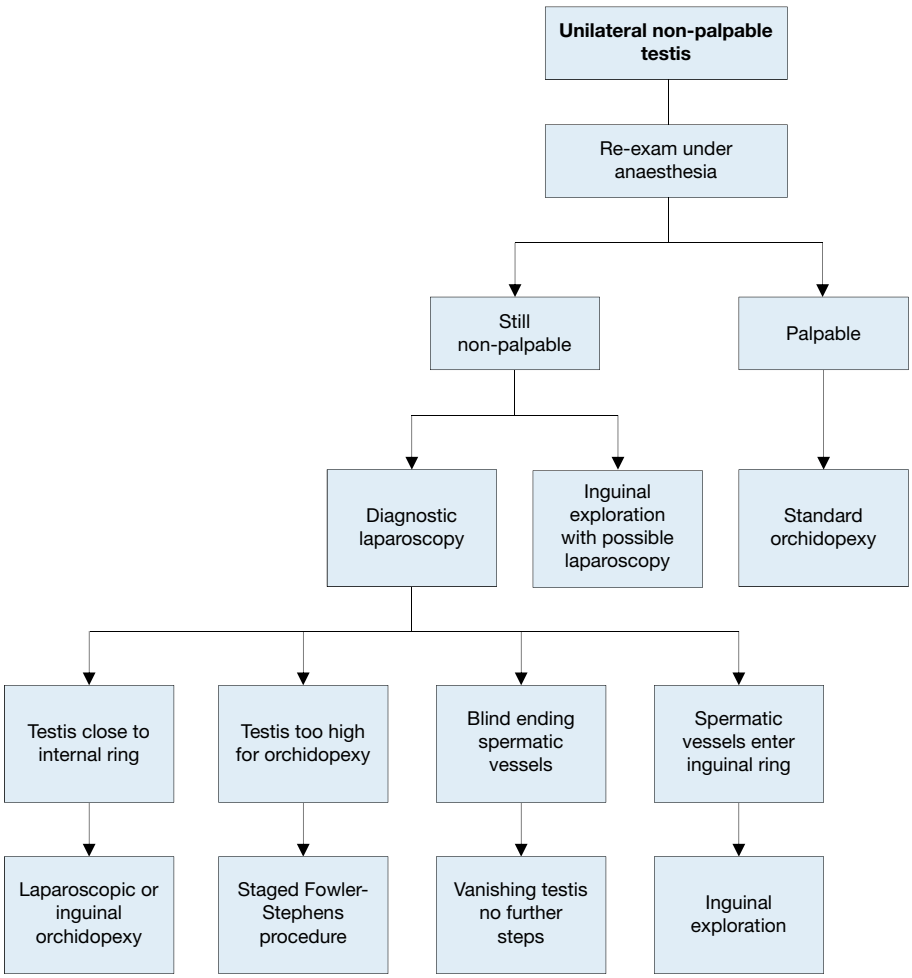
review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [105]. Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and haematoma.

3.2.4.2.4 Surgical therapy for undescended testes after puberty

A study on 51 men diagnosed with inguinal unilateral undescended testis and a normal contralateral one, with no history of any previous therapy, demonstrated a wide range of changes upon histological evaluation. Nearly half of the study population still had significant germ cell activity at different maturation levels. Importantly, the incidence of intratubular germ cell neoplasia was 2% [106].

The Panel consensus recommends orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position.

Figure 2: Treatment of unilateral non-palpable undescended testes



*3.2.5 **Undescended testes and fertility***

The association of undescended testes with compromised fertility [107] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [108], Leydig cell diminution and testicular fibrosis [109].

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes suffer both, lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual or population, whereas paternity reflects the actual potential of fatherhood [110]. The age at which surgical intervention for an undescended testis occurs seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at two years of age compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [111]. In addition, others demonstrated a relation between undescended testes and increased loss of germ cells and Leydig cells, which is also suggestive of prompt orchidopexy being a significant factor for fertility preservation [112]. Outcome studies for untreated bilateral undescended testes

revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [109].

In summary, early surgical correction of undescended testes is highly recommended before twelve months of age, and by eighteen months at the latest for preservation of fertility potential [66].

*3.2.6 **Undescended testes and malignancy***

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Screening and self-examination both during and after puberty is therefore recommended [113]. A Swedish study, with a cohort of almost 17,000 men (56 developed a testicular tumour) who were treated surgically for undescended testes and followed for 210,000 person-years, showed that management of undescended testes before the onset of puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before thirteen years of age was 2.2 compared to the Swedish general population; this increased to 5.4 for those treated after thirteen years of age [114].

A systematic review and meta-analysis of the literature have also concluded that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes [115].

*3.2.7 **Summary of evidence and recommendations for the management of undescended testes***

Summary of evidence	**LE**
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment.	2b

Recommendations	**LE**	**Strength rating**
Do not offer medical or surgical treatment for retractile testes but undertake close follow-up on a yearly basis until puberty.	2a	Strong
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	2b	Strong
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	1b	Strong
Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	1a	Strong
Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	2a	Weak
Offer endocrine treatment in case of bilateral undescended testes.	4	Weak
Inform the patient/caregivers about the increased risk of a later malignancy with an undescended testis in a post-pubertal boy or older and discuss removal in case of a contralateral normal testis in a scrotal position.	3	Weak

3.3 Hydrocele

*3.3.1 **Epidemiology, aetiology and pathophysiology***

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [116]. Pathogenesis of primary hydrocele is based on patency of the processus vaginalis in contrast with secondary hydrocele. Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia [117]. The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults [118]. If complete obliteration of the processus vaginalis occurs with patency of mid-portion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns [119]. Non-communicating hydroceles, based on an imbalance between the secretion and re-absorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation (due to ligation of

the lymphatics) or may appear as a recurrence after primary repair of a communicating or non-communicating hydrocele.

*3.3.2 **Diagnostic evaluation***

The classic description of a communicating hydrocele is that of a hydrocele that fluctuates in size, and is usually related to ambulation. It may be diagnosed by history-taking and physical investigation. Transillumination of the scrotum provides the diagnosis in the majority of cases, keeping in mind that fluid-filled intestine and some pre-pubertal tumours may transilluminate as well [120, 121]. If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually not tender. If there are any doubts about the character of an intrascrotal mass, scrotal US should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler US studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

*3.3.3 **Management***

In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months because of the tendency for spontaneous resolution [122] (LE: 2). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [122]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [123, 124] (LE: 2). Persistence of a simple scrotal hydrocele beyond twelve months of age may be an indication for surgical correction. There is no evidence that this type of hydrocele risks testicular damage. The natural history of hydrocele is poorly documented beyond the age of two years and according to a systematic review there is no good evidence to support current practice. Delaying surgery may reduce the number of procedures necessary without increasing morbidity [125].

The question of contralateral disease should be addressed by both history-taking and physical examination at the time of initial consultation (LE: 2) [126]. In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of six to nine months is recommended [127]. In the paediatric age group, the operation consists of ligation of the patent processus vaginalis or scrotal via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed [121, 123, 128, 129] (LE: 4). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3). Laparoscopic hernia repair with percutaneous ligation of the patent processes vaginalis is a minimally invasive alternative to open inguinal herniorrhaphy [130, 131]. Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [121, 123] (LE: 4). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

*3.3.4 **Summary of evidence and recommendations for the management of hydrocele***

Summary of evidence	**LE**
In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months due to the tendency for spontaneous resolution. Little risk is taken by initial observation as progression to hernia is rare.	2a
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.	4

Recommendations	**LE**	**Strength rating**
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	2a	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	Strong
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	4	Strong
Do not use sclerosing agents because of the risk for chemical peritonitis.	4	Strong

3.4 Acute scrotum

*3.4.1 **Epidemiology, aetiology and pathophysiology***

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis [132-137]. Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic

disease (e.g. Henoch-Schönlein purpura) [138-150]. Trauma can also be a cause of acute scrotum as it can relate to post-traumatic haematomas, testicular contusion, rupture dislocation or torsion [151-156]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in pre-pubertal overweight boys after exposure to cold [157].

In this chapter testicular torsion and epididymitis are discussed, while recurrent epididymitis is discussed in the chapter dealing with infections. Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testes occurs over a wider age range.

Epididymitis affects two age groups: less than one year and twelve to fifteen years [158, 159]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [160]. Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [161]. Most cases are extravaginal in contrast to the usual intravaginal torsion, which occurs during puberty.

*3.4.2 **Diagnostic evaluation***

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of invalidating pain in combination with vomiting is typical for torsion of the testis or appendix testes [162, 163].

In general, the duration of symptoms is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testes (62%) compared to epididymitis (31%) [134, 135, 159].

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas patients with testicular torsion are more likely to have a tender testicle, and patients with torsion of the appendix testis feel isolated tenderness of the superior pole of the testis [159].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [134]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [158, 163] (LE: 3). Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion.

Fever occurs more often in epididymitis (11-19%). The classical sign of a “blue dot” was found only in 10-23% of patients with torsion of the appendix testis [133, 134, 158, 164]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [132-137, 158, 164]. A positive urine culture is only found in a few patients with epididymitis [136, 158, 164, 165]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler US is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, a positive predictive value of 100% and negative predictive value of 97.5% [166-171] (LE: 3). The use of Doppler US may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in pre-pubertal patients [168, 172]. It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularisation [168]. A comparison with the other side should always be done.

Better results were reported using high-resolution US (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [168, 173] (LE: 2).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [174-177]. These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention [164].

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler US might suggest an erroneous diagnosis of epididymitis in children with torsion of the appendix testes [178]. Pre-pubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable [136, 158, 160].

*3.4.3 **Management***

3.4.3.1 Epididymitis

In pre-pubertal boys, the aetiology is usually unclear, with an underlying pathology in about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection [160, 179]. Epididymitis is usually self-limiting and with supportive

therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [180].

3.4.3.2 Testicular torsion

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination [181] (LE: 3;). Doppler US may be used for guidance [182]. Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including eleven patients who had reported pain relief after manual detorsion [181, 183].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4). During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [171].

3.4.3.3 Surgical treatment

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [184]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was > 360°. In cases of incomplete torsion (180-360°), with symptom duration up to twelve hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion > 360° and symptom duration > 24 hours [185].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [186]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion > 24 hours, semi-elective exploration is necessary [184, 185] (LE: 3). There is still controversy on whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration (> 24 hours). A study found that sperm quality was preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [187].

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation about the preferred type of fixation and suture material [188]. Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [189].

External cooling before exploration and multiple medical treatments seem effective in reducing ischaemia reperfusion injury and preserving the viability of the torsed and the contralateral testis [190-194]. It is good clinical practice to also perform fixation of the contralateral testis in prenatal and neonatal torsion, (although there is no literature to support this) and to remove an atrophied testicle.

3.4.4 ***Follow-up***

Patients require follow-up mainly for fertility issues and hormonal consequences. Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intraoperatively assessed as viable, and should be counselled accordingly [195].

3.4.4.1 Fertility

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20% [176]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [196].

A recent study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchidectomy [197].

3.4.4.2 Subfertility

Subfertility is found in 36-39% of patients after torsion. Semen analysis may be normal in only 5-50% in longterm follow-up [184]. Early surgical intervention (mean torsion time less than thirteen hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [186].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is caused by the cut-off of blood supply, but also by post-ischaemia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [184].

3.4.4.3 Androgen levels

Even though the levels of FSH, luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [187].

3.4.4.4 Unanswered questions

Although testicular torsion is a common problem the mechanism of neonatal and prenatal torsion is still not exactly known, as well as whether fixation of the contralateral testicle in these cases is really necessary. The influence of an atrophied testicle on fertility is also unclear.

Summary of evidence	**LE**
Diagnosis of testicular torsion is based on presentation and physical exam.	
Doppler US is an effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.	2a
Neonates with acute scrotum should be treated as surgical emergencies.	3

Recommendations	**LE**	**Strength rating**
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	3	Strong
In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	3	Weak
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	2a	Strong
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	3	Strong
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	3	Strong

3.5 Hypospadias

*3.5.1 **Epidemiology, aetiology and pathophysiology***

3.5.1.1 Epidemiology

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births (5.1-36.8) according to the recent EUROCAT registry-based study. This incidence was stable over the period of 2001 to 2010 [198, 199].
The mean worldwide prevalence of hypospadias according to an extended systematic literature review varies: Europe 19.9 (range: 1-464), North America 34.2 (6-129.8), South America 5.2 (2.8-110), Asia 0.6-69, Africa 5.9 (1.9-110), and Australia 17.1-34.8. There are conflicting data on the recent trends of prevalence – different trends in Europe and an increasing trend in the USA [200, 201].

*3.5.2 **Risk factors***

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [198, 199] (LE: 2b). Interactions between genetic and environmental factors may help explain non-replication in genetic studies of hypospadias. Single nucleotide polymorphisms seemed to influence hypospadias risk only in exposed cases [199, 202] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [202-205].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [202-205].
- Over the last 25 years, a significant increase in the incidence of hypospadias has been found.
- Endocrines disruptors are one component of a multi-factorial model for hypospadias.
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring, but their use after conception increased the risk of middle and posterior hypospadias [203-206] (LE: 2a).

*3.5.3 **Classification systems***

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most common type of hypospadias);

- intermediate-middle (penile);
- proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be different after skin release and should be reclassified accordingly. Anatomical location of the meatus may not always be enough to explain the severity and the complex nature of this pathology. Therefore, a simple classification related to severity of the problem, which considers penile length, glans size, shape, urethral plate quality and penile curvature is commonly used. In that classification there are two types: mild hypospadias (glanular or penile isolated hypospadias without associated chordee, micropenis or scrotal anomaly); severe hypospadias (penoscrotal, perineal hypospadias with associated chordee and scrotal anomalies).

*3.5.4 **Diagnostic evaluation***

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant which can only be seen after retraction of foreskin). Diagnosis includes a description of the local findings:

- position, shape and width of the orifice;
- presence of atretic urethra and division of corpus spongiosum;
- appearance of the preputial hood and scrotum;
- size of the penis;
- curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- cryptorchidism (in up to 10% of cases of hypospadias);
- open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, requires a complete genetic and endocrine work-up immediately after birth to exclude DSD, especially congenital adrenal hyperplasia. Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and associated anomalies of the upper- or lower urinary tract were not confirmed [207] (LE: 3).

*3.5.5 **Management***

3.5.5.1 Indication for reconstruction and therapeutic objectives

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision making.

The indications for surgery are:

- proximally located (ectopic) meatus causing ventrally deflected or spraying urinary stream;
- meatal stenosis;
- anterior curvature of the penis;
- cleft glans;
- rotated penis with abnormal cutaneous raphe;
- preputial hood;
- penoscrotal transposition;
- split scrotum.

Physical examination should check all anatomic components of the penis and evaluate the degree and nature of abnormality in each component. The examination should evaluate location of the meatus, the degree of proximal spongiosal hypoplasia, presence and degree of penile curvature, width and depth of the urethral plate, size of the glans, degree of ventral skin deficiency, availability of the foreskin and scrotal abnormalities like penoscrotal transposition and bifid scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the caregiver is crucial.

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected and a neo-urethra of an adequate size with opening on the glans formed with proper skin coverage of the penile shaft [208] (LE: 4) (Figure 3). The use of magnifying spectacles and fine synthetic absorbable suture materials (6.0-7.0) are required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Bipolar cautery is recommended. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome.

3.5.5.2 Pre-operative hormonal treatment

There is a lack of high-quality evidence to support that pre-operative hormonal treatment with androgen stimulation improves surgical outcomes. Yet, this treatment in the form of systemic testosterone, topical testosterone, and derivatives like dihydrotestosterone (DHT) and hCG are commonly being used to increase glans size pre-operatively to allow better tubularisation of the urethral plate and decrease the incidence of glans dehiscence. This treatment is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [206, 209, 210]. Studies have shown that it leads to significant enlargement of the glans and shaft of the penis (LE: 1b) [211, 212].

Moderate quality evidence from three randomised studies demonstrate significantly lower rates of urethracutaneous fistulae and reoperation rates in patients who received pre-operative hormonal treatment [213].

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child´s behaviour, increased genital pigmentation, appearance of pubic hair, penile skin irritation and redness, increased erections and peri-operative bleeding have been reported, but no persistent side effects related to hormonal stimulation have been reported in the literature. There is also no evidence about possible effects on bone maturation [210, 213, 214].

There are concerns regarding the negative impacts of testosterone on wound-healing and increased bleeding during surgery. Cessation of therapy is recommended one or two months prior to surgery to avoid adverse effects during or after surgery [215].

3.5.5.3 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [208, 216, 217] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [216] (LE: 2b). Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group according to a recent prospective controlled study [218] (LE: 2a).

3.5.5.4 Penile curvature

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [219]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [220, 221]. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty (modification of the Nesbit plication with or without elevation of the neurovascular bundle). In more severe curvature (> 45°), which is often combined with a short urethral plate requiring transection, ventral penile lengthening is recommended to prevent shortening of the penis. This consists of a ventral transverse incision of the tunica albuginea extending from the 3 to 9 o´clock position patched with tunica vaginalis flap or graft, or in several short ventral corporotomies without grafting (LE: 2b) [222]. After the ventral lengthening, a shorter dorsal midline plication is usually added.

According to a retrospective study, dorsal plication remained significantly associated with recurrent ventral curvature independently of the other factors. Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [223] (LE: 2b).

3.5.5.5 Urethral reconstruction

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [221]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [222] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended relaxing the plate by a midline incision and its subsequent tubularisation according to the Snodgrass-Orkiszewski TIP technique. This technique has become the treatment of choice in distal- and mid-penile hypospadias [224-227]. If the incision of the plate is deep, it is recommended to cover the raw surface with inner preputial (or buccal) inlay graft in primary and secondary repairs [228]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [229, 230] (LE: 2a).

For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [231] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [224-227, 232]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it

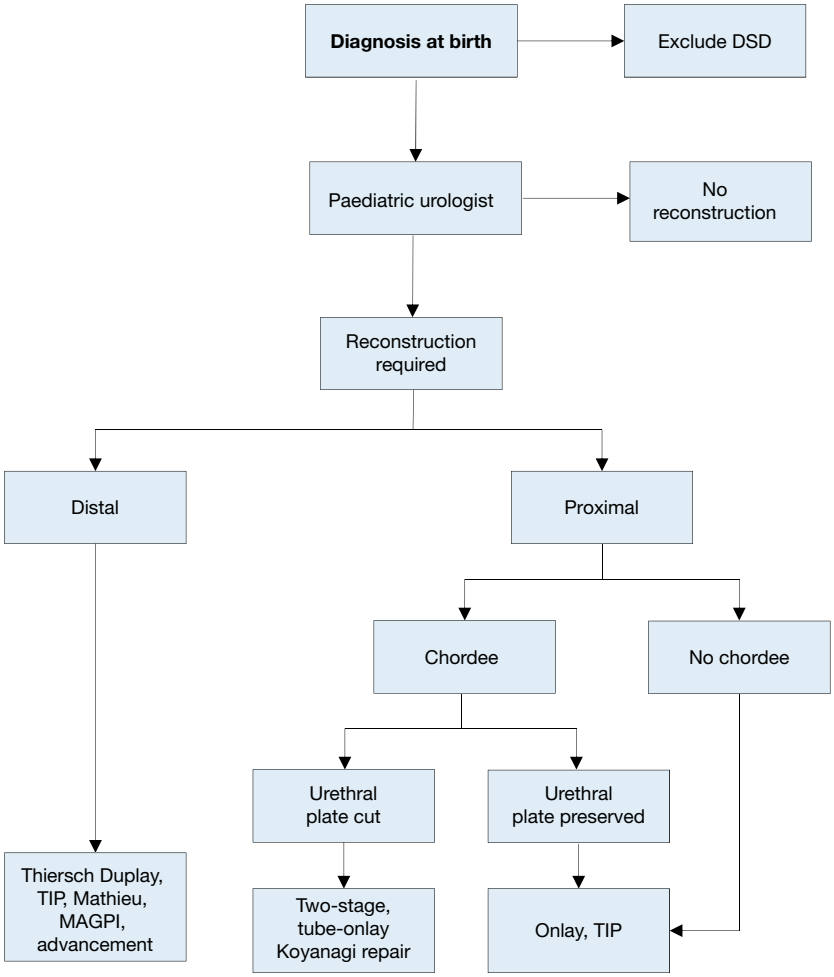
results in focal devascularisation of the neo-urethra with symptomatic stricture development [233] (LE: 2b). The onlay technique using a preputial island flap is a standard repair, preferred in proximal hypospadias, if a plate is unhealthy or too narrow [219]. An onlay preputial graft is an option for single-stage repair [234] (LE: 2b).

If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay flap on albuginea are used to prevent urethral stricture [235-237] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [238-241]. The two-stage procedure has become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results with variable long-term complication rates [230, 235, 242-246].

3.5.5.6 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual findings and needs of the patient.

Figure 3: Algorithm for the management of hypospadias



DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3.5.5.7 Penile reconstruction following formation of the neo-urethra

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum according to Cecil-Michalowski is used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. Preputial reconstruction carries a risk of specific complications but does not seem to increase the risk of urethroplasty complications [247]. In TIP repair, the use of a preputial dartos flap reduces the fistula rate [224, 225] (LE: 2b).

3.5.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (e.g. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [248, 249]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [249] (LE: 4). Post-operative prophylaxis after hypospadias repair is controversial [250, 251] (LE: 2b). There is no consensus on duration of stenting and dressing.

3.5.5.9 Outcome

Some studies have tried to determine risk factors for complications after hypospadias repair. An analysis of prospectively collected data found glans size (width < 14 mm), proximal meatal location and re-operation as independent risk factors for urethral complication [249, 252]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [249, 253] (LE: 3).

A meta-analysis of complication rates of TIP repair found lower complication rates and incidence of re-operations in primary distal repairs (in 4.5%) than in primary proximal repairs (in 12.2%) and in secondary repair (in 23.3%) [224-227, 231, 249]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [253, 254]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [232, 255, 256].

The complication rates of TIP and onlay repairs of primary severe hypospadias are similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [219]. The complication rates of single-stage Koyanagi and Hayashi modification repairs go up 61%, according to a comparative study [238, 249]. Staged buccal mucosa graft requires a redo grafting in 13% of patients, after the second stage more than one third of patients have complications, mostly with some degree of graft fibrosis [256, 257]. A recent long-term study on two-stage flap repair showed a complication rate of 68% [249], another study showed a re-operation rate of 28% [230, 249].

3.5.6 ***Follow-up***

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, diverticula, glanular dehiscence [258]. Up to half of complications requiring re-operation present after the first year post-operatively [259] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [260-263] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, but without significant association with lower urinary symptoms [264] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [265] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [266] (LE: 2a). The Pediatric Penile Perception Score (PPPS) is a reliable instrument to assess penile self-perception in children after hypospadias repair and for appraisal of the surgical result by caregivers and uninvolved urologists [267] (LE: 2a). Cosmetic results were judged more optimistically by surgeons as compared to caregivers using validated tools [268]. Current scoring systems have deficiencies in terms of patient reported outcomes, the long term outcomes and sexual function [269].

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not different from that of control groups [270, 271] (LE: 2a-b). Another long-term follow-up of men born with hypospadias revealed, in a controlled study, that these patients are less satisfied with penile cosmetic outcome according to all parameters of the PPPS; there was a difference in penile length (9.7 vs. 11.6 cm) and more patients had lower maximum urinary flow. More prominent results were found in proximal hypospadias vs. controls [249, 272].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [273]:

- patient perception of penile size does not differ greatly from the norm;
- patients approaching puberty have a more negative perception and are more critical about the cosmetic outcomes of surgery;
- patients report high levels of perception of deformity and social embarrassment.

The majority of identified instruments focused on post-operative cosmetic satisfaction, with only one instrument considering urinary function, and no instruments evaluating sexual function and psychosocial sequelae [274].

3.5.7 Summary of evidence and recommendations for the management of hypospadias

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6-18 (24) months.	3
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the new meatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
Androgen stimulation therapy results in increased penile length and glans circumference.	1b
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs. Higher and variable rates (between 28 and 68%) can occur in two-stage repairs.	3
Sexual functions are usually well preserved but patients report high levels of perception of deformity and social embarrassment.	2b

Recommendations	Strength rating
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option but the body of evidence to accentuate its harms and benefits is inadequate.	Weak
For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 3). Correct significant (> 30 degrees) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient´s satisfaction.	Strong
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

3.6 Congenital penile curvature

3.6.1 Epidemiology, aetiology and pathophysiology

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. The incidence at birth is 0.6% and congenital penile curvature is caused by asymmetry of the cavernous bodies and an orthotopic meatus [275] because of developmental arrest during embryogenesis [276]. On the other hand, the incidence of clinically significant congenital penile curvature is much lower, because the extent of the curvature and its associated sexual dysfunction varies widely [277]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [278]. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [279]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex.

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood (LE: 4). Minor penile curvature may be the result of ventral penile skin deficiency only and should be distinguished from corporal anomalies. For penile curvature associated with hypospadias or epispadias refer to the relevant chapters.

3.6.2 Diagnostic evaluation

Penile curvature is frequently not documented until later in childhood since the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [280]. Besides exact history taking to exclude any possibility of acquired penile curvature (e.g. post-traumatic) a thorough clinical examination is mandatory. In addition, photo documentation of the erect penis clearly showing the curvature from different angles serves as a pre-requisite in preoperative evaluation [281]. The exact degree of curvature is generally determined at the time of surgery using an artificial erection test.

3.6.3 Management

The treatment is surgical, starting with an artificial erection to determine the degree of curvature and to check symmetry after the repair [282]. The ultimate goal of any surgical method used to correct the curvature is to achieve corpora of similar size. Various procedures are in use ranging from simple de-gloving and plication procedures, to corporal rotation, use of free dermal or tunica vaginalis grafts, to complete penile disassembly techniques [283, 284]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [285] to plication procedures [286] were able to demonstrate that while there is a decreased risk of complications and loss of sensation, it remains unclear whether plication techniques can lead to increased risk of recurrence [287]. Altogether these methods include the risk of post-operative shortening of the penis with an average loss of 2.5 cm in stretched penile length depending on the pre-operative degree of curvature and the type of repair used [288, 289].

Recently the non-corporotomy technique has been introduced with promising results enabling correction of any degree of ventral curvature with neither shortening of the penis nor the risk of post-operative erectile dysfunction [290].

3.6.4 Summary of evidence and recommendations for the management of congenital penile curvature

Summary of evidence	LE
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	LE	Strength rating
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	1a	Strong
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	1b	Strong
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	Weak
At the beginning as well as at the end of surgery, perform artificial erection tests.	2a	Strong

3.7 Varicocele in children and adolescents

3.7.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under ten years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [291-293].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents [294, 295]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a meta-analysis [296] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [297] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [298]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [299-302] (LE: 1).

3.7.2 ***Classification systems***

Varicocele is classified into 3 grades [303]:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance).

3.7.3 ***Diagnostic evaluation***

Varicocele is mostly asymptomatic, rarely causing pain. It may be noticed by the patient or caregivers, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position [304]. Venous reflux detected on US only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by US examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [305] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal US should be routinely added in pre-pubertal boys and in isolated right varicocele (LE: 4).

In order to assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [301, 306].

3.7.4 ***Management***

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [307] (LE: 4). The recommended indication criteria for varicocelectomy in children and adolescents are [292]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [307].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [308]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [309-312].

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [309, 311]. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test [297, 309, 310, 313] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [309, 311, 314, 315]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [316, 317]. In suprainguinal approach, an artery sparing varicocelectomy may not offer any advantage in regards to catch-up growth and is associated with a higher incidence of recurrent varicocele [318, 319].

Angiographic occlusion of the internal spermatic veins also meets the requirements of lymphatic sparing repair. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [320, 321]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique [292, 320, 321] (LE: 2).

There is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration - based on current available RCTs. The ultimate effects on fertility and paternity rates are not known [322].

Microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception post-operatively. Patients with varicocele who underwent microsurgical varicocele repair had increased sperm parameters and 3.63 times greater odds of paternity than controls who did not undergo varicocele surgery [323].

The Panel recently conducted a systematic review (SR) and meta-analysis regarding the treatment of varicocele in children and adolescents [324]. Of 1,550 articles identified, 98 articles including 16,130 patients were eligible for inclusion (12 RCTs, 47 NRSs and 39 case series). The key findings are summarised in the following paragraphs:

The meta-analysis of the twelve RCTs revealed that varicocele treatment improved testicular volume (mean difference 1.52 ml, 95% CI 0.73-2.31) and increased total sperm concentration (mean difference 25.54, 95% CI 12.84-38.25) when compared with observation. Lymphatic sparing surgery significantly decreased hydrocele rates (p=0.02) and the OR was 0.08 (95% CI 0.01, 0.67). Due to the lack of RCTs, it was not possible to identify a surgical technique as being superior to the others. It remains unclear whether open surgery or laparoscopy is more successful for varicocele treatment (OR ranged from 0,13 to 2,84).

The success rates of the treatment (disappearance of varicocele) were between 85.1% and 100% whereas the complication rates were between 0% and 29% in the included studies. The most common complication reported was hydrocele. Resolution of pain after treatment was more than 90% in the reported series.

In conclusion, moderate evidence exists on the benefits of varicocele treatment in children and adolescents in terms of testicular volume and sperm concentration. Current evidence does not demonstrate superiority of any of the surgical/interventional techniques regarding treatment success. Lymphatic sparing surgery significantly decreases hydrocele formation. Long-term outcomes, including paternity and fertility, still remain unknown.

*3.7.5 **Summary of evidence and recommendations for the management of varicocele***

Summary of evidence	**LE**
Varicocele becomes more frequent at the onset of puberty and is found in 14-20% of adolescents. Fertility problems are expected in up to 20% of adolescents with a varicocele.	
Pubertal patients with a left grade II and III varicocele have the left testis smaller in up to 70% of cases; in late adolescence the contralateral right testis also becomes smaller.	1b
After adolescent varicocelectomy, left testis catch-up growth and improvement in sperm parameters has been demonstrated.	1a
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.	1b
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy.	1b
Lymphatic sparing surgery significantly decrease hydrocele rates.	1a

Recommendations	LE	Strength rating
Examine varicocele in the standing position and classify into three grades.	4	Strong
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.		Strong
In all pre-pubertal boys with a varicocele and in all isolated right varicoceles perform standard renal ultrasound to exclude a retroperitonal mass.		Strong
Inform caregivers and patients and offer surgery for: • varicocele associated with a persistent small testis (size difference of > 2 mL or 20%); • varicocele associated with additional testicular condition affecting fertility (cryptorchidism, history of torsion, trauma); • varicocele associated with pathological sperm quality (in older adolescents); • symptomatic varicocele.	2	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	2	Strong
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	1	Strong

3.8 Urinary tract infections in children

*3.8.1 **Epidemiology, aetiology and pathophysiology***

Urinary tract infections represent the most common bacterial infection in children [325-327]. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections not caused by *Escherichia coli* are more frequent; and there is a higher risk of urosepsis [328, 329].

The incidence varies depending on age and sex. One meta-analysis showed that in the first three months of life UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys, and 20.1% (CI: 16.8-23.4) of uncircumcised boys, who presented with fever [328]. In the first year of life, UTIs are more common in boys (3.7%) than girls (2%). Later, the incidence of UTIs changes to ~3% in pre-pubertal girls and 1% in pre-pubertal boys [328-330].

E. coli is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial infections. In the latter, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Enterococcus spp.*, *Pseudomonas spp.* and *Candida spp.* are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [331], however, it is less frequent in community-acquired than in nosocomial UTI [331, 332].

*3.8.2 **Classification systems***

There are five widely used classification systems according to; site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

3.8.2.1 Classification according to site

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder mucosa with general signs and symptoms including infection, dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (> 38°C), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

3.8.2.2 Classification according to episode

The first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage [333]. Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract (inadequate therapy, inadequate antimicrobial urinary concentration [poor renal concentration/ gastrointestinal malabsorption], and infection involving multiple organisms with differing antimicrobial susceptibilities).

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae, urachal cyst, urethral diverticulum, peri-urethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The

same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

In re-infection, each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

3.8.2.3 Classification according to severity

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI. In severe UTI, infection is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

3.8.2.4 Classification according to symptoms

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response (no leukocyturia, no symptoms). Asymptomatic UTI includes leukocyturia but no other symptoms.

Symptomatic UTI, includes irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

3.8.2.5 Classification according to complicating factors

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [334].

All neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract, are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from lower urinary tract dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux (VUR). Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities [335]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

3.8.3 ***Diagnostic evaluation***

3.8.3.1 Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or post-natal US screening); prior operation; family history; and, whether there is constipation or presence of lower urinary tract symptoms (LUTS).

3.8.3.2 Clinical signs and symptoms

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability and without fever). Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [336, 337]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are more than two years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

3.8.3.3 Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

3.8.3.4 Urine sampling, analysis and culture

Urine sampling has to be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy, it can be challenging and depends on the mode of urine sampling [338].

3.8.3.4.1 Urine sampling

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever. In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine:

(1) Plastic bag attached to the cleaned genitalia: This technique is most often used in daily practice. It is helpful when the culture results are negative. Also, if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture [339]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [340, 341].

(2) Clean-catch urine collection: The infant is placed in the lap of a caregiver or member of the nursing staff, who holds a sterile foil bowl underneath the infant's genitalia. The infant is offered oral fluids and urine collection is awaited [342]. This is time consuming and requires proper instruction of the caregivers. There seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [342, 343]; however, the contamination rate is higher compared to SPA [344].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, at a higher contamination rate [345]. In a prospective study using bladder catheterisation in febrile children aged < 36 months, contamination was defined by multiple pathogens, nonpathogens, or colony counts < 10,000 cfu/mL. True UTI was found in 10% of children and 14% of the cultures were contaminated. Univariate analysis of potential predictors identified age less than six months, difficult catheterisation, and uncircumcised boys. In children less than six months and uncircumcised boys a new, sterile catheter with each repeated attempt at catheterisation may lead to less contamination [346], otherwise SPA should be the method of choice.

(4) Suprapubic bladder aspiration: This is the most sensitive method to obtain an uncontaminated urine sample in this age group [347, 348]. Using US to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to 97% [347, 348]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [349]. However, bladder puncture causes more pain than catheterisation in infants less than two months old [350].

In older, toilet-trained children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the peri-urethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [351].

If the clinical situation necessitates, and for differential diagnosis of sepsis, it is most appropriate to obtain an adequate urine sample by catheterisation or SPA [343]. In infants, a bag can only be used if the dipstick is negative, otherwise the urine should be obtained through catheterisation or SPA. This is also recommended in children, who are severely ill and a UTI needs to be excluded or confirmed. Blood sampling is dependent on the clinical situation.

3.8.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately four hours in the bladder [343, 352]. However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) [343, 353].

Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [343]*

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, white blood cells	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leucocyte esterase test, nitrite test or microscopy positive	99.8 (99-100)	70 (60-92)

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(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/µL) [349]. In uncentrifuged urine, > 10 WBC/µL has been demonstrated to be sensitive for UTI [354] and this could perform well in clinical situations [355]. However, this is rarely done in an outpatient setting.

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [356]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [343].

3.8.3.4.3 Urine culture

After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

It is unclear what represents a significant UTI. In severe UTI, > 10^5 cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [329]. The classical definition of > 10^5 cfu/mL of voided urine is still used to define a significant UTI [357, 358]. The American Academy of Pediatric Guidelines on Urinary Tract Infection suggest that the diagnosis should be based on the presence of both pyuria and at least 10^5 cfu/mL. However, some studies have shown that, in voided specimens, < 10^4 organisms may indicate a significant UTI [359, 360]. If urine is obtained by catheterisation, 10^3 - 10^5 cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

Table 2: Criteria for UTI in children (adapted from the EAU Guidelines on Urological Infections [361])

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	> 10^3 - 10^5 cfu/mL	> 10^4 cfu/mL with symptoms > 10^5 cfu/mL without symptoms

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

3.8.3.5 Imaging

3.8.3.5.1 Ultrasound

Renal and bladder US within 24 hours is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in 15% of cases, and 1-2% have abnormalities that require prompt action (e.g. additional evaluation, referral, or surgery) [339]. In other studies, renal US revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed VUR in 27% of cases [328]. Dilating VUR is missed by US in around one third of cases [362]. Post-void residual (PVR) urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated PVR urine volume predicts recurrence of UTIs in toilet-trained children [363].

3.8.3.5.2 Radionuclide scanning

Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [364] and future renal scarring. In the acute phase of a febrile UTI (up to four to six weeks), DMSA-scan can demonstrate pyelonephritis by perfusion defects. Renal scars can be

detected after three to six months [365]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning [366]. The average effective radiation dose of a single DMSA scan was 2.84 (1-12) mSv in one study [367]. See also Chapter 3.13 on VUR.

3.8.3.5.3 Voiding cystourethrography

The gold standard to exclude or confirm VUR is VCUG. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls depending on sex, age and clinical presentation (see Figure 4 and Table 4) (see also Chapter 3.13). The timing of VCUG does not influence the presence or severity of VUR [368, 369]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [370]. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after UTI (see Chapter 3.13).

3.8.3.6 Bladder and bowel dysfunction

Bladder and bowel dysfunction (BBD) are risk factors for which each child with UTI should be screened upon presentation. Normalisation of micturition disorders or bladder over-activity is important to lower the rate of UTI recurrence. If there are signs of BBD at infection-free intervals, further diagnosis and effective treatment are strongly recommended [371-374]. Treatment of constipation leads to a decrease in UTI recurrence [375-377]. Therefore, exclusion of BBD is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of BBD.

3.8.4 ***Management***

3.8.4.1 Administration route

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged less than two months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can occur in these cases [378, 379].

Parental combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or, respectively, a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporins against common uropathogens; *enterococcus* gap is closed with ampicillin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective [335, 380, 381].

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity-testing of the isolated uropathogen [343]. Not all available antibiotics are approved by the national health authorities, especially in infancy. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI [380, 382, 383]. Delaying treatment in children with a febrile UTI for more than 48-72 hours increases the risk of renal scars [384, 385].

3.8.4.2 Duration of therapy

Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (one to three days) are inferior to those of seven to fourteen-day courses [343]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [331, 335]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [386]. Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual two to four days intravenous therapy followed by oral treatment [381, 387-389]. Similar data have been shown for amoxicillin-clavulanate [390]. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised [391].

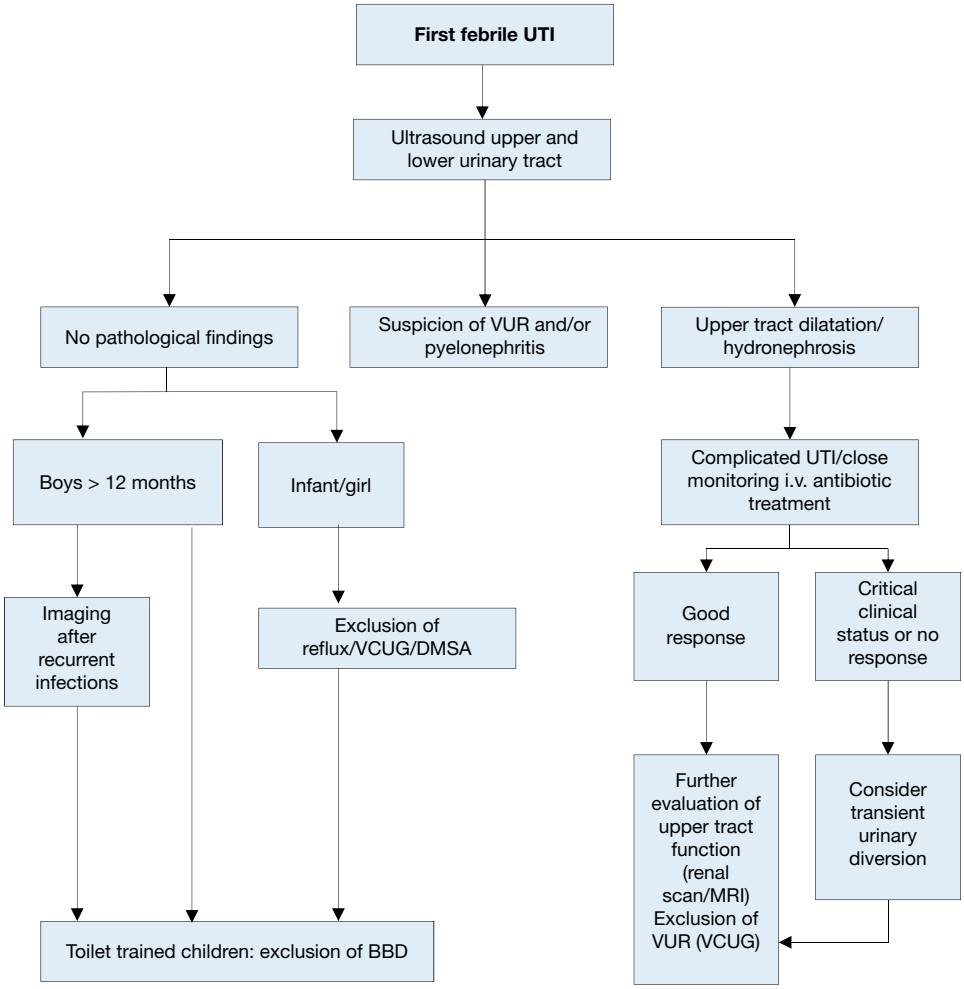
In complicated UTI, uropathogens other than *E. coli*, such as *Proteus mirabilis*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *enterococci* and *staphylococci* are more often the causative pathogens [335].

Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubiccystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy. Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending

infection due to pre-existing uropathy, especially vesicorenal reflux or urinary obstruction (mega-ureter).

Prolonged intravenous antibiotic treatment is sufficient in most cases [392], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [393].

Figure 4: Algorithm for disease management of first febrile UTI



BBD = Bladder Bowel Dysfunction; DMSA = technetium^{99}-labelled dimercaptosuccinic acid; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

3.8.4.3 Antimicrobial agents

There is a great difference in the prevalence of antibiotic resistance of uropathogenic *E. coli* in different countries, with an alarmingly high resistance in Iran and Vietnam [394]. There are upcoming reports of UTIs caused by extended spectrum ß-lactamase-producing *enterobacteriaceae* (ESBL) in children. In one study from Turkey, 49% of the children less than one year of age and 38% of those more than one year of age had ESBL producing bacteria that were resistant to trimethoprim/sulfamethoxazole in 83%, to nitrofurantoin in 18%, to quinolones in 47%, and to aminoglycosides in 40% [395]. Fortunately, the outcome appears to be the same as for children with non-ESBL-producing bacteria, despite the fact that initial intravenous empirical antibiotic therapy was considered inappropriate in one study [396].

Table 3: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children*

Chemotherapeutics	Daily dosage	Application	Comments
Parenteral cephalosporins			
Group 3a, e.g. cefotaxime	100-200 mg/kg *(Adolesc.: 3-6 g)*	i.v. in 2-3 D	
Group 3b, e.g. ceftazidime	100-150 mg/kg *(Adolesc.: 2-6 g)*	i.v. in 2-3 D	
Ceftriaxone	75 mg/kg	i.v. in 1 D	
Oral cephalosporins			
Group 3, e.g. ceftibuten	9 mg/kg *(Adolesc.: 0.4 g)*	p.o. in 1-2 D p.o. in 1-2 D	
Group 3, e.g. cefixime	8-12 mg/kg *(Adolesc.: 0.4 g)*	p.o. in 1-2 D	
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kg *(Adolesc.: 0.4 g)*	p.o. in 2 D	
Group 2, e.g. cefuroximaxetil	20-30 mg/kg *(Adolesc.: 0.5-1 g)*	p.o. in 3 D	
Group 1, e.g. cefaclor	50 -100 mg/kg *(Adolesc.: 1.5-4 g)*	p.o. in 2-3 D	
Trimethoprim or Trimethoprim/sulfamethoxazole	5-6 mg/kg 5-6 mg/kg (TMP-Anteil) *(Adolesc.: 320 mg)*	p.o. in 2 D p.o. in 2 D	
Ampicillin Amoxicillin Amoxicillin/clavulanic acid (parenteral) Amoxicillin/clavulanic acid (oral) Piperacillin	100-200 mg/kg *(Adolesc.: 3-6 g)* 50-100 mg/kg *(Adolesc.: 1.5-6 g)* 60-100 mg/kg *(Adolesc.: 3.6-6.6 g)* 45-60 mg/kg *(Amoxicillinfraction)* *(Adolesc.: 1500 + 375 mg)* 300 mg/kg	i.v. in 3 D i.v. in 3-4 D p.o. in 2-3 D p.o. in 2-3 D i.v. in 3 D i.v. in 3 D p.o. in 3 D p.o.in 3 D i.v. in 3-4 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Tobramycin Gentamicin	5 mg/kg *(Adolesc.: 3-5 mg/kg, max. 0.4 g)* 5 mg/kg *(Adolesc.: 3-5 mg/kg, max. 0.4g)*	i.v. in 1 D i.v. in 1 D	Drug monitoring
Ciprofloxacin	Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally) Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	i.v. in 3 D p.o. in 2 D	Approved in most European countries as second- or third-line medication for complicated UTIs, “reserve-antibiotic”!
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

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Dosage for adolescents in paracentesis, if differing. 1 Infants 2 D, children 1-12 ys. 3 D.
i.v. = intravenous; p.o. = by mouth.

Table 4: Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection*

Diagnosis	Proposal	Application	Duration of therapy	LE
Pyelonephritis during the first 0-6 months of life	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	3-7 D parenterally, for at least 2 D after defervescence, then oral therapy[2] In newborns: parenteral therapy for 7-14 D, then oral therapy[2]	10 (-14) D Newborns 14-21 D	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3[2]	Orally (initially parenterally, if necessary)	(7-)10 D	1
Complicated pyelonephritis/ urosepsis (all ages)	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	7 D parenterally, then oral therapy[2]	10-14 D	4

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[1] after receipt of microbiological findings (pathogen, resistance) adaptation of therapy.

[2] i.v.: e.g. cefotaxime; orally: e.g. cefpodoxime proxetil, ceftibuten, cefixime.

Table 5: Frequently used antibacterial agents used for the treatment of cystitis and cystourethritis (Dosages for children up to twelve years of age)*

Chemotherapeutics	Daily dosage	Application
Oral cephalosporins		
Group 1, e.g. cefaclor	50 (-100) mg/kgbw	p.o. in 2-3 D
Group 1, e.g. cefalexin	50 mg/kgbw	p.o. in 3-4 D
Group 2, e.g. cefuroximaxetil	20-30 mg/kgbw	p.o. in 2 D
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kgbw	p.o. in 2 D
Group 3, e.g. ceftibuten	9 mg/kgbw	p.o. in 1 D
Trimethoprim	5-6 mg/kgbw	p.o. in 2 D
Trimethoprim/sulfamethoxazole	5-6 mg/kgbw (TMP-fraction)	p.o. in 3 D
Amoxicillin/clavulanic acid	37.5-75 mg/kgbw (Amoxicillin-fraction)	p.o. in 3 D
Nitrofurantoin	3-5 mg/kgbw	p.o. in 2 D

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3.8.4.4 Chemoprophylaxis

Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage. Some recently published prospective randomised studies do not support the efficacy of antibacterial prophylaxis [398-401]. However, two prospective randomised trails as well as one recent meta-analysis demonstrated a significant risk reduction of developing another UTI by using continuous antibiotic prophylaxis [387, 402, 403] (see also Chapter 3.13 on VUR).

Cranberry juice as well as probiotics may also prevent recurrence of UTI as demonstrated by RCTs [404-406]. A Cochrane review could not rule out some benefit of using probiotics [407].

Table 6: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	1	Until six weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under two months of age
Nitrofurantoin**	1	Until three months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	***
Cefuroximaxetil	5	***

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*** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.*

**** In Germany, ceftibuten is not approved for infants < 3 months old.*

3.8.4.5 Monitoring of UTI

With successful treatment, urine usually becomes sterile after 24 hours, and leukocyturia normally disappears within three to four days. Normalisation of body temperature can be expected within 24-48 hours after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate US examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation with first febrile UTI [408]. In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

3.8.5 Summary of evidence and recommendations for the management of UTI in children

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary and is related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs.	2b
The classical definition of > 10^5 cfu/mL in voided urine is still used to define a significant UTI.	3
Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage. If it is positive, reflux may be present.	2a

Recommendations	LE	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any child with febrile and/or recurrent UTI and do not delay diagnosis and treatment of bladder-bowel-dysfunction.	3	Strong
The most effective way to collect an uncontaminated urine sample in an infant is through suprapubic bladder aspiration; bladder catheterisation is an alternative with a higher contamination rate.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results. Clean catch urine is an acceptable technique for toilet-trained children.	2a	Strong
Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation. Using flow imaging analysis, the numbers of white blood cells (WBCs), squamous epithelial cells and red cells correlate well with manual methods.	2a	Weak
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; complicated pyelonephritis.	2a	Strong
Treat UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Weak
Treat complicated UTI with broad-spectrum antibiotics (parenteral).	1b	Weak
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract.	3	Strong
In all infants, exclude vesicoureteral reflux (VUR) after the first episode of febrile UTI, using voiding cystourethography (VCUG) or a dimercaptosuccinic acid (DMSA) scan first (in case of a positive DMSA-scan, follow-up with VCUG). In boys more than one year of age, exclude VUR after the second febrile UTI.	2a	Strong

3.9 Day-time lower urinary tract conditions

*3.9.1 **Terminology, classification, epidemiology and pathophysiology***

Urinary incontinence in children may be caused by congenital anatomical or neurologic abnormalities such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence, and they are referred as having functional bladder problems. The most recent International Children's Continence Society (ICCS) document suggests using the term day-time lower urinary tract (LUT) conditions to group together all functional bladder problems in children.

Normal storage and emptying of the bladder at a socially accepted place and time is mostly achieved by age three to four. Children with LUT conditions would present with failure to achieve continence (being still wet after the age of four), urgency, weak stream, hesitancy, frequency and accompanied UTIs. Isolated night-time wetting without any day-time symptoms is known as 'enuresis' and considered as a different entity (see chapter 3.10) [409].

As different studies have used varying definitions and criteria, it is difficult to give reliable percentages regarding the incidence of this problem. Reported prevalence ranges widely from 1% to 20% [410-418]. Due to increasing awareness and better access to specialised health care, the prevalence seems to be increasing [419, 420].

Lower urinary tract conditions in children may be due to disturbances of the filling phase, the voiding phase or a combination of both in varying severity. Mainly the conditions are divided into either overactive bladder (OAB) or dysfunctional voiding. They can, of course, coincide and one may even be causative of the other. Dysfunctional bowel emptying may also be part of the clinical problems and bladder bowel dysfunction (BBD) is the term used to cover concomitant bladder and bowel disturbances.

Lower urinary tract conditions are considered to be the result of incomplete or delayed maturation of the bladder sphincter complex. The pons is considered to be responsible for detrusor sphincter co-ordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition. Therefore overactivity would be the result of delayed maturation of cortical control, while dysfunctional voiding would be the result of non-maturation of the co-ordination. Detrusor overactivity should not be considered as

a sole bladder based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel and even mood and behaviour [421].

A link between LUT and behavioural disorders such as ADHD (attention deficit/ hyperactivity disorder) has also been shown [422-424].

3.9.1.1 Filling-phase (storage) dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB, or underactive, as in underactive bladder (UAB). Overactivity of the bladder is the most common problem, seen mostly around five to seven years of age. This may lead to disturbances characterised by urgency, frequency and at times urgency incontinence. Some children habitually postpone micturition leading to voiding postponement. Therefore, holding manoeuvres such as leg crossing and squatting can often be seen in this group. Recurrent UTIs are common and high-pressure state of the bladder can be a cause of VUR. Constipation can be an additional aetiological factor, which needs to be assessed. In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals. Urinary tract infections, straining to void, constipation and incontinence is common. Incontinence often occurs when the bladder is over-distended in the form of overflow incontinence.

3.9.1.2 Voiding-phase (emptying) dysfunctions

In voiding-phase (emptying), incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles results in staccato voiding pattern (continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in fractions). The general term for this condition is dysfunctional voiding and is associated with elevated bladder pressures and PVRs. Symptoms will vary depending on the severity of inco-ordination between bladder and the sphincter. Staccato voiding is in less severe forms and interrupted voiding and straining is in more severe forms. Children with dysfunctional voiding are also prone to constipation and recurrent UTIs [425].

In incomplete emptying, high voiding pressures generated by bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only UTIs but also VUR. It is been shown that LUTD is more significant for the occurrence of UTI than VUR itself [426]. In the majority of children with dysfunctional voiding the recurrent infections disappear following successful treatment, which confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections. Spontaneous resolution of VUR may also be seen after successful treatment of dysfunctional voiding.

*3.9.2 **Diagnostic evaluation***

The evaluation of LUT conditions includes medical and voiding history (bladder diaries and structured questionnaires), a physical examination, a urinalysis, and uroflowmetry with PVR. The upper urinary tract (UUT) needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles during voiding. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [424, 427-430].

In addition to a comprehensive medical history a detailed voiding diary provides documentation of voiding and defecation habits, frequency of micturition, voided volumes, night-time urine output, number and timing of incontinence episodes, and fluid intake. Voiding diary should at least be done for two days, although longer observation periods are preferred. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the paediatric age group, where the history is taken from both the caregivers and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the caregivers and should be specifically requested, using the questionnaire as a checklist. Some symptom scorings have been developed and validated [431, 432]. Although the reliability of questionnaires are limited they are practical in a clinical setting to check the presence of symptoms and have also been shown to be reliable to monitor the response to treatment. History taking should also include assessment of bowel function. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [433, 434].

Urinalysis and urinary culture are essential to evaluate for UTI. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms. During clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with PVR evaluates the emptying ability, while an UUT US screens for (secondary) anatomical changes. A flow rate which reaches its maximum quickly and levels off ('tower shape') may be indicative of OAB whereas interrupted or staccato voiding patterns may be seen in dysfunctional voiding. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not always be representative of the clinical situation and muliple uroflowmetry tests, which all give a similar result, are more reliable. Uroflowmetry examination should be done when there is desire to empty the bladder and the voided volume should at least be 50% of the age-expected capacity ((age in years) + 1] x 30 mL for the children. While testing the child in a clinical environment, the impact of stress and mood changes on bladder function should also be taken into account [435, 436].

In the case of treatment failure re-evaluation is warranted and (video)-urodynamic (VUD) studies and neurological evaluation may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using VUD. In these cases, structured psychological interviews to assess social stress should be added [437] (LE: 1b).

Video-urodynamics may also be used as initial investigational tool in patients with suspicion of reflux. In this case reflux may be observed along with bladder dynamics. In the case of anatomical problems, such as posterior urethral valve (PUV) problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

*3.9.3 **Management***

The treatment of LUTD involves a multimodal approach, involving strategies such as behavioural modification, and anticholinergic medication along with underlying and potentially complicating conditions such as constipation and UTIs.

Behavioural modification, mostly referred to as urotherapy, is a term which covers all non-pharmacological and non-surgical treatment modalities. It includes standardisation of fluid intake, bowel management; timed voiding and basic relaxed voiding education. The child and family are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are treated. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Strategies to achieve these goals include:

1. Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
2. Instructions about what to do about the problem:
    - Regular voiding habits, sound voiding posture, pelvic floor awareness and training to relax pelvic floor and avoiding holding manoeuvres.
    - Lifestyle advice, regarding fluid intake, prevention of constipation, etc.
    - Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
    - Support and encouragement via regular follow-up by the caregiver.

Recurrent UTIs and constipation should also be treated and prevented during the treatment period. In case of combined BBD it is advised to treat the bowel dysfunction first [419] as LUTS may disappear after successful management of bowel dysfunction.

Addition of other strategies, as below, may be needed:

- Pelvic floor muscle awareness practices with repeated sessions of biofeedback visualisation of uroflow curves and/or pelvic floor activity and relaxation.
- Clean intermittent self-catheterisation for large PVR volumes of urine.
- Antimuscarinic drug therapy if detrusor overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, α-blocker drugs may be introduced.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is

poorly described. A high success rate has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled [438].

3.9.3.1 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neuromodulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [371, 439-444].

A systematic review reports that biofeedback is an effective, non-invasive method of treating dysfunctional voiding, and approximately 80% of children benefited from this treatment. However, most reports were of low level of evidence and studies of more solid design such as RCTs should be conducted [445].

A more recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin and bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard urotherapy [437] (LE: 1b).

Two RCTs on underactive bladder without neurophatic disease have recently been published. Transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [446, 447]. In some cases, pharmacotherapy may be added. Some studies on orthosympathicomimetics have been published with a low level of evidence [448].

Overactive bladder is common in the paediatric population. Although a stepwise approach starting with behavioural therapy is advised, antimuscarinic agents remain the mainstay of medical treatment for OAB. Oxybutynin is the most commonly used antimuscarinic in the paediatric population. The response to antimuscarinics varies and many children experience serious side effects. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, to date, most of them are off-label depending on age and national regulations. A few RCTs have been published, one on tolterodine showed safety but not efficacy [449], while another on propiverine showed both safety and efficacy [450] (LE:1). The recent study on solifenacin showed its efficacy with side effects like constipation and electrocardiogram changes [451].

The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α-blocking agents are used occasionally, an RCT showed no benefit [452]. Botulinum toxin injection seems promising, but can only be used off-label [453].

A meta-analysis reports that neuromodulation therapy may lead to better partial improvement of non-neurogenic OAB; however, it may not render a definitive complete response. Office-based neuromodulation seems more efficacious than self-administered neuromodulation [454].

These new treatment modalities can only be recommended for standard therapy-resistant cases [455]. Despite early successful treatment, there is evidence that there is a high recurrence rate of symptoms in the long term which necessitates long-term follow-up [456]. In addition, many patients may present later in adulthood with different forms of LUTD [457].

*3.9.4 **Summary of evidence and recommendations for the management of day-time lower urinary tract conditions***

Summary of evidence	**LE**
The term ‘bladder bowel dysfunction’ should be used rather than ‘dysfunctional elimination syndrome and voiding dysfunction’.	4
Day-time LUTS has a high prevalence (1% to 20%).	2

Recommendations	LE	Strength rating
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment.	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy in overactive bladder.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centres.	3	Weak

3.10 Monosymptomatic nocturnal enuresis - bedwetting

3.10.1 Epidemiology, aetiology and pathophysiology

Monosymptomatic nocturnal enuresis, also known as bedwetting, is defined as an intermittent nocturnal incontinence. It is a relatively frequent symptom in children, 5-10% at seven years of age and 1–2% in adolescents. With a spontaneous yearly resolution rate of 15% (at any age), it is considered as a relatively benign condition [435, 458]. Seven out of 100 seven-year-old bedwetting children will continue to wet their bed into adulthood. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry (six months). The term “secondary nocturnal enuresis” is used when a child or adult begins wetting again after having stayed dry.

Non-monosymptomatic nocturnal enuresis is defined as the condition of nocturnal enuresis in association with day-time lower urinary tracts symptoms (LUTS, recurrent UTIs and/or bowel dysfunction) [458, 459].

Nocturnal enuresis has significant secondary stressful, emotional and social consequences for the child and their caregivers. Therefore treatment is advised from the age of six to seven years onwards considering mental status, family expectations, social issues and cultural background.

There is a clear hereditary factor in nocturnal enuresis. If none of the parents or their immediate relatives has suffered from bedwetting, the child has a 15% chance of wetting its bed. If one of the parents, or their immediate relatives have suffered from bedwetting, the chance of bedwetting increases to 44%, and if both parents have a positive history the chance increases to 77%. However, from a genetic point of view, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [459]. There is also a gender difference: two boys to one girl at any age.

High arousal threshold is the most important pathophysiological factor; the child does not wake up when the bladder is full. In addition to the high arousal threshold, there needs to be an imbalance between night-time urine output and night-time bladder capacity and activity [435, 458, 459]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder is postulated [460] (LE: 1).

A high incidence of comorbidity and correlation between nocturnal urine production and sleep disordered breathing, such as obstructive sleep apnoea, has been found and investigated. Symptoms such as habitual snoring, apnoeas, excessive sweating at night and mouth breathing in the patient history or via sleep questionnaires can lead to the diagnosis of adenotonsillar hypertrophy.

*3.10.2 **Diagnostic evaluation***

The diagnosis is mainly obtained by history-taking. Focused questions to differentiate monosymptomatic vs. non-monosymptomatic, primary vs. secondary, comorbid factors such as behavioural or psychological problems and sleep disorder breathing, should be asked. In addition, a two day complete voiding and drinking diary, which records day-time bladder function and drinking habits will further exclude comorbid factors such as LUTS and polydipsia.

The night-time urine production should be registered by weighing the night-time diapers in the morning and adding the first morning voided volume [461]. The night-time urine production should be recorded over (at least) a two week period to diagnose an eventual differentiation between a high night-time production (more than 130% of the age expected bladder capacity) vs. a night-time OAB.

A physical examination should be performed with special attention to the external genitalia and surrounding skin as well as to the condition of the clothes (wet underwear or encopresis).

Urine analysis is indicated if there is a sudden onset of bedwetting, a suspicion or history of UTIs, or inexplicable polydipsia.

A uroflowmetry and US is indicated only if there is a history of previous urethral or bladder surgery, straining while voiding, interrupted voiding, an abnormal weak or strong stream, or a prolonged voiding time.

If the comorbid factor of possible sleep disordered breathing occurs, a referral to an ear-nose-throat (ENT) specialist should be advised.

If the comorbid factor is developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child, a referral to a psychologist should be advised and followed-up.

*3.10.3 **Management***

Before introducing any form of possible treatment, it is of utmost importance to explain the bedwetting condition to the child and the caregivers in order to demystify the problem.

3.10.3.1 Supportive treatment measures

Initially, supportive measures including normal and regular eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights, also called as basic bladder advice, has not been shown to be successful in the early treatment of nocturnal enuresis [462] (LE: 1a).

3.10.3.2 Conservative "wait and see" approach

If the child and its family is unable to comply with a treatment, if the treatment options are not possible for the family situation, and if there is no social pressure, a "wait and see" approach can be chosen. However, in this approach, it is important to emphasise the fact that the child should wear diapers at night to ensure a normal quality of sleep.

3.10.3.3 Nocturnal enuresis wetting alarm treatment

The nocturnal alarm treatment is the use of a device that is activated by getting wet. The goal is that the child wakes up by the alarm, which can be acoustic or tactile, either by itself or with the help of a caregiver. The method of action is to repeat the awakening and therefore change the high arousal to a low arousal threshold, specifically when a status of full bladder is reached. It is of utmost importance that the child is collaborating. Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis does not exceed age-expected bladder capacity [463]. Regular follow-up will improve the success.

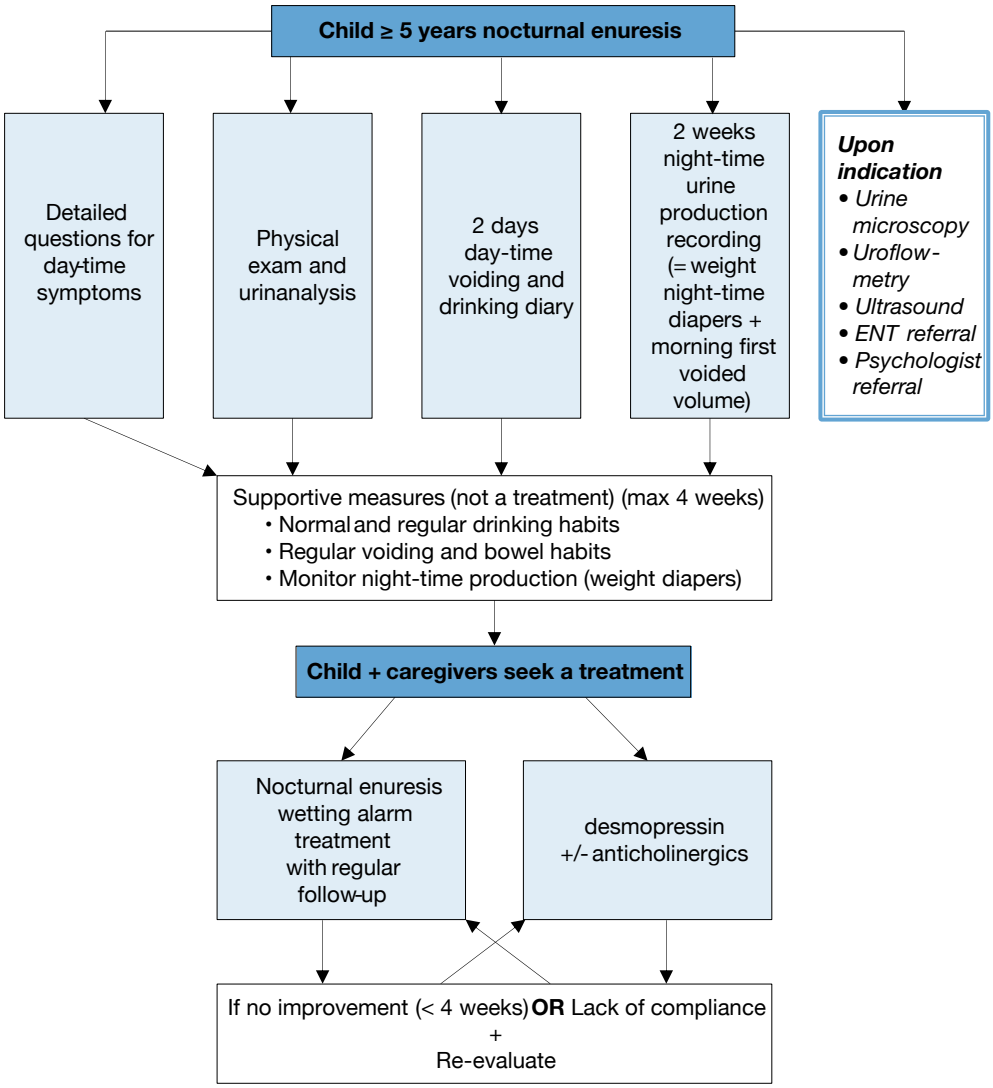
3.10.3.4 Medical therapy

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets (200-400 µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose [464, 465] (LE: 1). Relapse rates can be high after DDAVP discontinuation [458], however recently, structured withdrawal has shown lower relapse rates [466] (LE: 1).

In the event of desmopressin-resistant treatment for nocturnal enuresis or if a suspicion exists for night-time OAB, combination with antispasmodics or anticholinergics is safe and efficient [461]. Imipramine, which has been popular for treatment of enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death from overdose are described, its use should therefore be discouraged as the first-line therapy [467] (LE: 1). Figure 5 presents stepwise assessment and management options for nocturnal enuresis.

Although several forms of neuromodulation and acupuncture have been investigated for nocturnal enuresis treatment, present data precludes their use because of its inefficiency, or at least no additional benefit.

Figure 5: A stepwise assessment and management options for nocturnal enuresis



ENT = ear, nose and throat.

3.10.4 Summary of evidence and recommendations for the management of monosymptomatic enuresis

Summary of evidence	LE
Chronobiology of micturition, in which the existence of a circadian clock has been proven in kidney, brain and bladder, and disturbances in this chronobiology play a major role in the pathophysiology of enuresis.	1

Recommendations	LE	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition.	2	Strong
Use voiding diaries or questionnaires to exclude day-time symptoms.	2	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	Strong
Offer desmopressin in proven night-time polyuria.	1	Strong
Offer alarm treatment in motivated and compliant families.	1	Strong

3.11 Management of neurogenic bladder

3.11.1 Epidemiology, aetiology and pathophysiology

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and ultimately to renal scarring and renal failure requiring dialysis and/or transplantation. Conservative treatment starting in the first year of life is the first choice, however, surgery may be required at a later stage to establish adequate bladder storage, continence and drainage later on [468-470]. The main goals of treatment concerning the urinary tract are prevention of UTI's, urinary tract deterioration, achievement of continence at an appropriate age and promoting as good a QoL as possible. With regard to the associated bowel dysfunction, stool continence, with evacuation at a social acceptable moment, is another goal as well as education and treatment of disturbance in sexual function. Due to the increased risk of development of latex allergy, latex-free products (e.g., gloves, catheters etc.) should be used from the very beginning whenever possible [471].

Neurogenic bladder in children with myelodysplasia presents with various patterns of Detrusor-Sphincter-Dyssynergia with a wide range of severity [472]. About 12% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth [473]. Newborns with myelodysplasia and initially normal urodynamic studies are at risk for neurological deterioration secondary to spinal cord tethering, especially during the first six years of life. Close follow-up of these children is important for the early diagnosis and timely surgical correction of tethered spinal cord, and for the prevention of progressive urinary tract deterioration [473]. At birth, the majority of patients have normal UUTs, but up to 60% develop upper tract deterioration due to bladder changes, UTI and /or VUR, if not treated properly [474-477]. Even today in a contemporary series around 50% of the patients are incontinent and 15% have an impaired renal function at the age of 29 years [478]. A recent SR concerning the outcome of adult meningomyelocele patients demonstrated that around 37% (8-85%) are continent, 25% have some degree of renal damage and 1.3% end stage renal failure [479]. The term "continence" is used differently in the reports, and the definition of "always dry" was used in only a quarter of the reports [480].

The most common presentation at birth is myelodysplasia. The incidence of neural tube defects in Europe is 9.1 per 10,000 births and has not decreased in recent years, despite longstanding recommendations concerning folic acid supplementations [481]. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions include spina bifida aperta and occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental.

With antenatal screening spina bifida can be diagnosed before birth with the possibility of intrauterine closure of the defect [482, 483]. Traumatic and neoplastic spinal lesions of the cord are less frequent in children, but can also cause severe urological problems. Other congenital malformations or acquired diseases can cause a neurogenic bladder, such as total or partial sacral agenesis which can be part of the caudal regression syndrome [484]. In any child presenting with anorectal malformation (ARM) and cloacal malformations, the development of a neurogenic bladder is possible [485]. Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting. Finally, a "non-neurogenic neurogenic" bladder, such as Hinman or Ochoa syndrome, has been described, in which no neurogenic anomaly can be found, but severe bladder dysfunction as seen in neurogenic bladders is present [486, 487].

3.11.2 Classification systems

As bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion, urodynamic and functional classifications are much more practical for defining LUT pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to act as a single functional unit. In patients with a neurogenic disorder, the storage and emptying phase of the bladder function can be disturbed. The bladder and sphincter may function either overactive or underactive and present in 4 different combinations. This classification system is based on urodynamic findings [488-490]:

- Overactive sphincter and overactive bladder.
- Overactive sphincter and underactive bladder.
- Underactive sphincter and overactive bladder.
- Underactive sphincter and underactive bladder.

*3.11.3 **Diagnostic evaluation***

Today several guidelines and timetables are used [491-493]. The Panel advocate proactive management in children with spinal dysraphism. In those with a safe bladder during the first urodynamic investigation, the next urodynamic investigation can be delayed until one year of age.

3.11.3.1 History and clinical evaluation

History should include questions on clean intermittent catheterisation (CIC) frequency, urine leakage, bladder capacity, UTI, medication, bowel function as well as changes of neurological status. A thorough clinical evaluation is mandatory including the external genitalia and the back. A two day diary, recording drinking volume and times as well as CIC intervals, bladder volume and leakage can provide additional information about the efficacy of the treatment.

3.11.3.2 Laboratory and urinalysis

After the first week of life, the plasma creatinine level should be obtained, later in life; the cystatin level is more accurate [494, 495]. If there is any sign of decreased renal function, physicians should be encouraged to optimise the treatment as much as possible.

The criteria for urine analysis are the same as for UTI (refer to Chapter 3.8). However, it is much easier for caregivers or patients to obtain catheter urine in patients who are on CIC. They can also perform a dip stick analysis to screen for UTI at home. (For relevance see Section 3.11.4.5.)

3.11.3.3 Ultrasound

At birth, US of the kidneys and bladder should be performed and then repeated at least annually. If there are any clinical changes in between, another US should be performed. Dilatation of the UUT should be reported according to the classification system of the Society of Foetal Urology [496], including the measurement of the caliceal dilatation and anterior posterior diameter of the renal pelvis. Residual urine and bladder wall thickness should also be mentioned. A dilated ureter behind the bladder should be recorded. Bladder wall thickness has been shown not to be predictive of high pressures in the bladder during voiding and storage and cannot be used as a non-invasive tool to judge the risk for the UUT [497].

3.11.3.4 Urodynamic studies/videourodynamic

Urodynamic studies (UD) are one of the most important diagnostic tools in patients with neurogenic bladders. In newborns with spina bifida aperta (failure of mesodermal in-growth over the developing spinal canal results in an open lesion most commonly seen in the lumbosacral area including an incomplete closure of the vertebral column and not covered by skin), the first UD should be performed after the phase of the spinal shock after closure, usually between the second and third months of life [498]. Especially in newborns, performing and interpretation of UD may be difficult, as no normal values exist. After that it should be repeated annually, depending on the clinical situation. During and after puberty bladder capacity, maximum detrusor pressure and detrusor leak point pressure increase significantly [499]. Therefore, during this time, a careful follow-up is mandatory.

3.11.3.4.1 Preparation before urodynamic studies

Before any UD a urine analysis should be done. The first assessment should be done under antibiotic prophylaxis. A Cochrane analysis of nine randomised controlled trials showed, that the administration of prophylactic antibiotics compared to placebo reduced the risk of significant bacteriuria from 12% to 4% after UD studies. However, this was without significant difference for symptomatic UTI (20% versus 28%), fever or dysuria [500]. If there is a significant bacteriuria, antibacterial treatment should be discussed; especially in older patients a single shot may be sufficient [501].

Generally UD-parameters should include:

- the bladder cystometric capacity;
- the intravesical filling pressure;
- detrusor compliance;
- the intravesical pressure at the moment of voiding or leakage;
- the presence or absence of overactive detrusor;
- the competence of the internal and external sphincter;
- the degree of synergy of the detrusor and sphincter during voiding;
- the PVR urine volume.

In infants, information on detrusor filling pressure and the pressure and bladder volume at which the child voids or leaks can be obtained [498]. Detrusor leak point pressure is more accurate than abdominal leak point pressure, but keeping the rectal probe in an infant in place can be challenging [498]. Addition of fluoroscopy (video-urodynamic study) will provide information about presence of VUR, at what pressures VUR starts and the configuration of the bladder neck during filling and leakage or voiding.

3.11.3.4.2 Uroflowmetry

Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry can rarely be used since most affected patients do not void spontaneously. In those with cerebral palsy, non-neurogenic-neurogenic bladder or other neurological conditions allowing active voiding it may be a practical tool. It provides an objective way of assessing the efficiency of voiding, while recording of pelvic floor activity with electromyography (EMG) can be used to evaluate synergy between detrusor and the sphincter. The PVR urine is measured by US. The main limitation of uroflowmetry is a compliant child to follow instructions [502-505].

3.11.3.5 Urodynamic studies

The standards of the ICCS should be applied to UDs in patients with neurogenic bladders and accordingly reported [427, 488]. Natural fill UD in children with neurogenic bladder detects more overactivity compared with diagnoses delivered by conventional UD [506, 507]. It may be an option in patients where the findings in the normal UD are inconsistent with clinical symptoms and other clinical findings [507].

3.11.3.6 Voiding cystourethrogram

If video-urodynamic equipment is not available, a VCUG with UD is an alternative to confirm or exclude VUR and visualise the LUT including the urethra.

3.11.3.7 Renal scan

DMSA (Technetium Dimercapto-Succinic Acid) Renal scan is the gold standard to evaluate renal parenchyma. In contemporary series, renal scars can be detected in up to 46% as patients get older [508-510]. A positive DMSA-Scan correlates well with hypertension in adulthood, whereas US has a poor correlation with renal scars [510]. Therefore, a DMSA scan as a baseline evaluation in the first year of life is recommended.

3.11.4 ***Management***

The medical care of children with neurogenic bladder requires an on-going multidisciplinary approach. There is some controversy about optimal timing of the management; proactive vs. expectant management [468-470]. Even with a close expectant management e.g. in one series 11/60 need augmentation within a follow-up of 16 years and 7/58 had a decrease in total renal function, which was severe in two [511]. During the treatment it should be also taken into account with spina bifida patients, that QoL is related to urinary incontinence independent from the type and level of spinal dysraphism and the presence or absence of a liquor shunt [512].

Foetal open and endoscopic surgery for meningomyelocele are performed to close the defect as early as possible to reduce the neurological, orthopaedic and urological problems [513]. In the MOMS-Trail, Brooks *et al.* found no difference between those closed *in utero* vs. those closed after birth concerning the need for CIC [483], but less trabeculation was found in the prenatal surgery group. Mean gestation age (28.3 vs. 35.2) seems to have no initial impact on bladder function in the first few years of life [514]. Despite some promising reports [514-517], caregivers need to be aware about the high risk of developing a neurogenic bladder as demonstrated by a Brazilian group [518]. Regular and close follow-up examinations including UD are indicated in all these patients.

3.11.4.1 Early management with intermittent catheterisation

Starting intermittent catheterisation (IC) soon after birth and closure of the defect by the neurosurgeon in all infants has shown to decrease renal complications and the need for later augmentation [519-521]. In infants

without any clear sign of outlet obstruction, this may be delayed but only in very selected cases. These infants should be monitored very closely for UTIs and changes of the urinary tract with US and UD. The early initiation of IC in the newborn period makes it easier for caregivers to master the procedure and for children to accept it, as they grow older [522, 523].

A Cochrane review as well as some recent studies showed, that there is a lack of evidence to state that the incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy [524-527]. Looking at the microbiological milieu of the catheter, there was a trend for reduced recovery of potentially pathogenic bacteria with the use of hydrophilic catheters. Also, a trend for a higher patient satisfaction with the use of hydrophilic catheters was seen [528]. Based on the current data, it is not possible to state that one catheter type, technique or strategy is better than another.

3.11.4.2 Medical therapy

Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers intravesical pressure [529, 530]. Effects and side effects depend on the distribution of the M1-M5 receptors [531]. In the bladder, the subtype M2 and M3 are present [530, 532]. Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93% [533, 534]. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit its use. Intravesical administration has a significant higher bioavailability due to the circumvention of the intestinal first pass metabolism, as well as possible local influence on C-fiber-related activity and can be responsible for different clinical effect [535, 536]. Intravesical administration should be considered in patients with severe side-effects, as long-term results demonstrated that it was well-tolerated and effective [537, 538]. The transdermal administration leads also to a substantial lower ratio of N-desethyloxybutynin to oxybutynin plasma levels, however, there are treatment-related skin reactions in 12/41 patients [539]. There are some concerns about central anticholinergic adverse effects associated with oxybutynin [540, 541]. A double blinded cross-over trial, as well as a case control study, showed no deleterious effect on children's attention and memory [542, 543]. Tolterodine, solifenacin, trospium chloride and propiverine and their combinations can be also used in children [544-550]. The oral dosage for oxybutynin is up to 0.2 mg/kg/every 8 hours [530] given three times daily. The intravesical dosage can be up to 0.7 mg/kg/daily and transdermal 1.3-3.9 mg/daily. The dosage of the other drugs is: Tolterodine 0.5 – 4 mg/day divided in two doses, Solifenacin 1.25 up to 10 mg per day (single dose), Propiverin 0.8 mg/kg/day divided in two dosages and trospium chloride up to 3 times 15 mg starting with 3 times 5 mg. Except for oxybutynin, all other anticholinergic drugs are off-label use, which should be explained to the caregivers.

Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation [519, 521, 551]. Beta-3 agonists like mirabegron may be also an alternative agent and may be effective in patients with neurogenic bladders. Up to date, there is almost no experience with this drug [552], therefore no recommendation can be made.

Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder [553]. Doxazosin with an initial dose of 0.5 to 1.0 mg or tamsulosin hydrochloride in a medium (0.0002-0.0004 mg/kg/day) or high dose (0.0004-0,0008 mg/kg/day) has been given to children with neurogenic bladders [553-555]. It was well tolerated but not effective at least in one study [554].

Botulinum toxin A injections: In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option [556, 557]. In children, continence could be achieved in 32-100% of patients, a decrease in maximum detrusor pressure of 32% to 54%, an increase of maximum cystometric capacity from 27% to 162%, and an improvement in bladder compliance of 28%-176% [556]. Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [558, 559]. Also, the injections into the trigone seems to be save in regard of reflux and upper tract damage; if it has some benefit is not further investigated [560].

The most commonly used dose of onabotulinum toxin A is 10 to 12 U/kg with a maximum dose between 200 U and 360 U [556]. However, in one study, 5 U/kg were used with comparable results [561]. Up to date, no randomised dose titration study has been published in children. The optimal dose in children as well as the time point when to inject which child is still unclear. Onabotolinum toxin A can be effective between three to twelve (0-25) months and repeated injections are effective up to ten years in one study [557, 562, 563].

Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [564, 565].

Neuromodulation
Intravesical electrical stimulation of the bladder [566-568], sacral nerve stimulation [569, 570] and transcutaneous neuromodulation [571] are still experimental and cannot be recommended outside of clinical trials. The same is true for the intradural somatic-to-autonomic nerve anastomosis [572, 573].

Urethral Dilatation
The aim is to lower the pop-off pressure by lowering the detrusor leak-point pressure by dilatation of the external sphincter under general anaesthesia up to 36 Charr. Some studies showed, that especially in females, the procedure is safe and in selected patients, effective [574-576].

Vesicostomy
Vesicostomy - preferably a Blocksom stoma [577] - is an option to reduce bladder pressure in children/newborns, if the caregivers are incompliant with IC and/or IC through the urethra is extremely difficult or impossible [578]. Especially in the young infant with severe upper tract dilatation or infections, a vesicostomy should be considered. Drawbacks are the problem to fit and maintain a collecting appliance in older patients. A cystostomy button may be an alternative, with a complication rate (mostly UTI) of up to 34% within a mean follow-up of 37 months [579].

3.11.4.3 Management of faecal incontinence
Children with neurogenic bladder usually have also a neurogenic bowel function. Faecal incontinence may have an even greater impact on QoL, as the odor can be a reason for social isolation. The aim of each treatment is to obtain a smooth, regular bowel emptying and to achieve continence and impendence. The regime should be tailored to the patient's need, which may change over time. Beside a diet with small portioned fibre food and adequate fluid intake to keep a good fluid balance [530], follow-up options should be offered to the patients and caregivers.

At the beginning, faecal incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time rectal suppositories as well as digital stimulation by parents or caregivers can be used. Today, transanal irrigation is one of the most important treatments for patients with neurogenic bowel incontinence. Regular irrigations significantly reduce the risk for faecal incontinence and may have a positive effect on the sphincter tonus as well as the rectal volume [580]. The risk of irrigation induced perforation of the bowel is estimated as one per 50,000 [581]. During childhood, most children depend on the help of the caregivers. Later in some of them, transanal irrigation becomes difficult or impossible due to anatomic or social circumstances. In these patients antegrade irrigation using a MACE-stoma (Malone Antegrade Continence Enema) is an option, which can also be placed in the left abdomen [582, 583]. In a long-term study of 105 patients, 69% had successful bowel management. They were started on normal saline, but were switched to GoLYTELY (PEG-3350 and electrolyte solution). Additives (biscodyl, glycerin etc.) were needed in 34% of patients. Stomal complications occurred in 63% (infection, leakage, and stenosis) of patients, 33% required surgical revision and 6% eventually required diverting ostomies [584]. In addition, patients need to be informed, that the antegrade irrigation is also time consuming with at least 20-60 minutes.

3.11.4.4 Urinary tract infection
Urinary tract infections are common in children with neurogenic bladders. However, there is no consensus in most European centres, for prevention, diagnosing and treating UTIs in children with neurogenic bladders performing CIC [585]. Although bacteriuria is seen in more than half of children on CIC, patients who are asymptomatic do not need treatment [586, 587]. Continuous antibiotic prophylaxis (CAP) creates more bacterial resistance as demonstrated by a randomised study. Those on stopping the prophylaxis had reduced bacterial resistance, however, 38/88 started antibiotic prophylaxis again due to recurrent UTIs or the caregivers request [588]. A cohort study with 20 patients confirmed these findings. Continuous antibiotic prophylaxix was not protective against the development of symptomatic UTIs and new renal scarring, however, increased the risk of bacterial resistance [589]. A randomised study in 20 children showed that cranberry capsules significantly reduced the UTI-rate as well as the rate of bacteriuria [590]. If VUR is present, prophylactic antibiotics should be started when patients experience recurrent UTIs [591, 592].

3.11.4.4.1 Urinary tract infection and clean intermittent catherisation
The incidence of asymptomatic bacteriuria ranges between 42%-76% [522, 530, 593]. A cross-over study in 40 children with neurogenic bladder demonstrated, that the reuse of CIC-catheters for up to three weeks compared to one week increased the prevalence of bacteriuria from 34% to 74% (it was 60% at the start of the study). During the study-period of eighteen weeks, none of the patient developed a febrile UTI [594]. There is no medical benefit in performing CAP in children with neurogenic bladder, who perform CIC [530]. In those with recurrent UTI, intravesical instillation of gentamycin may be an option [595, 596].

Reflux

Secondary reflux in patients with neurogenic bladder increases the risk for pyelonephritis. The treatment is primary related to bladder function including anticholinergic therapy, CIC and may be later augmentation [597]. Those with early and post-therapy persistent reflux during videourodynamic studies at low pressure have a higher risk of pyelonephritis [598]. Patients with a high-grade reflux before augmentation have a higher risk for persistent symptomatic reflux after the enterocystoplasty [599]. Therefore simultaneous ureteral re-implantation in high-grade symptomatic reflux especially in those with low-pressure high-grade reflux should be discussed with the patient/caregivers. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years [600] which is in contrast to the open techniques with a higher success rate, but may have an increased risk of inducing obstruction [601].

3.11.4.5 Sexuality

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters [602]. The prevalence of precocious puberty is higher in girls with meningomyelocele [603]. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

Women seem to be more sexually active than men in some studies from the USA and the Netherlands [602, 604]; in an Italian study men were more active [604]. The level of the lesion was the main predictor to be sexually active [605, 606]. Erectile function can be improved by sildenafil in up to 80% of the male patients [607, 608]. Neurosurgical anastomosis between the inguinal nerve and the dorsal penile nerve in patients with a lesion below L3 and disturbed sensation is still to be considered as an experimental treatment [604, 609]. Only 17% to 1/3 of the patients talk to their doctors about sexuality, 25–68% were informed by their doctors about reproductive function [602]. Therefore, early discussion about sexuality in the adolescent is recommended and should be promoted by the paediatric urologist taking care of these patients.

3.11.4.6 Bladder augmentation

In patients where conservative treatment including onabotulinum toxin A (for indication see 3.11.4.3) fails to keep a low-pressure reservoir with a good capacity and compliance, bladder augmentation should be offered. For augmentation, ileal and colonic segments can be used [610]. Gastric segments are rarely used due to its associated complications like the haematuria-dysuria syndrome as well as secondary malignancies, which arise earlier than with other intestinal segments [611-614]. Enterocystoplasty increases bladder capacity, reduces storage pressure and can improve UUT drainage [615]. A good socially acceptable continence rate can be achieved with or without additional bladder outlet procedures [616]. In those, who are not able to perform CIC through the urethra, a continent cutaneous channel should be offered. Surgical complications and revision rate in this group of patients is high. The 30-day all over event rate in the American College of Surgeons' National Surgical Quality Database is approximately 30% (23-33%) with a re-operation rate in this short time period of 13% [617, 618]. In these patients with long-life expectancy the complication rate clearly increases with the follow-up period [617-620]. The ten-year cumulative complication incidence from the Paediatric Health Information System showed a rate of bladder rupture in up to 6.4%, small bowel obstruction in up to 10.3%, bladder stones in 36%, pyelonephritis in more than a third of the patients and a re-augmentation rate of up to 13% [621]. Bladder perforation, as one of the worst complications, occurs in 6-13% [622]. The rate of VP-shunt infections after gastrointestinal and urological procedures ranges between 0-22%. In a recent study, bowel preparation seems not to have a significant influence on the infection rate (10.5 vs 8.3%) [623]. Not only surgical complications must be considered; also metabolic complications and consequences after incorporating bowel segments have to be taken into account, such as imbalance of the acid base balance, decrease in vitamin B12 levels and loss of bone density. Stool frequency can increase as well as diarrhoea after exclusion of bowel segments [624] and last, but not least, these patients have a lifelong increased risk to develop secondary malignancies [625-627]. Therefore, a lifelong follow-up of these patients is required including physical examination, US, blood gas analysis, (pH and base excess), renal function and vitamin B12 if Ileum is used. Endoscopic evaluation starting ten years after augmentation is not cost-effective [628, 629], but may prevent some advanced cancer. Woodhouse *et al.* do not recommend cystoscopy within the first fifteen years after surgery [630]. The real value of annual cystoscopic evaluation has not been proven by any study. Urodynamic studies after bladder augmentation are only indicated, if upper tract dilatation and/or incontinence after the operation has not improved [631].

Adverse effects of intestinal cystoplasties can be avoided by the use of ureterocystoplasty. The combination of a small contracted bladder, associated with a severe dilation of the ureter of a non-functioning kidney is quite rare. The technique was first described in 1973 by Eckstein [632]; the success rate depends on patient selection and the re-augmentation rate can reach 73% [633, 634].

Auto-augmentation with partial detrusorectomy or detrusormyotomy creating a diverticulum avoids metabolic complications with the use of intestinal segments. The reports are conflicting, therefore, it may be used in very selected cases [635-638]. For a successful outcome, a pre-operative bladder capacity of 75-80% of the expected volume seems necessary [639, 640]. Seromuscular cystoplasty has also not proven to be as successful as standard augmentation with intestine [641]. Tissue engineering, even if successful *in vitro* and some animal models, does not reach the results by using intestinal segments with a higher complication rate [642, 643]. Therefore, these alternatives for bladder augmentation should be considered as experimental and should be used only in controlled trials.

3.11.4.7 Bladder outlet procedures

So far, no available medical treatment has been validated to increase bladder outlet resistance. Alpha-adrenergic receptor stimulation of the bladder neck has not been very effective [644-649]. Using fascial slings with autologous fascial strip or artificial material a continence rate between 40-100% can be achieved. In most cases this is achieved in combination with bladder augmentation [650, 651]. Catheterising through a reconstructed bladder neck or a urethra compressed by a sling may not be easy; many surgeons prefer to combine this approach with a catheterisable channel [468]. In contrast to the autologous slings, artificial slings in girls with CIC through the urethra have a high complication rate [652]. In males, it may be an option [653], however as long as long-term results are missing this method has to be classified as experimental and should only be carried out in studies. Artificial urinary sphincters were introduced by Scott in 1973 [654]. The continence rates in the literature in selected patients can be up to 85% [655-658]. Post-pubertal patients, who can void voluntary are good candidates, if they are manually dexterous. In very selected patients, CIC through the sphincter in an augmented bladder is possible [659]. The erosion rate can be up to 29% and the revision rate up to 100% depending on the follow-up time [660].

Patients, who underwent a bladder neck procedure only, have a chance of > 30% for an augmentation later on, half of them developed new upper tract damage in that time [661, 662]. In patients with a good bladder capacity and bladder compliance without an indication for bladder augmentation, there is a risk of post-operative changes of the bladder function. Therefore, a very close follow-up of these patients with UD is required to avoid upper tract damage and chronic renal failure.

Bladder neck reconstruction is used mostly in exstrophy patients with acceptable results. However, in children with a neurogenic bladder the results are less favourable [663]. In most patients, the creation of a continent catheterisable stoma is necessary due to difficulties to perform the CIC via the urethra. In one series, 10% to a third still perform CIC via the urethra with a re-operation rates between 67% and 79% after a median follow-up between seven and ten years [664]. In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterisable stoma is an option. The combination of a sling procedure together with a urethral lengthening procedure may improve the continence rates [665].

Bulking agents have a low success rate (10-40%), which is in most cases only temporary [666-668]. However, it does not adversely affect the outcome of further definite surgical procedures [669].

Bladder neck closure is often seen as the last resort to gain urinary continence in those patients with persistent urinary incontinence through the urethra. In girls, the transection is done between bladder neck and urethra and in boys above the prostate with preservation of the neurovascular bundle. It is an effective method to achieve continence together with a catheterisable cutaneous channel +/- augmentation as a primary or secondary procedure [670, 671]. A complication rate of up to 1/3 and a vesicourethral/vesicovaginal fistula in up to 15% should be considered [672], together with a higher risk for bladder stones, bladder perforation and deterioration of the upper tract function, if the patient is not compliant with CIC and bladder irrigations [672, 673].

3.11.4.8 Catheterisable cutaneous channel.

In most patients with a neurogenic bladder IC is required. If this is not possible, or very time and/or resources consuming via the urethra, a continent cutaneous catheterisable channel should be offered as well as in those with bladder outlet procedures. It is especially beneficial to wheelchair-bound patients who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. In long-term studies the revision rate due to stenosis or incontinence can be as high as 50 to 60% depending on the type of channel [674, 675].

The stoma can be placed at the umbilicus or in the lower right abdominal wall using a VQZ plasty [676]. It should be carefully evaluated pre-operatively: it is extremely important that the patient can reach the stoma easily. Sometimes it has to be placed in the upper abdominal wall due to sever scoliosis mostly associated with obesity.

3.11.4.9 Continent and incontinent cutaneous urinary diversion

Incontinent urinary diversion should be considered in patients who are not willing or able to perform a CIC and who need urinary diversion because of upper tract deterioration or gain urinary continence due to social reasons. In children and adolescents, the colonic conduit has shown to have less complications compared to the ileal conduit [677-680]. Total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience in the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [616, 681, 682].

Algorithms can be used for management of these patients (Figures 6 and 7).

*3.11.5 **Follow-up***

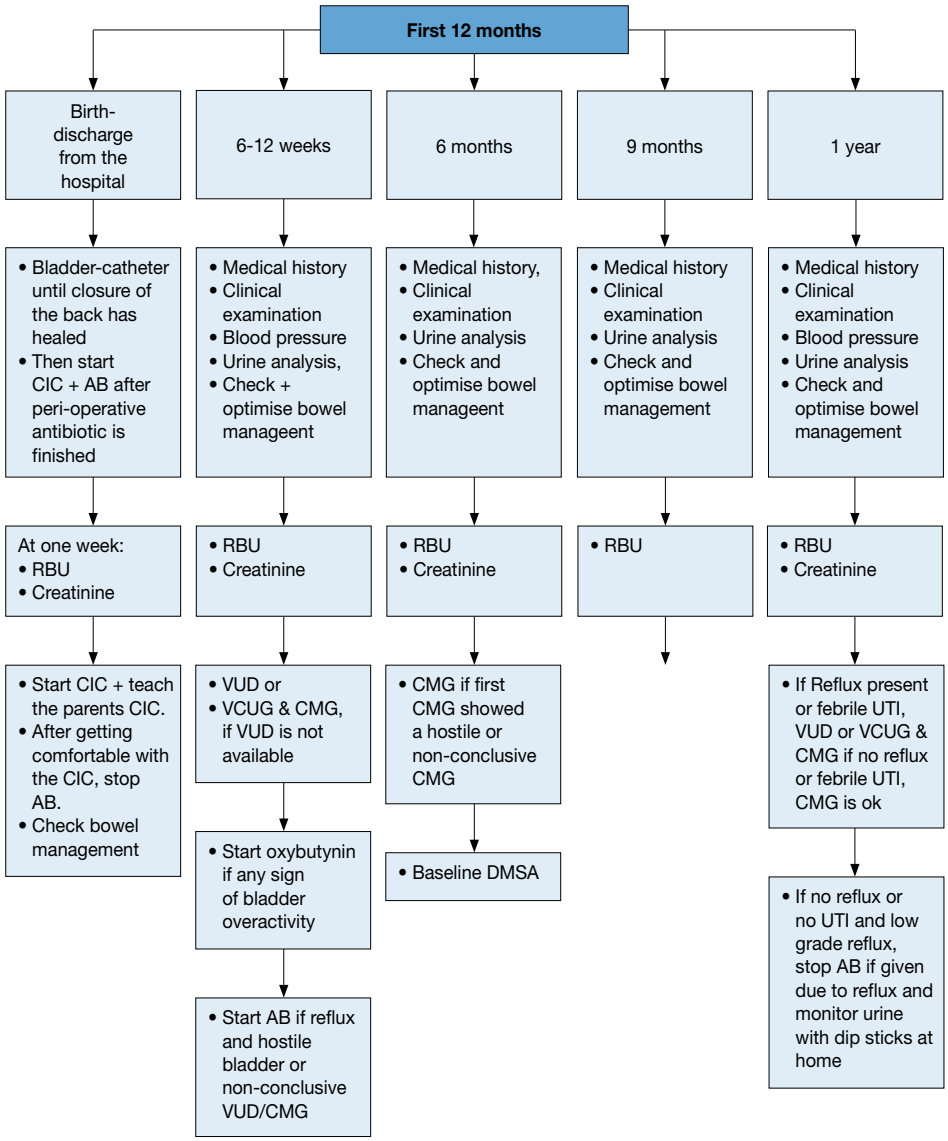
Neurogenic bladder patients require lifelong follow-up including not only urological aspects but also neurological and orthopaedic aspects. Regular investigation of upper and lower urinary tract is mandatory. In patients with changes of the function of the upper and/or lower urinary tract, a complete neurological re-investigation should be recommended including a total spine MRI to exclude a secondary tethered cord or worsening of the hydrocephalus. In addition, if some neurological changes are observed a complete investigation of the urinary tract should be undertaken.

In those patients with urinary tract reconstruction using bowel segments, regulatory investigations concerning renal function, acid base balance and vitamin B12 status are mandatory to avoid metabolic complications. There is an increased risk for secondary malignancies in patients with a neurogenic bladder either with or even without enteric bladder augmentations [626, 627, 683-689]. Therefore, patients need to be informed about this risk and possible signs like haematuria. Although there are poor data on follow-up schemes to discover secondary malignancies, after a reasonable follow-up time (e.g. ten to fifteen years), an annual cystoscopy can be considered.

*3.11.6 **Self-organisation of patients***

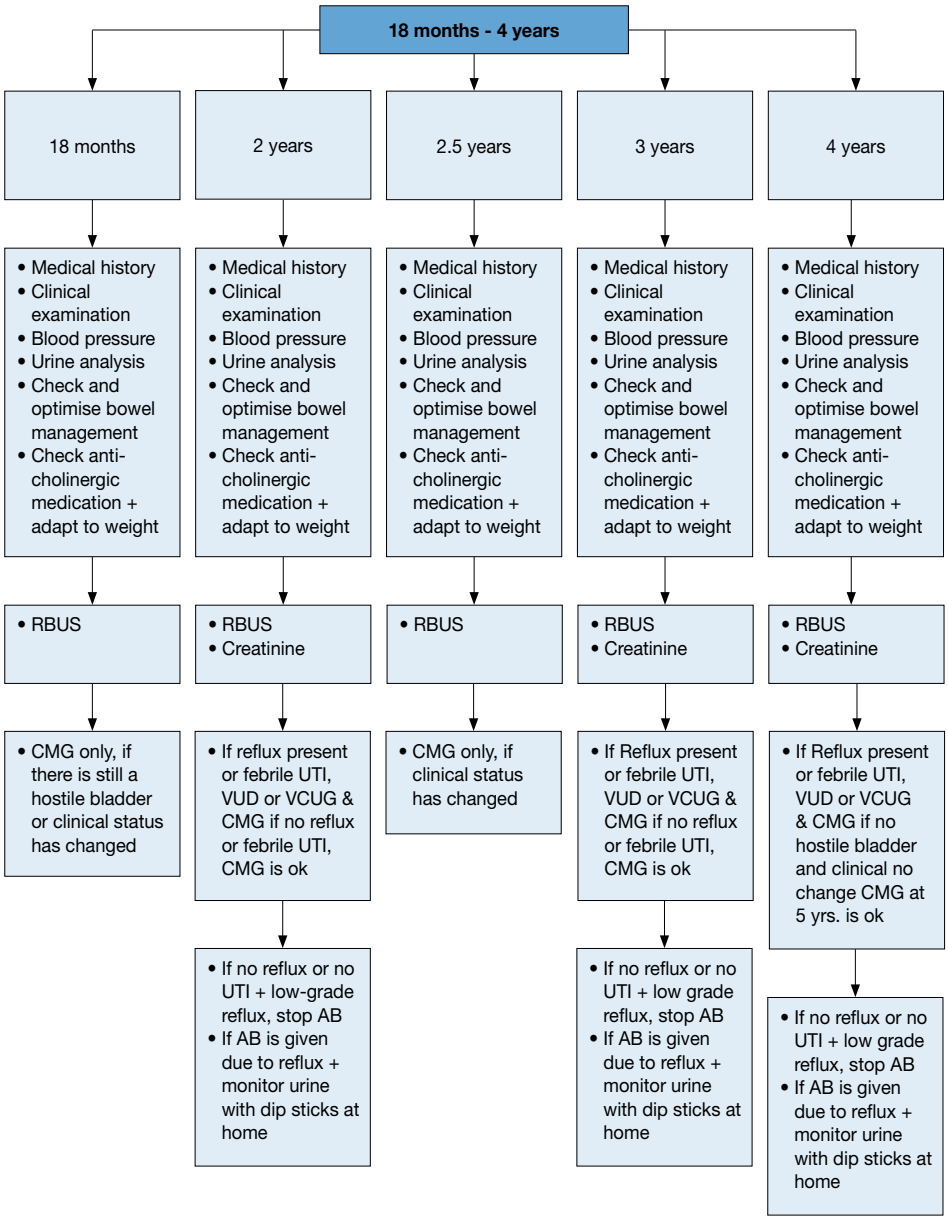
As patients' self-organisations can support the parents, caregivers and the patients in all aspects of their daily life, patients should be encouraged to join these organistions.

Figure 6a: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - First twelve months



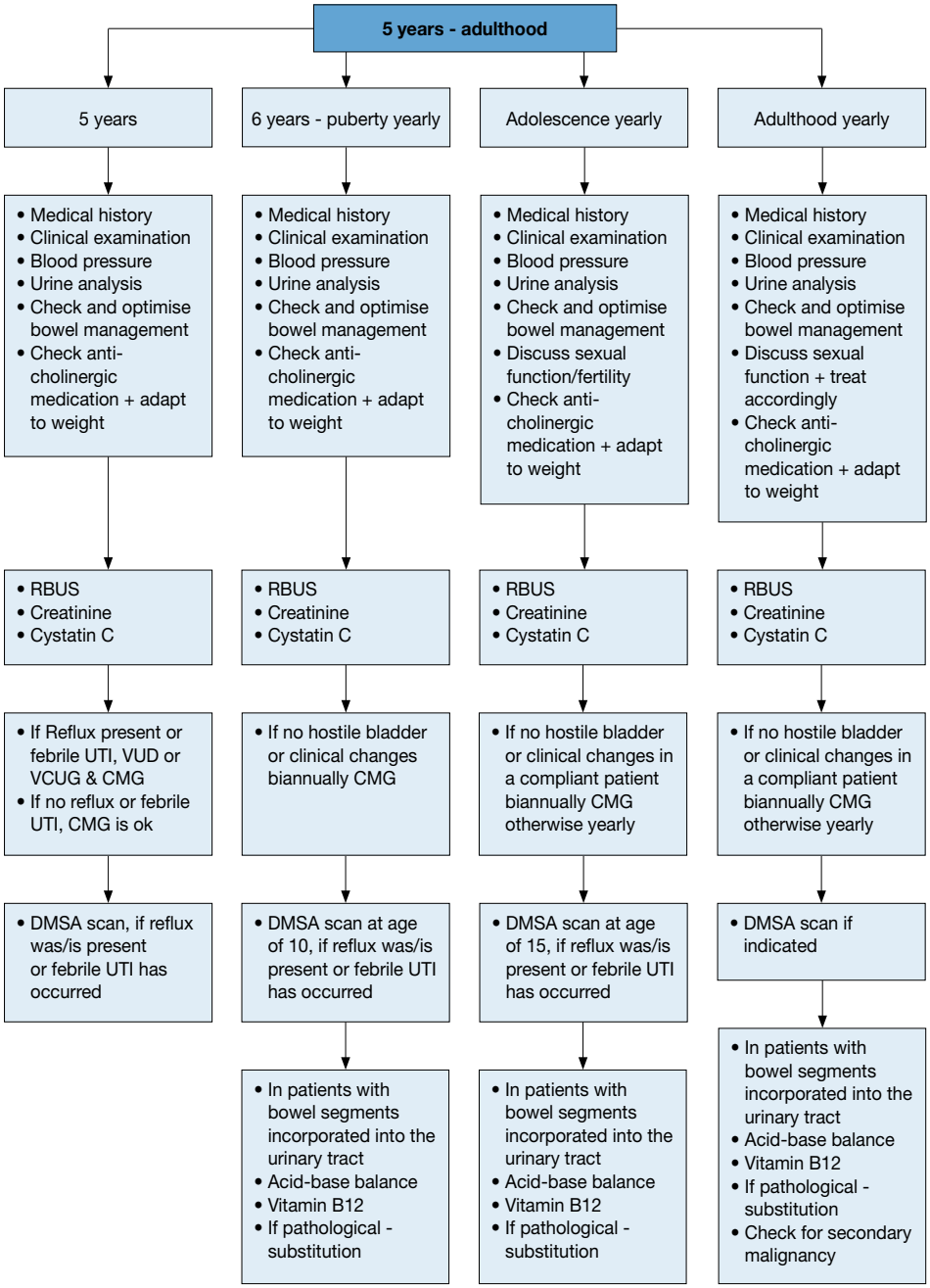
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 6b: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - 18 months - 4 years



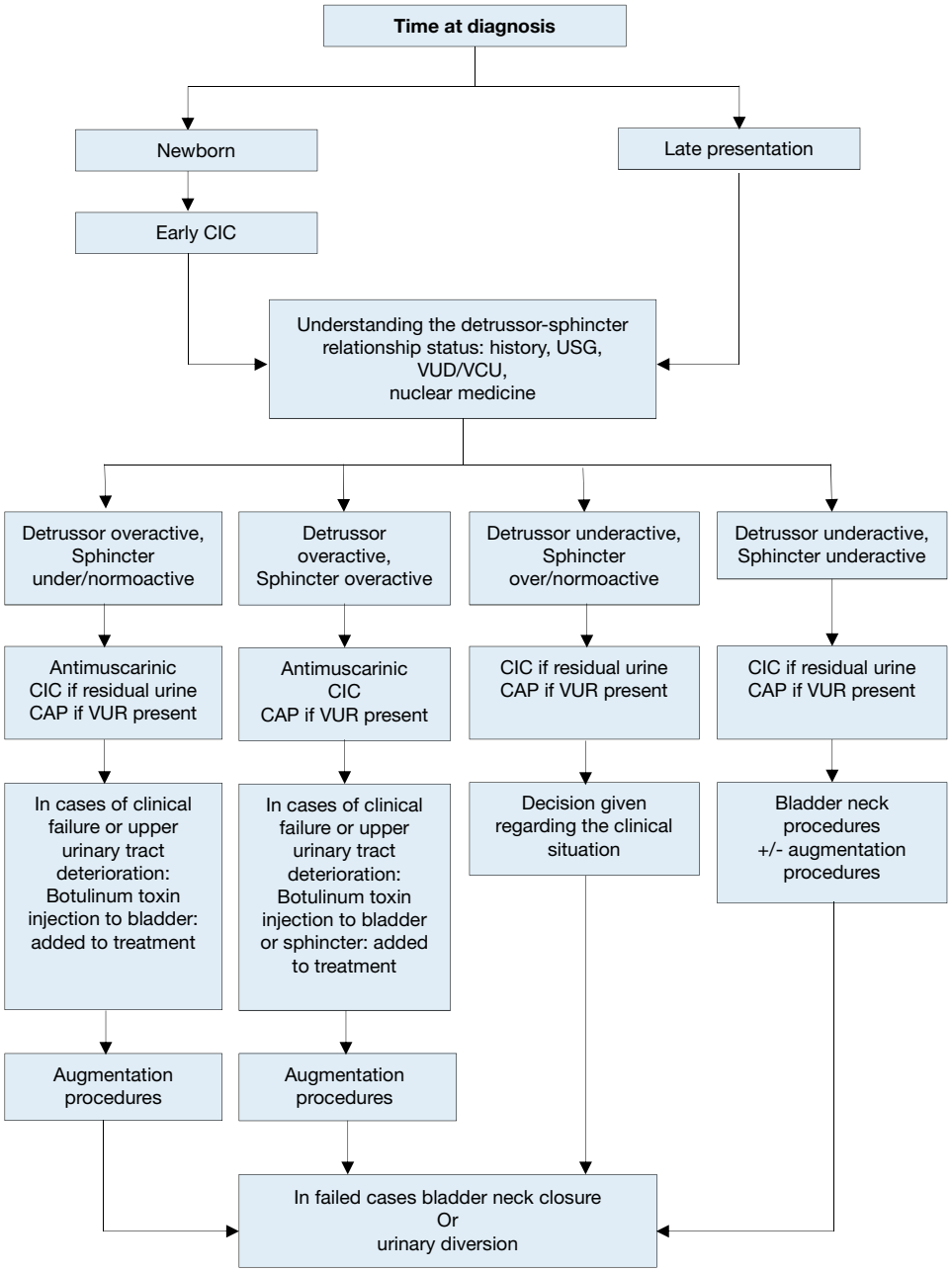
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 6c: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - 5 years to adulthood



RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 7: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

3.11.7 ***Summary of evidence and recommendations for the management of neurogenic bladder***

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction may result in different forms of LUTD and ultimately result in incontinence, UTIs, VUR, and renal scarring.	2a
In children, the most common cause of NDSD is myelodysplasia (a group of developmental anomalies that result from defects in neural tube closure).	2
Bladder sphincter dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are more practical in defining the extent of the pathology and in guiding treatment planning.	2a
Children with neurogenic bladder can have disturbances of bowel function as well as urinary function which require monitoring and, if needed, management.	2a
The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.	2a
Injection of botulinum toxin into the detrusor muscle in children who are refractory to anticholinergics, has been shown to have beneficial effects on clinical and urodynamic variables.	2a

Recommendations	LE	Strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and the lower tract (UD).	3	Strong
Start early anticholinergic medication in the newborns with suspicion of an overactive detrusor.	2	Strong
The use of suburothelial or intradetrusoral injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	2	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital stimulation. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	3	Strong
Ileal or colonic bladder augmentation is recommended in patients with therapy-resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and nonsurgical complications and consequences outweigh the risk for permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	2	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	3	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing an IC through the urethra.	3	Weak
A life long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	3	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3	Weak

3.12 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

*3.12.1 **Epidemiology, aetiology and pathophysiology***

Dilatation of the UUT remains a significant clinical challenge in deciding which patient will benefit from treatment. Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [690]. It has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [691]. It can be very difficult to define 'obstruction' as there is no clear division between 'obstructed' and 'non-obstructed' urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration [692].

*3.12.2 **Diagnostic evaluation***

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [693]. The challenge in the management of dilated UUT is to decide which child should be observed, which should be managed medically, and which requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from nonobstructive cases (see Figure 8).

3.12.2.1 Antenatal ultrasound

Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week. If dilatation is detected, US should focus on:

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume [694].

3.12.2.2 Postnatal ultrasound

Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended [695]. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

3.12.2.3 Voiding cystourethrogram

In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

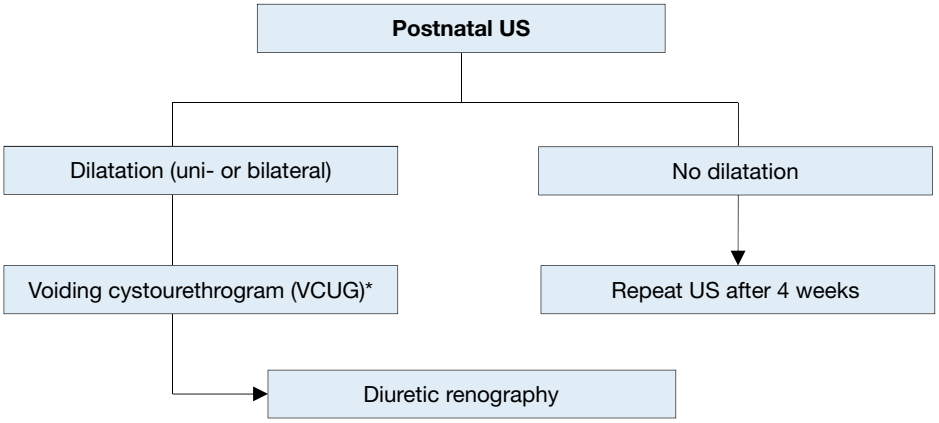
- vesicoureteral reflux (found in up to 25% of affected children) [696];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [697].

3.12.2.4 Diuretic renography

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (^{99m}Tc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [698]. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the entire time of the investigation [699]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40 mg.

Figure 8: Diagnostic algorithm for dilatation of the upper urinary tract



** A diagnostic work-up including VCUG must be discussed with the caregivers, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [695].*
US = ultrasound.

*3.12.3 **Management***

3.12.3.1 Prenatal management

Counselling the caregivers of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, as it may still be capable of meaningful renal function, unlike a severely hypoplastic and dysplastic kidney. It is important to be able to tell the caregivers exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected; there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia. Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres [700].

3.12.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis

The benefits and harms of continous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. Currently, only two RCTs have been published, one of which is a pilot trial [701] and the other publication is only available as a congress abstract [702]. Both publications present incomplete data and outcomes.

The Panel conducted a SR assessing the literature from 1980 onwards [703]. The key findings are summarised below.

Due to the heterogeneity of the published literature it was not possible to draw strong conclusions as to whether CAP is superior to observation alone in children diagnosed with antibiotic prophylaxis for antenatal hydronephrosis (ANH). In the first RCT, a prospective longitudinal study [701], female gender, uncircumcised males, lack of CAP, high-grade hydronephrosis, hydroureteronephrosis and VUR were found to be the independent predictors for the development of UTI. The second RCT included in the SR, was published as an abstract only, presented limited data [702]. This trial seemed to focus mainly on patients with ANH and VUR and did not report any beneficial effect of CAP on UTI rates, but details on the study population were limited.

Key findings of the SR are that CAP may or may not be superior to observation in children with antenatal hydronephrosis in terms of decreasing UTI. Due to the low data quality it was also not possible to establish whether boys or girls are at a greater risk of developing a UTI, or ascertain whether the presence or absence of VUR impacts UTI rates. A correlation between VUR-grade and UTI could not be established either. However, noncircumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing a UTI.

The SR also tried to identify the most effective antibiotic regimen and present data on adverse effects but, due to heterogeneity, the available data could not be statistically compared. The most commonly used antibiotic in infants with antenatal hydronephrosis is trimethoprim, but only one study reported side effects [701].

In conclusion, based on the currently available evidence, the benefits and harms of CAP in children with

antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis and high-grade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk.

3.12.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances.

Symptomatic obstruction (recurrent flank pain, UTI) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [704]. In experienced hands, laparoscopic or retroperitoneoscopic techniques and robot-assisted techniques have the same success rates as standard open procedures. In asymptomatic cases, conservative follow-up is the treatment of choice.

Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation as defined by the Society for Fetal Urology [496].

Well-established benefits of conventional laparoscopy over open surgery are the decreased length of hospital stay, better cosmesis, less post-operative pain and early recovery [705, 706]. A recent meta-analysis in children has shown that laparoscopic pyeloplasty (LP) was associated with decreased length of hospital stay and complication rates but prolonged operative time when compared to open pyeloplasty (OP). Additionally, both LP and OP had equal success rates [707]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better manoeuvrability, improved vision, ease in suturing and increased ergonomics but higher costs [708, 709]. There does not seem to be any clear benefit of minimal invasive procedures in a very young child but current data is insufficient to defer a cut-off age.

3.12.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3.13.3.

3.12.3.3.1 Non-operative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs, although there are no existing prospective randomised trials evaluating the benefit of this regimen [710]. With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTIs, deterioration of split renal function and significant obstruction [711].

3.12.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children and if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [712]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [713].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an anti-reflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [714]. Some institutions perform endoscopic stenting, but there is still no long-term data and no prospective randomised trials to confirm their outcome.

3.12.4 ***Conclusion***

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardised and have a good clinical outcome.

3.12.5 Summary of evidence and recommendations for the management of UPJ-, UVJ-obstruction

Summary of evidence	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal US investigation.	2
Ureteropelvic junction obstruction is the leading cause of hydronephrotic kidneys (40%).	1
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendations	LE	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourehrography in postnatal investigations.	2	Strong
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	2	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	Weak
Offer surgical intervention in case of an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the US, and grade IV dilatation as defined by the Society for Fetal Urology.	2	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	2	Weak
Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	2	Strong

3.13 Vesicoureteric reflux

Lack of robust prospective RCTs limits the strength of the established guidelines for the management of VUR. The scientific literature for reflux disease is still limited and the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies. The Panel have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on Panel consensus.

These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis and selective indications for both diagnostics and intervention. Although the Panel tried to summarise most of the possible scenarios in one single table, the table itself is still quite busy. The Panel strongly share the view that making simple and practical guidelines would underestimate the complexity of VUR as a sign of a wide range of pathologies [715].

3.13.1 Epidemiology, aetiology and pathophysiology

Vesicoureteric reflux is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension and renal failure. Patients with VUR present with a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention [716]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

The main management goal is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, LUTD, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or surgical), and the timing of treatment.

Many children present without symptoms of UTI and, because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence

of VUR in non-symptomatic children has been estimated at 0.4-1.8% [717]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [718]. Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) [718].

However, reflux detected by sibling screening is associated with lower grades [718] and significantly earlier resolution [719]. When VUR is discovered in siblings after UTI, it is usually high-grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient [720].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). Urinary tract infections are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve itself [721-724].

There is a clear co-prevalence between LUTD and VUR [372]. Lower urinary tract dysfunction refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction and may be accompanied with bowel problems [372]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [725]. A published Swedish reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [726].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [719]. Faster resolution of VUR is more likely with age less than one year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy [726-728].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [729-731].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general well-being [732-734].

Scar rates vary in different patient groups. Patients with higher grades of VUR present with higher rates of renal scars. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [735-740], whereas in patients with LUTD, this may increase up to 30% [508, 734, 741]. Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease [742].

*3.13.2 **Diagnostic evaluation***

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and LUT function. A basic diagnostic work-up comprises a detailed medical history (including family history, and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities.

The standard imaging tests include renal and bladder US, VCUG and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR [743]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [744, 745] (Table 7). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG [745].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [746]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [747-749]. Contrast enhanced voiding urosonography with intravesical instillation of different ultrasound contrast agents has been shown to be highly sensitive giving comparable results with conventional VCUG while avoiding exposure to ionising radiation [750, 751]. However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.

Table 7: Grading system for VUR on VCUG, according to the International Reflux Study Committee [752]

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. Dimercaptosuccinic acid scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up [753]. Dimercaptosuccinic acid can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [754]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [754, 755].

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of PUV. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [372]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

3.13.2.1 Infants presenting with prenatally diagnosed hydronephrosis

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [756, 757].

Ultrasound should be delayed until the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal US excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first one to two months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is rare, and if present it is likely to be low-grade [735, 758]. The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis [718]. The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR [718]. Dimercaptosuccinic acid provides more reliable and quantitative measurement of the degree of cortical abnormalities, first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [718, 737, 759-761].

When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [760]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need further evaluation to exclude obstruction.

3.13.2.2 Siblings and offspring of reflux patients

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR. In screened populations the prevalence of VUR is 27.4% in siblings and 35.7% in offspring [752]. The overall estimate for renal cortical abnormalities is 19.3% (11-54%), with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only,

the rate of renal damage is 14.4% (0-100%). Although early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [718, 720, 762, 763], screening in all siblings and offspring cannot be recommended based on the available evidence. The lack of RCTs for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

3.13.2.3 Recommendations for paediatric screening of VUR

Recommendations	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong
Use renal ultrasound (US) for screening of sibling(s).	Strong
Use voiding cystourethrography if there is evidence of renal scarring on US or a history of urinary tract infection.	Weak
Do not screen older toilet-trained children since there is no added value in screening for VUR.	Weak

3.13.2.4 Children with febrile urinary tract infections

A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. Children with febrile infections and abnormal renal US findings may have higher risk of developing renal scars and they should all be evaluated for reflux [764]. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan.

An alternative “top-down” approach is also an option, as suggested by several studies in the literature. This approach carries out an initial DMSA scan close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to identify VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in > 50% of those screened [365, 765-767].

3.13.2.5 Children with lower urinary tract symptoms and vesicoureteric reflux

Detection of LUTD is essential in treating children with VUR. It is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring [724, 768]. The co-existence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

Among toilet-trained children, those with both LUTD and VUR are at higher risk of developing recurrent UTIs than children with isolated VUR [769].

In LUTD, VUR is often low-grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously investigated. The co-existence of LUTD and VUR means it would be better to do a test covering both conditions, such as a VUDS. Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Furthermore, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

*3.13.3 **Disease management***

There are two main treatment approaches: conservative (non-surgical and surgical).

3.13.3.1 Non-surgical therapy

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- Vesicoureteric reflux resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within four to five years of follow-up. Spontaneous resolution is low for bilateral high-grade reflux [770].
- Vesicoureteric reflux does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD [508, 768, 771-773].
- Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children [774].

3.13.3.1.1 Follow-up

Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

3.13.3.1.2 Continuous antibiotic prophylaxis

Vesicoureteral reflux increases the risk of UTI and renal scarring especially when in combination with LUTD. Many prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent UTI and renal scarring.

It is clear that antibiotic prophylaxis may not be needed in every reflux patient [775-777]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. Toilet-trained children and children with LUTD derive much better benefit from CAP [398-401, 777, 778]. The RIVUR trial was the largest, randomised, placebo-controlled, double blind, multi-centre study, involving 607 children aged 2-72 months with grade I-IV VUR. The RIVUR study showed that prophylaxis reduced the risk of recurrent UTI by 50% but not renal scarring and its consequences (hypertension and renal failure), at the cost of increased antimicrobial resistance. The benefit of prophylaxis was insignificant in patients with grade III or IV VUR and in the absence of LUTD [403, 779-781]. Additional review of the RIVUR data based on a risk classification system defines a high-risk group (uncircumcised males; presence of BBD and high grade reflux) who would benefit from a antibiotic prophylaxis significantly. Therefore selective prophylaxis for this group is recommended [782].

It may be difficult and risky to select patients who do not need CAP. A safe approach would be to use CAP in most cases. Decision-making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female sex, and circumcision status. Although the literature does not provide any reliable information about the duration of CAP in reflux patients, a practical approach would be to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. Continuous antibiotic prophylaxis is mandatory in patients with LUTD and reflux. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an anti-reflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and caregivers. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

3.13.3.2 Surgical treatment

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral re-implantation.

3.13.3.2.1 Subureteric injection of bulking materials

With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow.

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon™), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, a solution of dextranomer/hyaluronic acid (Deflux™, Dexell®) and more recently polyacrylatepolyalcohol copolymer hydrogel (Vantris®) [783, 784].

Although the best results have been obtained with PTFE [785], due to concerns about particle migration, PTFE has not been approved for use in children [786]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux™ was approved by the USA FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux [787]. Studies with long-term follow-up have shown that there is a high recurrence rate which may reach as high as 20% in two years [777].

In a meta-analysis [788] of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) vs. single (73%) systems, and neuropathic (62%) vs. normal (74%) bladders.

Obstruction at UVJ may happen in the long term follow-up after endoscopic correction of reflux. Patients with high-grade reflux and dilated ureters are at risk of late obstruction. It is significantly more common when polyacrylate-polyalcohol copolymer is used as bulking substance [789-791].

Clinical validation of the effectiveness of anti-reflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms: i) endoscopic injection; ii) antibiotic prophylaxis; iii) surveillance without antibiotic prophylaxis in 203 children aged one to two years with grade III/IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms ii and iii, respectively, after two years' follow-up. The recurrence rate at two years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) [792]. Longer follow-up studies are needed to validate these findings.

3.13.3.2.2 Open surgical techniques

Various intra- and extravesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) [793].

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen [791]. The main concern with this procedure is the difficulty of accessing the ureters endoscopically, if needed, when the child is older. Alternatives are suprahiatal re-implantation (Politano-Leadbetter technique) and infrahiatal re-implantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical anti-reflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [794]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

3.13.3.2.3 Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal, extravesical and pneumovesicoscopic intravesical ureteral re-implantation, which have shown the feasibility of the techniques. Various anti-reflux surgeries have been performed with the robot and the extravesical approach is the most commonly used. Although initial reports give comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux, recent meta-analysis of results of Robotic-Assisted Laparoscopic Ureteral Reimplantation (RALUR) are within a wide range of variation and on average they are poor compared to open surgery. Operative times, costs and post-operative complications leading to secondary interventions are higher with RALUR but post-operative pain and hospital stay is less compared to open surgery [795-798].

Also, laparoscopic- or robotic-assisted approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. It can be offered as an alternative to the caregivers in centres where there is established experience [774, 799-807].

3.13.4 *Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood*

Summary of evidence
There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.
The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.
The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

Recommendations	**Strength rating**
Initially treat all patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer open surgical correction to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Initially manage all children presenting at age one to five years conservatively.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong
Select the most appropriate management option based on: • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; • parental preference. Refer to Table 8 for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

Table 8: Management and follow-up according to different risk groups

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

3.14 Urinary stone disease

*3.14.1 **Epidemiology, aetiology and pathophysiology***

Paediatric stone disease is an important clinical problem in paediatric urology practice. Due to its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with close follow-up are of the utmost importance, although, it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

Bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [808]. Patients with augmented bladder constitute another important group with a risk of up to 15% [809].

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American countries. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [810-812], especially in girls, Caucasian ethnicity, African Americans and older children [813]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [814].

*3.14.2 **Classification systems***

Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

3.14.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesemia) play a major role in the formation of calcium oxalate stones. Higher super-saturations of calcium oxalate was shown to be associated with multiple stone disease [815].

Hypercalciuria: This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day (0.1 mmol/kg/day) in a child weighing < 60 kg. In infants younger than three months, 5 mg/kg/day (0.125 mmol/kg/day) is considered to be the upper limit for normal calcium excretion [816].

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause leading to hypercalcaemia. Urinary calcium may increase in patients with high sodium chloride intake. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary hypercalcaemic hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [817].

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children [816, 817]. If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed.

However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the standard criterion for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted: levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH [816-818]. In addition to calcium, the 24-hour urine analysis should also include phosphorus, sodium, magnesium, uric acid, citrate and oxalate.

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child [819]. A brief trial of a low calcium diet can be carried out to determine if exogenous calcium intake and/or calcium hyperabsorption is contributing to high urinary calcium. Any recommendation to restrict calcium intake below the daily needs of the child should be avoided. Moreover, low calcium intake is a risk factor for stone formation [820] (LE: 3).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria, especially with calcium renal leak, at a starting dosage of 0.5-1 mg/kg/day [821-824] (LE: 3). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia, hypocitraturia, hyperuricaemia and hypomagnesaemia. Therefore, control of blood and serum values should be performed with regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [821, 825] (LE: 4).

Hyperoxaluria: Only 10-15% of oxalate comes from diet.
The average child excretes less than 50 mg (0.57 mmol)/1.73 m^2/day [826-828], while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In rare primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children have 'mild' (idiopathic) hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria. Citrate administration increases inhibitory urine activity [821, 829] (LE: 4).

Hypocitraturia: Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size [830-832].

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease [831, 833]. The urine calcium-to-citrate ratios were higher in recurrent calcium stone forming children than solitary formers [834].

The restoration of normal citrate levels is advocated to reduce stone formation, although there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses [822] (LE: 3). The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalemic and chronic renal failure conditions.

3.14.2.2 Uric acid stones

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day (0,6 mmol/kg/day) is considered to be hyperuricosuria [821].

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of < 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones [821]. In cases who failed with conservative measures with sustaining hyperuricosuria and hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

3.14.2.3 Cystine stones

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cysteine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shockwave lithotripsy (SWL). Cystinuric patients present with larger stones at the time of diagnosis, higher new stone formation rates, and are at higher risk of surgery [835].

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0 (better above 7.5). If this treatment fails, the use of α-mercaptopropionyl glycine or D-penicillamin may increase cystine solubility and reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever and rash, however they can be associated with severe side-effects, such as bone marrow depression, nephrotic syndrome and epidermolysis [836] (LE: 4).

3.14.2.4 Infection stones (struvite stones)

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over 10% in younger ages [837] and in non-endemic regions [814, 838]. Bacteria capable of producing urease enzyme (*Proteus, Klebsiella, Pseudomonas*) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, alkalinising the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

3.14.3 ***Diagnostic evaluation***

Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually visible, occurring with or without pain, is less common in children. However, nonvisible haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified [839, 840].

3.14.3.1 Imaging

Generally, US should be used as a first approach. Renal US is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination. The most sensitive test for identifying stones in the urinary system (especially for ureteric stones) is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity [841-843] (LE: 2). Despite its high diagnostic accuracy, because of the potential radiation hazards, its use should be reserved for cases with non-informative US and/or plain abdominal roentgenogram. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [844]. Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

3.14.3.2 Metabolic evaluation

Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with a urinary stone should be given a complete metabolic evaluation [808, 836, 845, 846]. A limited

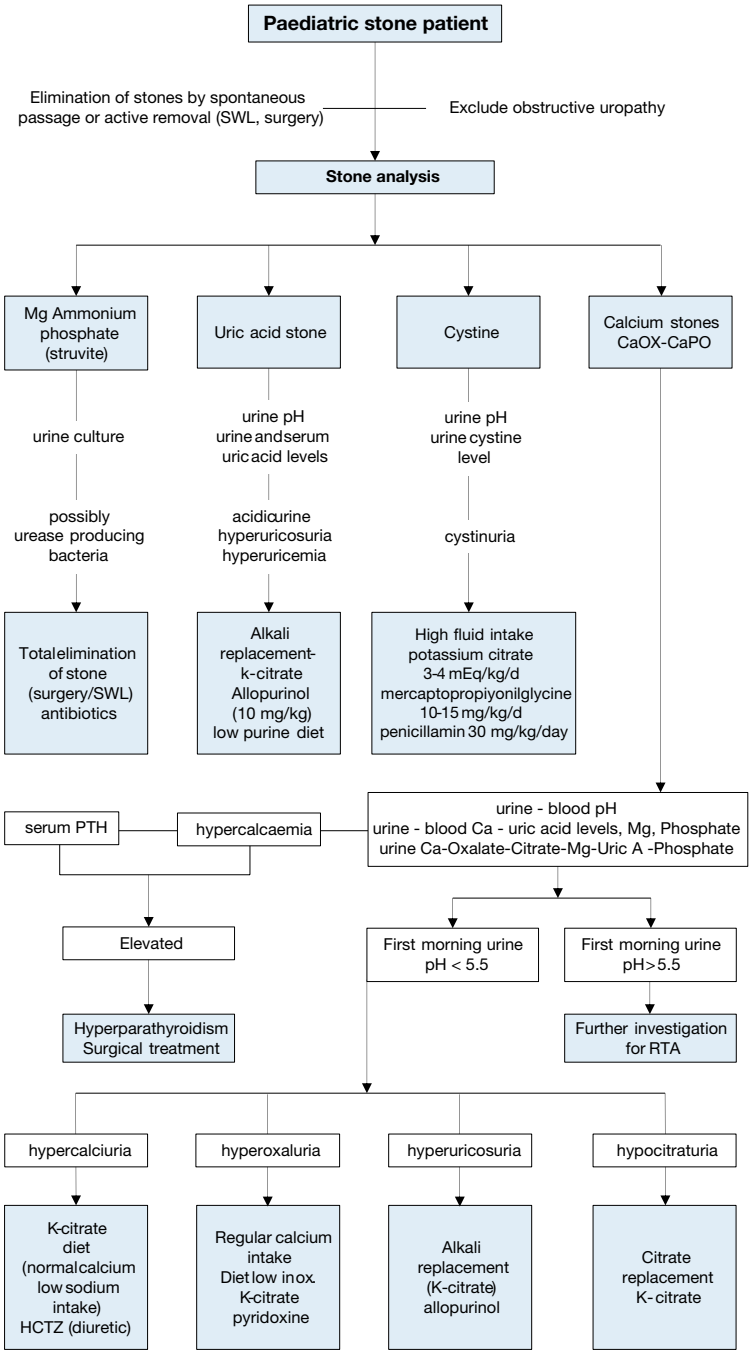
urinary metabolic evaluation (24-h calcium, citrate, and oxalate and low urinary volume) is able to detect the vast majority of clinically significant metabolic abnormalities [847]. However collections are most of the time inadequate and should be repeated in this case [847, 848].

Metabolic evaluation includes:

- family and patient history of metabolic problems and dietary habits;
- analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type);
- electrolytes, blood/urea/nitrogen (BUN), creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia);
- spot urinalysis and culture, including ratio of calcium to creatinine;
- urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, protein, and creatinine clearance;
- 24-hour cystine analysis if cystinuria is suspected (positive sodium nitroprusside test, cystine stone, cystine hexagonal crystals in urine).

Figure 9 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

Figure 9: Algorithm for metabolic investigations in urinary stone disease in children



Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric-A = uric acid.

3.14.4 ***Management***

Adequate fluid intake and restricting the use of salt within daily allowance range are the general recommendations besides the specific medical treatment against the detected metabolic abnormalities. With the advance of technology, stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding on the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [846, 849, 850]. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. There is no consensus on the size of stones for different ages eligible for clearance and the duration of conservative follow-up. Adult literature reveals the benefits of medical expulsive therapy (MET) using α-blockers. Although, experience in children is limited showing different results [851], a meta-analysis of three randomised and two retrospective studies demonstrate that treatment with MET results in increased odds of spontaneous ureteral stone passage and a low rate of adverse events [852]. Currently, most paediatric

stones can easily be managed by SWL. Endoscopic treatment can be applied for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will require open surgery but all attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [853, 854]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

3.14.4.1 Extracorporeal shockwave lithotripsy

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [855-862].

The mean number of shockwaves for each treatment is approximately 1,800 and 2,000 (up to 4,000 if needed) and the mean power settings vary between 14 kV and 21 kV. The use of US and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults [849, 863, 864]. Concerns about anaesthesia no longer present a problem due to advances in technique and medication, even in the infant age group. The type of anaesthesia should be general or dissociative for children under ten years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate [865] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and retreatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [849, 863, 864, 866-870].

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in the renal pelvis and upper ureter seem to respond better to SWL. For these locations, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones; particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% [871-873].

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and controversial. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children [872-875].

The type of machine used significantly influences success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma, however, additional treatments may be needed. The success rate is higher in younger children [868].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [868, 870]. Stenting is essential in solitary kidneys undergoing SWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after SWL. Post-SWL stent or nephrostomy tube placement may be needed in prolonged obstruction [836, 867].

The Hounsfield Unit (HU) of stone on non-contrast tomography has also been shown to be a predictive factor for success in children and SWL was found to be more successful in stones with HU less than 600 [854] and 1,000 [876]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower pole localisation and negative history for previous intervention are favourable factors for stone clearance in paediatric SWL [877, 878]. A recent comparative study reported that these two nomograms are independent predictors of stone-free rate following SWL in paediatric patients [879]. Although, the invention of miniaturised endoscopic instruments seems to reduce the importance and popularity of SWL, it has the advantage of not carrying the risk of certain complications related to endoscopic surgeries and moreover studies comparing SWL and RIRS showed that besides having similar stone-free rates, SWL was cheaper, had shorter hospital stay [880],with less post-operative emergency visit, pain and anaesthetic session [881]. Complications arising from SWL in children are usually self-limiting and transient. The most common are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- UTI;
- formation of Steinstrasse;
- sepsis;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [882]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [883-892].

3.14.4.2 Percutaneous nephrolithotomy

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children and adults. In most cases, percutaneous nephrolithotomy (PCNL) is used as monotherapy, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase blood loss. However, the development of small-calibre instruments means that PCNL can be used in children. In children (particularly smaller children), PCNL has some advantages, such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [882, 893, 894].

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session [886, 895-899].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% [900-905] and is closely associated with stone burden, operative time, sheath size and the number of tracts [904, 906, 907]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [900, 901, 903-905, 908] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('miniperc') through a 13F or 14F sheath [894, 909, 910] as well as ultramini-PCNL (UMP) through 12F sheaths [911] have become possible, with decreased transfusion rates [909]. The mini- and supermini-PCNL (SMP) were shown to have higher efficacy with acceptable complication rates which were deemed to be a safe alternative to SWL by some authors [912, 913]. The SMP was shown to be advantageous over mini-PCNL in terms of complications with similar stone-free rates [914, 915]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique is still experimental and enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [916]. A study revealed that microperc provides a similar stone-free rate with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [917] (LE: 3). For stones 10-20 mm, micro-PNL was shown to have comparable results, with lesser bleeding, compared to mini-PCNL [918] and similar outcomes with less anaesthetic sessions compared to RIRS [919] (LE: 3). As experience has accumulated in adult cases, new approaches have also started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones < 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [902, 908] or totally tubeless [920]. Moreover, use of US for establishment of access is gaining popularity [921, 922] and supine approach [923] was also reported to be feasible in children.

The mean post-operative hospital stay is similar to adults. It is reported as three to four days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2) [900, 902, 903, 905-908, 910, 911, 916-918, 920, 923, 924].

3.14.4.3 Ureterorenoscopy

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of the ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed much less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [882, 884, 890, 925-928] (LE: 3).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [883-892].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1). The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [929]. A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate [930]. However, for proximal ureteral stones semi-rigid ureteroscopy is not a good first option because of higher complication and failure rates [931].

A recent literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach [932-937]. In these series, the authors generally did not use active orifice dilation, but attempted to use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [933, 935]. This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice, and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications [932, 934-936, 938]. The need for additional procedures was related to stone size [936]. A comparative study showed that retrograde intra-renal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [939], however for stones larger than 2 cm, RIRS monotherapy has lower stone-free rates than mini-PCNL with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [940] (LE: 3). On the other hand, for stones between 10-20 mm, RIRS has similar success and complication rates and shorter hospital stay and low radiation exposure when compared to micro-PNL [941] (LE: 3). Two recent meta-analyses revealed that RIRS has similar operative time and stone-free rate with an overall lower complication rate [942] where PCNL has higher stone-free rate in stones larger than 20 mm [943].

3.14.4.4 Open or laparoscopic stone surgery

Most stones in children can be managed by SWL and endoscopic techniques. However, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system, which also require surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with a well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant ureteropelvic junction (UPJ) obstruction or caliceal diverticula, mega-ureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is very limited experience with these techniques and they are not routine therapeutic modalities [944-947].

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to the advantages and disadvantages of each treatment modality for the specific size and location of the stone, one will have to consider the availability of the instruments and the experience with each treatment modality before the choice of technique is made. Recommendations for interventional management are given in Table 9.

Table 9: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	Secondary treatment options	Comment
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	PCNL/RIRS/ MicroPerc/Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
< 10 mm	SWL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx	SWL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
> 10 mm	PCNL	SWL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	PCNL/URS/Open	
Lower ureteric stones	URS	SWL/Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.

** Cystine and uric acid stones excluded.*
PCNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

*3.14.5 **Summary of evidence and recommendations for the management of urinary stones***

Summary of evidence	LE
The incidence of stone disease in children is increasing.	2
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.	2a
The term ‘clinically insignificant residual fragments’ is not appropriate for children since most of them become symptomatic and require intervention.	2b

Recommendations	LE	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	2b	Strong
Use low-dose non-contrast computed tomography in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	2a	Strong
Perform a metabolic evaluation in any child with urinary stone disease. Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	2a	Strong
Limit open surgery under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopaedic deformities that limit positioning for endoscopic procedures.	2a	Strong

3.15 Obstructive pathology of renal duplication: ureterocele and ectopic ureter

*3.15.1 **Epidemiology, aetiology and pathophysiology***

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal US detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

3.15.1.1 Ureterocele

Ureterocele is four to seven times more frequent in female than in male patients; the overall incidence in autopsies is around one in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral [948].

3.15.1.2 Ectopic ureter

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio is 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [949]. Eighty per cent of ectopic ureters are associated with complete renal duplication; however, in male patients about 50% of ectopic ureters are associated with a single system [950].

3.15.2 Classification systems

3.15.2.1 Ureterocele

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [951-953]. A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole.

Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele [954]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [955]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [956, 957]. The corresponding ureter is a mega-ureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional. Histological evaluation demonstrated that the changes represent a process of maldevelopment and may not result from infections or obstruction [956, 957].

3.15.2.1.1 Ectopic (extravesical) ureterocele

If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive mega-ureter. A contralateral renal duplication is associated with 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

3.15.2.1.2 Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is diagnosed more in older children or adults.

3.15.2.2 Ectopic ureter

The term ectopic ureter describes a ureter with the orifice located at the bladder neck, in the urethra, or outside the urinary tract. The ureter can drain the upper pole of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located [958]:

- in the urethra, from the bladder neck to the meatus (35%);
- in the vaginal vestibule (34%);
- in the vagina (25%);
- in the uterus and Fallopian tube (6%).

In boys, the ureteral orifice may be located [958]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%);
- in the vas deferens or ejaculatory ducts (10%).

*3.15.3 **Diagnostic evaluation***

3.15.3.1 Ureterocele

Prenatal US easily reveals voluminous obstructive ureteroceles [959]. In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult.

If prenatal diagnosis is impossible, the following clinical symptoms, besides incidental findings, can reveal the congenital anomaly at birth or later:

- At birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis, at birth US confirms the ureteral dilatation that ends at the upper pole of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA, however this requires a careful systematic review of the images [960]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney as well as it can detect renal scars [961, 962]. Using functional MR urography, differential renal function can be assessed with low intra- and interobserver variability [963]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux and assessing the degree of intra-urethral prolapse of the ureterocele [964]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic mega-ureter.

3.15.3.2 Ectopic ureter

Most of the ectopic mega-ureters are diagnosed primarily by US. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [965].
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasound, radionuclide studies (DMSA, VCUG, MR urography, high-resolution MRI, and cystoscopy) are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction [966]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [967].

Girls who present with life-long minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal US are very suspicious for ectopic ureter. This needs to be excluded or confirmed by MRI as it is the most sensitive method [968].

*3.15.4 **Management***

3.15.4.1 Ureterocele

Management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [969-973]. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and caregivers' and the surgeon's preferences [974]. When the diagnosis is made by US, prophylactic antibiotic treatment maybe indicated until a VCUG is performed.

3.15.4.1.1 Early treatment

In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non

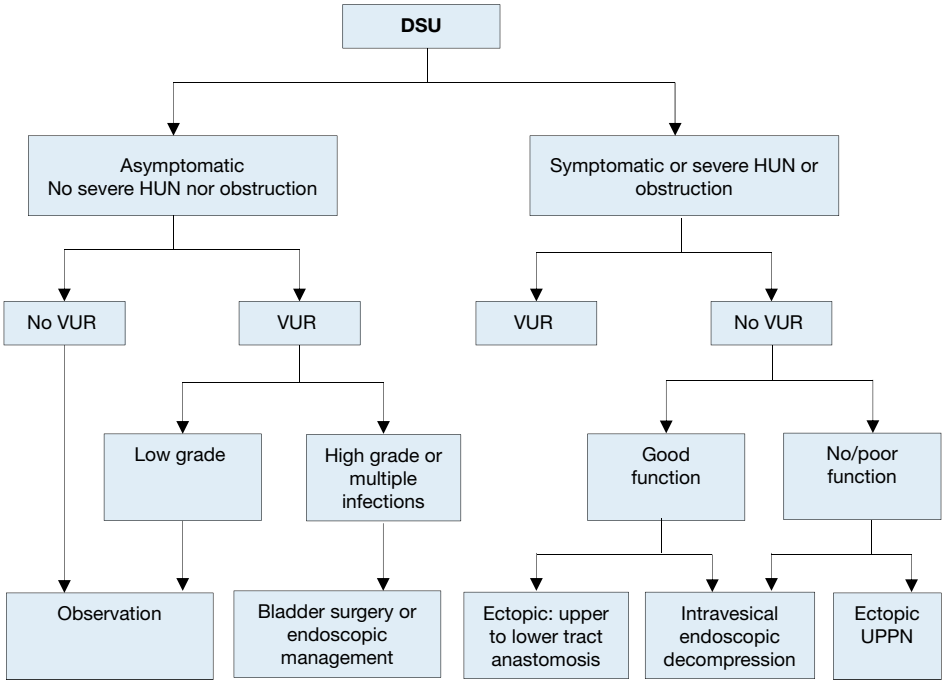
or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated. Decompression of the dilated system facilitates later reconstructive surgery [975, 976].

3.15.4.1.2 Re-evaluation

Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [974, 977]. A meta-analysis showed that, after primary ureterocele-incision, the re-operation rate is higher in those with an ectopic ureterocele compared to those with an intravesical ureterocele [970]. Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction or retained ureterocele [978].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [973, 979-981]. In an ectopic ureterocele with severe hydroureteronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) has an 80% chance of being the definitive treatment [974, 982]. Also a LUT approach in those with a poorly or non-functioning upper pole is an option [983]. Today, despite successful surgery, some authors think, that surgery may not be necessary at all in some patients [984], as less aggressive surgical treatment and non-operative management over time can achieve the same functional results [985].

Figure 10: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [974]



DSU = duplex system ureterocele; HUN = hydroureteronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

3.15.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and poorly functioning. There are a variety of therapeutic options, each with its advantages and disadvantages. In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definite solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic options especially in cases in which the upper pole has function worth preserving. These procedures can be performed through an open laparoscopic or robotic assisted approach [986-989]. So far there is no superior approach [990]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function of the patient is necessary. Usually the bladder neck is insufficient in these patients [991].

3.15.5 Summary of evidence and recommendations for the management of obstructive pathology of renal duplication: ureterocele and ectopic ureter

Summary of evidence	LE
Ureterocele and ectopic ureter are associated with complete renal duplication, but they also occur in a single system.	1
In most cases, in young children (first years of life) diagnosis is done by US.	1
In older children clinical symptoms will prompt assessment.	1
Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on: • clinical status of the patient (e.g., urosepsis); • patient age; • function of the upper pole; • presence of reflux or obstruction of the ipsilateral or contralateral ureter; • presence of bladder neck obstruction caused by ureterocele; • intravesical or ectopic ureterocele;	3

Recommendations			LE	Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureteretomy, complete primary reconstruction. Offer, early endoscopic decompression to patients with an obstructing ureterocele.	3	Weak
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	Weak
	Treatment	In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	3	Weak

3.16 Disorders of sex development

3.16.1 Introduction

The formerly called ‘intersex disorders’ were the subject of a consensus document in which it was decided that the term ‘intersex’ should be changed to ‘disorders of sex development’ (DSD) [992, 993].

The new classification has arisen due to advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and negative terminology, e.g. ‘pseudohermaphroditism’ and ‘hermaphroditism’, have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis and cloacal exstrophy, which could not be categorised, have also been included. The term ‘disorders of sex development’ is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex.

In addition, in 2017, the Parliamentary Assembly of the Council of Europe decided on a resolution called: “Promoting the human rights of and eliminating discrimination against intersex people” [994]. The Parliamentary Assembly concluded that the majority of intersex people are physically healthy and only a few

suffer from medical conditions that put their health at risk. Furthermore, they state that the prevailing medical view has been that intersex children's bodies can and should be made to conform to either a male or a female paradigm, often through surgical and/or hormonal intervention and that this should be done as early as possible and that the children should then be raised in the gender corresponding to the sex assigned to their body. The Parliamentary Assembly considers that this approach involves serious breaches of physical integrity, in many cases concerning very young children or infants who are unable to give consent and whose gender identity is unknown.

Therefore the Parliamentary Assembly call on Council of Europe member states with regard to effectively protecting children's right to physical integrity and bodily autonomy and to empowering intersex people as regards the following rights: medically unnecessary sex-"normalising" surgery, sterilisation and other treatments practised on intersex children without their informed consent should be prohibited and in addition that it has to be ensured that, except in cases where the life of the child is at immediate risk, any treatment that seeks to alter the sex characteristics of the child, including their gonads, genitals or internal sex organs, is deferred until such time as the child is able to participate in the decision, based on the right to self-determination and on the principle of free and informed consent.

The Panel refers to the consensus documents mentioned above as well as on the Parliamentary Assembly resolution. This chapter will focus on what is relevant for the practising paediatric urologist as the urologist is likely to be involved in neonates with DSD conditions.

Overall, evidence-based literature on DSD is sparse. There are no RCTs and most studies are based on retrospective clinical descriptive studies or on expert opinion. An exception is the risk of gonadal cancer, for which the level of evidence is higher [995].

Disorders of sex development can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or US findings; neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty. In this guideline focus is on the neonatal presentation where the paediatric urologist plays a major role. For late diagnosis we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty where paediatric urologists play a minor role [996, 997].

Dealing with neonates with DSD requires a multidisciplinary approach, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have treated enough patients to ensure experience.

*3.16.2 **Current classification of DSD conditions***

Since the International Consensus Conference on intersex and its subsequent publications on classification of the various conditions of DSD, several updates have been published with the latest published by the Global DSD Update Consortium in 2016 [998]. As the field of DSD is continuously developing and knowledge and viewpoints change over time, an effort was made to include representatives from a broad perspective including support and advocacy groups with the goal to focus patient care upon the best possible quality of life.

According to the international consensus in 2005, DSDs were defined as congenital conditions within which the development of chromosomal, gonadal and anatomic sex is atypical. The changes that were made according to terminology are as follows:

46XX DSD group formerly called female pseudohermaphrodite, over-virilisation of an XX female, and masculinisation of an XX female. In this group the vast majority is due to classic congenital adrenal hyperplasia (CAH) with various degrees of masculinisation. Among all DSD conditions together, 46XX CAH patients comprise approximately 80%. These conditions are extremely important since they can be potentially life threatening after birth because of salt loss phenomenon and immediate medical care is mandatory.

46XY DSD group in the past named male pseudohermaphrodite, undervirilisation of an XY male, and undermasculinisation of an XY male. This group is often quite heterogenous and includes the partial androgen insensitivity syndrome (PAIS) as well as the complete androgen insensitivity syndrome (CAIS) formerly called testicular feminisation.

Sex chromosome mosaicism DSD group (45X, 45X/46XY, 47XXY) consists of multiple variants with the mixed gonadal dysgenesis being the most important one. Many have a normal male phenotype and others asymmetric genitalia. One scrotal half often contains a gonad which is likely to be a testis whereas the other side is more a labia majora with usually no palpable gonad, most likely to be a streak gonad.

Ovotesticular DSD group was in the past called true hermaphrodite because of the presence of ovarian and testicular tissue in the same individual meaning that both – female and male structures – live together. There is great variability in phenotype with uni- or bilateral undescended gonads which can present as one ovary and one testis or as one or two ovotestes.

Non-hormonal/non-chromosomal DSD group was introduced as well, including newborns with cloacal exstrophy where bladder and intestines are exposed, patients with aphallia, and severe micropenis. The latter one is a normally formed penis with a stretched length of < 2.5 standard deviation below the mean [992, 993, 999].

Micropenis should be distinguished from buried and webbed penis, which are usually of normal size. The length of the penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [993].

*3.16.3 **Diagnostic evaluation***

3.16.3.1 The neonatal emergency

The first step is to recognise the possibility of DSD (Table 10) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. Diagnosis of a 46XX DSD due to congenital adrenal hyperplasia should not be delayed and represents a neonatal emergency situation since the possibility of salt loss phenomenon can be fatal.

Table 10: Findings in a newborn suggesting the possibility of DSD
(adapted from the American Academy of Pediatrics)

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

3.16.3.2 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination including various laboratory tests and imaging modalities (Table 11).

Table 11: Diagnostic work-up of neonates with disorders of sex development

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure

Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test to confirm presence of testicular tissue
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone.

A thorough clinical examination in a neonate presenting with ambiguous genitalia is important. As well as an accurate description of the ambiguous genitalia, detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis. Medical photography can be useful but requires sensitivity and consent [1000].

Palpable gonad: If it is possible to feel a gonad, it is most likely to be a testis; this clinical finding therefore virtually excludes 46XX DSD.

Phallus: The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening: The opening of the urogenital sinus must be well evaluated. A single opening has to be identified as well as a hymenal ring. Attention needs to be paid to the fusion of the labioscrotal folds as well as whether they show rugae or some discolouration.

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity are not high. Mülllerian structures like the vagina or utricular structures can be evaluated as well [1001, 1002].

Genitography can provide some more information on the urogenital sinus, especially on the exact position of the confluence. Moreover it gives evidence of possible duplication of the vagina.

Invasive diagnostics under general anaesthesia can be helpful in some cases.
On cystoscopy, the urogenital sinus can be evaluated as well as the level of confluence. It allows also for evaluation of the vagina or utriculus, the possible presence of a cervix at the top of the vagina.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed [1003, 1004].

These investigations will help to distinguish the various conditions of DSD and provide quick evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD and the one that can become life-threatening within the first days of life because of salt loss phenomenon.

*3.16.4 **Gender assignment***

Nowadays it is obvious and clear that open and complete communications with caregivers and eventually the affected person are mandatory. Education and psychological support regarding the impact are needed for each individual to make sense of the condition, relate to their community and establish relationships. The lack of outcome data and different preferences make it extremely difficult to determine whether and when to pursue gonadal or genital surgery. Shared decision making is necessary, combining expert healthcare knowledge and the right of a patient or surrogate to make fully informed decisions. This entails a process of education, sharing of risks/benefits, articulating the uncertainties in DSD care and outcomes and providing time for the patient and family to articulate back the risks and benefits of each option. The goal of all involved should be to individualise and prioritise each patient.

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Recently the Parliamentary Assembly of the Council of Europe, the European Society for Paediatric Urology (ESPU) as well as the Societies for Pediatric Urology have taken a position in the debate on surgery for DSD [994, 1005, 1006].

In an open letter to the Council of Europe, the European Society for Paediatric Urology expressed its attitude to the abovementioned resolution and concentrated on a worrying issue dealing with medico-surgical care for children with DSD. They state that surgical interventions in children with DSD only being applied in emergency conditions is discordant with the definition of health according to the World Health Organization (WHO), stating that health is not merely the absence of disease, but is a much broader concept, including physical, mental, and social domains. This especially applies to children, as favourable physical, social and emotional conditions are all critical factors for their optimal growth and development, which enables them to reach their full potential at adult age. As social and emotional interactions with the parents or caregivers, being the most important adults in a young child's life, form the basis for their future, treatment of children with DSD can best be organised in a patient- and family-centred multidisciplinary setting, in an atmosphere based on openness, commitment and trust. Physicians, who daily take care of children with a variety of congenital conditions, the same as their parents or caregivers, are committed to the current as well as the future health and well-being of all children entrusted to their care. In contrast to what is alleged in the recommendation, parents and caregivers implicitly act in the best interest of their children and should be respected as their outstanding representatives, and should not be put aside by claiming prohibition regulations regarding the well-informed decisions they make on their behalf. Finally in that open letter the ESPU advocate keeping the dialogue open with the professionals active in specialised centres for multidisciplinary, patient- and familycentred care as well as with patient societies, for which the present resolution is recognised as being a solid starting base [1007].

*3.16.5 **Risk of tumour development***

Individuals with DSD have an increased risk of developing cancers of the germ cell lineage, malignant germ cell tumours or germ cell cancer in comparison with to the general population [1008].

It is well recognised that the highest risk prevalence (30-50%) is seen in conditions characterised by disturbed gonadal development such as incomplete testis development combined with a full block of embryonic germ cell maturation in patients with 46XY gonadal dysgenesis and in some patients with 45X/46XY DSDs. Conversely, patients with testosterone biosynthesis disorders and androgen action disturbances show a much lower risk (1-15%) for carcinoma in situ (CIS) development during childhood and a limited tendency towards invasive progression of the lesions [1009]. With regard to clinical management a gonadal biopsy at the time of a possible orchidopexy can be obtained for an initial assessment including regular self-exams and annual ultrasound [995].

*3.16.6 **Recommendations for the management of disorders of sex development***

Recommendations	Strength rating
Newborns with DSD conditions warrant a multidisciplinary team approach.	Strong
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	Strong
Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	Strong

3.17 Congenital lower urinary tract obstruction (CLUTO)

Introduction

The term congenital lower urinary tract obstruction (CLUTO) is used for a foetus, which shows during intrauterine US screening a dilatation of the upper and lower urinary tract. At that time of life, the diagnosis is usually based only on US examinations. There is a broad spectrum of conditions, which could cause an intrauterine dilatation of the urinary tract. Postpartum diagnosis comprises PUV in 56-63%, urethral atresia/dysplasia in 9%, urethral stenosis in 3-7%, anterior urethral valve in less than 1%, a prune belly syndrome in up to 25% and a dilating reflux in up to 13%. Cloacal malformation can be found in 5-15%, ureterocele in 1-2%, a Megacystis-Microcolon-intestinal hypoperistalsis syndrome in 1-3% and also a Megacystis-Megaureter Syndrome in 1% [1010-1013].

Megacystis

In the first trimester, foetal megacystis is defined as a bladder with a longitudinal diameter ≥ 7 mm, and in the 2nd and 3rd trimester as an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes. Two thirds of cases are secondary to CLUTO and the remainder are associated with genetic syndromes, developmental or chromosomal abnormalities including anorectal malformations [1014]. A more recent SR showed that at least 45% of cases have oligohydramnios and 15% have chromosomal abnormalities, most of them being trisomy 13, 18 and 21. Final diagnoses were PUV (57%), urethral

atresia/stenosis (7%), prune-belly syndrome (4%), megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) (1%), cloacal abnormality (0.7%) and undefined pathologies (36.5%). Termination of pregnancy rate was 50% [1015].

The prognosis of the foetus depends on the underlying pathology, the timing of diagnosis, presence of an oligo-, an-hydramnios and bladder volume. Fontanella *et al* developed a staging system of LUTO. They described three groups: severe (Bladder volume ≥ 5.4 cm^3 and/or oligo-, an-hydramnios before 20 weeks), moderate (Bladder volume < 5.4 cm^3 and/or normal amniotic fluid at 20 weeks) and mild (Normal AF at 26 weeks) [1016]. This staging system can be used to predicted perinatal mortality and postnatal estimated GFR. Another recent SR on prognosis of megacystis patients revealed an overall intrauterine spontaneous resolution of 32% that is better in early (before 18 weeks) megacystis cases (40% vs. 12%) [1017].

*3.17.1 **Posterior urethral valves***

3.17.1.1 Epidemiology, aetiology and pathophysiology

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. A recent systematic review showed, that the risk for chronic kidney disease (CKD) could be up to 32% and for ESKD up to 20% [1018]. Up to 17% of paediatric ESKD can be attributed to PUV [1019]. An incidence of PUV of 1 in 7,000-8,000 live-births has been estimated [1011, 1020].

*3.17.2 **Classification systems***

3.17.2.1 Urethral valve

Despite some attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane' (COPUM) [1021], the original classification by Hugh Hampton Young remains the most commonly used [1022]. Hugh Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and III are as follows:

Type I (90-95%). 'In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbomembranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet, the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists' [1022].

Type III. 'There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre [1011]. The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [1023]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [1024].

*3.17.3 **Diagnostic evaluation***

An obstruction above the level of the urethra affects the whole urinary tract to varying degrees.

- The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux.
- The bladder neck is hypertrophied and rigid.
- The hypertrophied bladder occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both upper urinary tract. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder.
- If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal US screening, bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. A thick-walled bladder seems to be of better prediction of a PUV than a dilated posterior urethra ('keyhole' sign) [1025]. In the presence of increased echogenicity of the kidney, dilatation of the urinarytract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

Voiding cystourethrogram confirms the diagnosis of a PUV . This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV [1026]. Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis [1027]. Other types of pop-off

mechanisms include bladder diverticula and urinary extravasation, with or without urinary ascites [1028]. However, in the long-term, this supposed protective effect did not show a significant difference compared to other patients with PUV [1029, 1030].

Nuclear renography with split renal function is important to assess kidney function (DMSA or MAG3). Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. Initial management includes a multi-disciplinary team involving a paediatric nephrologist. The clinician must be aware of a noteworthy association between PUV and undescended testicles and/or inguinal hernia [1031]. Undescended testicles occurred in 12-17% of PUV consistent with a 10-fold increase. [1032].

*3.17.4 **Management***

3.17.4.1 Antenatal treatment

About 40-60% of PUV are discovered before birth [1033]. The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a foetus with PUV.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90 mmol/L and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis [1034]. Urine samples before 23 weeks of gestation (ß2-microglobline, sodium, chloride and calcium) may be helpful to distinguish between those who could benefit from intrauterine therapy and those in whom the outcome is most likely to be compromised [1035]. The status of amnion fluid, the appearance of the kidneys as well as the foetal urine biochemistry is helpful in counselling the caregivers.

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% [1034, 1036, 1037]. Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV [1036, 1037]. The PLUTO-trail (randomised study) as well as a recent meta-analysis failed to show any long-term benefit on renal function by placing a visual analogue scale (VAS) [1038, 1039]. Foetal cystoscopy with laser ablation has a high complication rate without evidence for the effectiveness of these interventions [1040, 1041]. The number of patients included and designs of these studies are insufficient to give any recommendations.

3.17.4.2 Postnatal treatment

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterised with a small catheter without a balloon, preferably a feeding tube. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. In cases were the urethra is too small to safely pass a small foetal cystoscope, a suprapubic diversion is performed until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are now available either to incise, ablate or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid extensive electrocoagulation, as the most common complication of this procedure is stricture formation. Two studies demonstrated a lower urethral stricture rate using the cold knife compared to diathermy [1042, 1043]. Within the three months following initial treatment, effectiveness of the treatment should be demonstrated either by clinical improvement (US and renal function) control VCUG or a re-look cystoscopy, depending on the clinical course [1044-1046].

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a suprapubic diversion is performed to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for six to twelve weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of the upper urinary tract in up tp 90% of cases [1047]. Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations [1048, 1049]. Moreover, it was shown in PUV patients with stage 3 CKD that adding vesicostomy to valve ablation no long-term benefit was noted from diversion in the ultimate incidence of ESKD [1050].

High diversion. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages [1051-1053]. Diversion can delay progression to end stage renal failure [1050]. Reconstructive surgery should be delayed until the UUT has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [1054]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [777] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [1055]. However, there are no randomised studies to support this for patients with PUV. Early administration of oxybutynin may improve bladder function as shown in one study with eighteen patients [1056]. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor [1057, 1058]. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. Moreover, in the long term it may be necessary to augment the bladder and in this case the ureter may be used [1059]. Deterioration of renal function without a fixed obstruction and higher urine output (polyuria) may lead to an overdistension of the bladder during the night. Drainage of the bladder during the night by a catheter may be beneficial for the hydronephrosis as well as for renal function [1060, 1061]. Patients with high daytime PVR urine may benefit from CIC [1062, 1063]. In those who do not want or are not able to perform a CIC via urethra, the placement of a Mitrofanoff is a good alternative [1064].

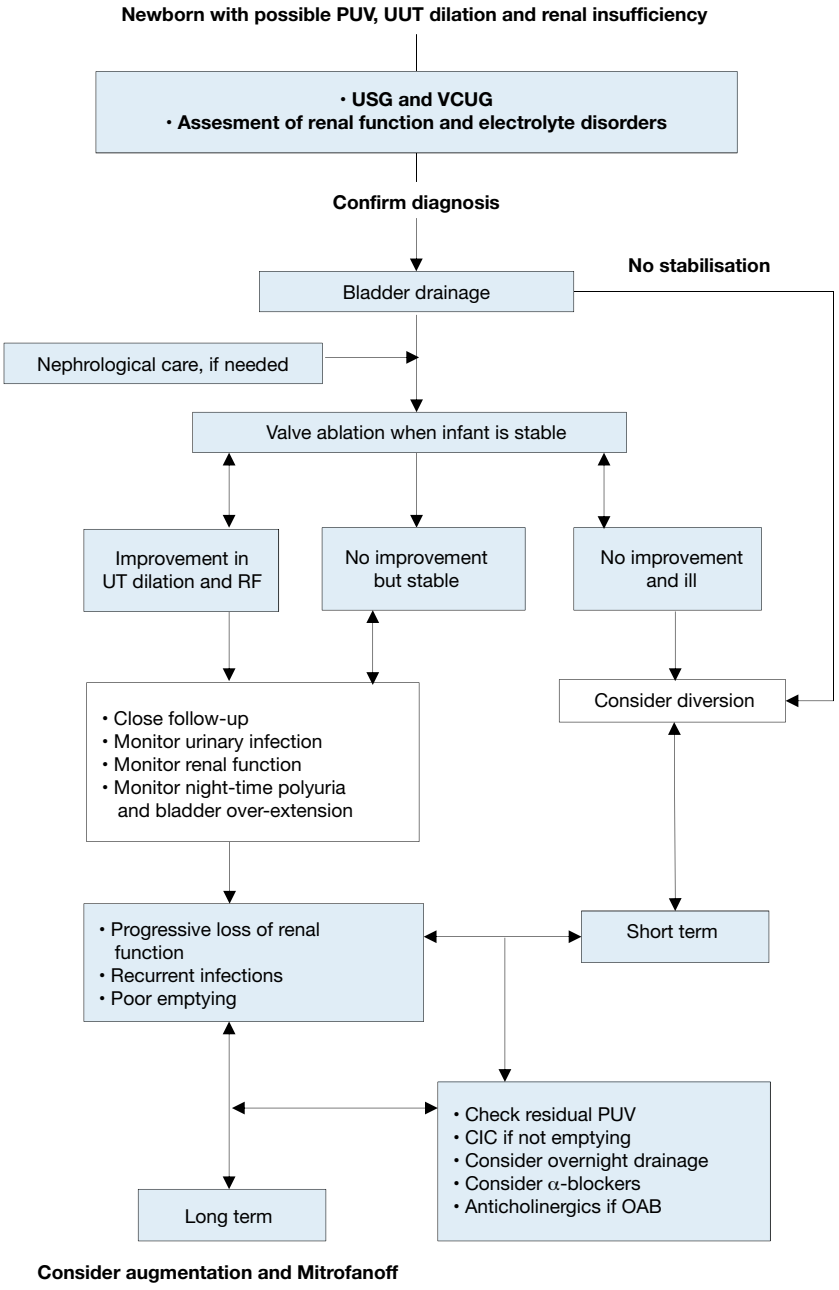
3.17.5 ***Follow-up***

Several prognostic factors have been described. Different serum nadir creatinine levels are given in the literature (0.85 mg/dl-1.2 mg/d (µmol/L); [1065-1068]. Renal parenchyma quantity (total renal parenchymal area) and quality (corticomedullary differentiation and renal echogenicity) on initial postnatal ultrasound also have prognostic value [1069].

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is not uncommon and the delay in day- and night-time continence is a major problem [1026, 1070, 1071]. The literature demonstrates that urodynamic studies plays an important role in the management of patients with valve bladder especially in those with suspicion of bladder dysfunction [1072, 1073]. Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, with a low risk of reversible myogenic failure (3/37 patients in one study) [1074, 1075]. In patients with poor bladder emptying, α-blocker can be used to reduce the PVR urine, as demonstrated in one study with 42 patients using terazosin (mean PVR was reduced from 16 to 2 mL) [1076]; in another study tamsulosin was effective [1077]. Concerning bladder neck incision, there is no panel consensus concerning indication and efficacy. High creatinine nadir (> 1 mg/dl) and severe bladder dysfunction are risk factors for renal replacement therapy [1078, 1079]. Renal transplantation in these patients can be performed safely and effectively [1080, 1081]. Deterioration of the graft function is mainly related to LUTD [1080]. An assessment and treatment algorithm is provided in Figure 11.

There are only few reports on sexual function and fertility in patients with PUV demonstrating some impairment especially in those who are on dialysis [1082, 1083]. In a review the majority have good erectile function (74-94%) and a fertility comparable to the normal population [1084]. However, a negative influence of the individual patient's fertility has to be taken into account as these patients have a higher risk for bilateral cryptorchidism, recurrent epididymitis and ESRD [1084].

Figure 11: An algorithm on the assessment, management and follow-up of newborns with possible PUV



CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve; RF = renal function; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

3.17.6 ***Summary***

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a PUV in neonates. A VCUG confirms a PUV diagnosis. Nuclear renography with split renal function is important to assess kidney function and serum creatinine nadir above 80 µmol/L is correlated with a poor prognosis.

Postnatal treatment includes bladder drainage either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long-term between 10% and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

Anterior urethral valve (AUV)

Anterior urethral valve is a semilunar or iris-like band of tissue on ventral aspect of urethra. It can be isolated, in association with or confused with urethral diverticulum. The aetiology of isolated AUV is speculated to be secondary to congenital urethral obstruction, malunion of glanular and penile urethra, congenital cystic dilatation of peri-urethral glands or ruptured distal lip of a syringocele [1085]. Anterior urethral valve occurs less frequently than PUV. It can be present in the bulbous urethra, the penoscrotal junction and penile urethra. Patient may present with poor urinary stream, penile ballooning, UTI or haematuria. Anterior urethral valves have been classified by Firlit *et al* depending on the presence of diverticulum and the dilatation of urethra and upper tract [1086]. The diagnosis is based on VCUG with possible findings of dilated or elongated posterior urethra, a dilatation of the anterior urethra, a thickened trabeculated bladder, a hypertrophied bladder neck, VUR, and urethral diverticula. In doubtful cases retrograde urethrography may be helpful showing linear filling defect along the ventral wall, or it may show a dilated urethra ending in a smooth bulge or an abrupt change in the caliber of the dilated urethra on VCUG [1087]. Treatment is performed mainly by endoscopic valve ablation. In selected patients, a temporary diversion may be considered until the child is big enough for endoscopy to be possible. Open surgery is reserved in patients with very large diverticulum and defective spongiosum. Renal failure may develop in 22% and the risk is highest in patients with pre-treatment azotaemia, VUR and UTI [1088].

Anterior urethral diverticulum (AUD):

Common postnatal presenting features of AUD are compressible ventral penile swelling, urinary dribble post-micturition, voiding difficulty, poor stream, and recurrent UTIs [1089-1091]. Diagnosis is made by VCUG with or without a retrograde urethrogram. In small AUD, endoscopic cutting or deroofing of distal lip of the diverticulum can be used as a treatment modality. Larger diverticulum requires excision of the diverticulum with a two-layered urethroplasty; or marsupialisation with staged urethroplasty. In cases of urosepsis and obstructive uropathy, a suprapubic catheter may be placed. Once the infant gets better temporary urinary diversion with vesicostomy or proximal cutaneous urethrostomy can be performed before definitive surgical management [1092, 1093]. The diverticulum is associated with a distal lip-like tissue which may be confused with a valve. Anatomically, AUV have normal corpus spongiosum development whereas AUD have incomplete spongious tissue formation [1092].

Syringocele

Cowper glands are two bulbourethral glands located within the urogenital diaphragm and secrete pre-ejaculatory mucus on both sides through the external sphincter into the urethra 1-2 cm distal to the sphincter. Syringocele is the cystic dilatation of these glands. The aetiology can be congenital (retention cyst of the intraurethral portion of the duct) or acquired (trauma or infection). It has been classified as simple, imperforate, perforate and ruptured [1094]. A simpler grouping is suggested to merge simple, perforate and ruptured ones into “open syringocele” and imperforate to “closed syringocele”. Closed syringoceles cause obstructive symptoms and open ones act as a diverticula and cause post-voiding drippling and sometimes obstruction due to orientation of one membrane into urethra [1095]. However, it is better to simply categorise into two groups as obstructing and non-obstructing in terms of understanding pathophysiology and management [1096]. Depending on the syringocele type, patients present with post-void dribbling, urethral discharge, UTI, perineal pain, haematuria, obstructive voiding symptoms, dysuria and retention. Diagnosis is based on antegrade and/or retrograde urethrogram which shows a cystic defect distal to prostate. If the VUC/RGU are inconclusive, US and/or MRI may be used if open reconstruction is being planned. Endoscopic deroofing of the cyst in both obstructing and non-obstructing syringoceles is an effective method of marsupialisation [1097]. In cases where endoscopic approach is not feasible open correction may be considered.

Cobb’s collar

Cobb’s collar is a congenital membranous stricture of the bulbar urethra. It is different from congenital obstructive posterior urethral membrane (COPUM) and is independent of the verumontanum and external sphincter and may represent a persistence of part of the urogenital membrane [1098]. VCUG shows narrowing in the proximal bulbar urethra with folds extending proximally, a dilated posterior urethra, prominent bladder neck and other findings of infravesical obstruction. Treatment is an endoscopic incision; using cold-knife showed lower recurrence rates than electrocautery [1099].

Urethral atresia/hypoplasia

Male urethral atresia is a congenital, complete obstruction of the urethra caused by a membrane that is usually located at the distal end of the prostatic urethra. The urethra distal to this point is usually hypoplastic, presumably from lack of foetal voiding [1100]. Urethral atresia is associated with bladder distention, VUR, hydronephrosis and renal dysplasia [1101]. Most cases reported have the phenotypic characteristics of the

prune belly syndrome. Antenatal intervention may be beneficial in terms of fetal survival [1102]. Although progressive augmentation by dilating the urethra anterior (PADUA) procedure was described as a treatment modality, the majority of cases requires some form of supravesical diversion [1100, 1101].

Posterior Urethral Polyps (PUP):
Although, PUP does not cause antenatal hydronephrosis, but could causes obstruction later on in life. Posterior Urethral Polyps is a polypoid, pedunculated, fibroepithelial lesion arising in posterior urethra proximal to the verumontanum. It lies on the floor of the urethra with its tip reaching into the bladder neck and obstruction occurs because of distal displacement of polyp during urination [1103]. Patients complain of dysuria, hematuria and obstructive symptoms such as poor urinary stream and intermittent retention episodes. Diagnosis can be suspected by VCUG and/or US but is confirmed by during cystourethroscopy. Treatment is usually an endoscopic resection of the polyp. The course of the disease is benign and no recurrences were reported in the literature [1104, 1105].

3.17.7 Summary of evidence and recommendations for the management of posterior urethral valves

Summary of evidence	LE
Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period.	1b
Despite optimal treatment nearly one-third of the patients end up in renal insufficiency.	2b
Bilateral hydroureteronephrosis and a distended bladder are suspicious signs on US; a VCUG confirms the diagnosis.	2b
Serum creatinine nadir above 85 µmol/L is correlated with a poor prognosis.	2a
In the long-term up to 20% of patients develop end-stage renal failure due to primary dysplasia and/or further deterioration because of bladder dysfunction. Renal transplantation in these patients is safe and effective, if the bladder function is normalised.	2a

Recommendations	LE	Strength rating
Diagnose posterior urethral valves (PUV) initially by ultrasound but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis.	3	Strong
Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine (MAG3) clearance. Use serum creatinine as a prognostic marker.		Strong
Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	1b	Weak
Offer endoscopic valve ablation after bladder drainage and stabilisation of the child.	3	Strong
Offer suprapubic diversion for bladder drainage if the child is too small for valve ablation.		Strong
Offer a high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract and the child remains unstable.		Strong
Monitor bladder and renal function life-long, in all patients.	3	Strong

3.18 Paediatric urological trauma

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes [1106]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [1107]. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

3.18.1 Paediatric renal trauma

3.18.1.1 Epidemiology, aetiology and pathophysiology

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [1106].

Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child's kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The paediatric kidney is also less well protected than the adult kidney. Children have less peri-renal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [1108].

Blunt renal trauma is usually a result of sudden deceleration of the child's body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

3.18.1.2 Classification systems

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 12) [1109].

Table 12: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [1109]

Grade	Type of injury	Description
I	Contusion	Non-visible or visible haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
	Vascular	Vascular injury
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

3.18.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

3.18.1.3.1 Haematuria

Haematuria may be a reliable finding. In severe renal injuries, 65% suffer visible haematuria and 33% nonvisible, while only 2% have no haematuria at all [1110].

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant nonvisible haematuria in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine [1111]. It is therefore compulsory to consider all the clinical aspects involved, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child needs further imaging studies.

3.18.1.3.2 Blood pressure

It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation [1112]. Because blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

3.18.1.3.3 Choice of imaging method

Nowadays, CT is the best imaging method for renal involvement in children. Computed tomography scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma.

Computed tomography scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation. In acute trauma, US may be used as a screening tool and for reliably following the course of renal injury. However, US is of limited value in the initial and acute evaluation of trauma. The standard intravenous pyelogram (IVP) is a good alternative imaging method if a CT scan is not available. It is superior to US but not as good as CT scanning for diagnostic purposes.

3.18.1.4 Disease management

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial imaging, and frequent re-assessment of the patient's overall condition. Therefore, a good initial trauma CT with delayed images to check for urinary extravasation is recommended since this may prevent repeat ionising scans. In stable patients with grade 2 or higher lesions a close follow up with US 48 to 72 hours after the initial scan is sufficient and should be considered before repeating a CT scan [1113]. A systematic review supports application of conservative management protocols also to high-grade blunt paediatric renal trauma. At this time, emergent operative intervention only for haemodynamic instability is recommended. Minimally invasive interventions including angio-embolisation, stenting, and percutaneous drainage should be used when indicated [1114]. Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [1115]. A recently published meta-analysis concluded with the following recommendations: (1) In paediatric patients with blunt renal trauma of all grades, non-operative management vs. operative management in hemodynamically stable patients is strongly recommended. (2) In haemodynamically stable paediatric patients with high-grade (AAST grade III-V) renal injuries, angio-embolisation vs. surgical intervention for ongoing or delayed bleeding is strongly recommended; and, (3) In paediatric patients with renal trauma, routine blood pressure checks to diagnose hypertension is recommended in the long-term follow-up [1116]. However, long-term data on the risk of developing hypertension is lacking.

3.18.1.5 Recommendations for the diagnosis and management of paediatric renal trauma

Recommendations	Strength rating
Use imaging in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use rapid spiral computed tomography with delayed images scanning for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	Strong

3.18.2 ***Paediatric ureteral trauma***

Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma [1117]. Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

3.18.2.1 Diagnostic evaluation

Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable. A study of eleven disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies [1117]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [1118]. The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Due to symptoms being often quite vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

3.18.2.2 Management

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [1119]. If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal

stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, auto-transplantation or ureteral replacement with bowel or appendix [1120].

3.18.2.3 Recommendations for the diagnosis and management of paediatric ureteral trauma

Recommendations	Strength rating
Diagnose suspected ureteral injuries by retrograde pyelogram.	Strong
Manage ureteral injuries endoscopically, using internal stenting or drainage of an urinoma, either percutaneously or via a nephrostomy tube.	Weak

*3.18.3 **Paediatric bladder injuries***

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is full, due to:

- Its higher position in the abdomen and its exposure above the bony pelvis.
- The fact that the abdominal wall provides less muscular protection.
- The fact that there is less pelvic and abdominal fat surrounding the bladder to cushion it in trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children because the paediatric bladder sits above the pelvic ring. In a large prospective study, only 57% of children with pelvic fractures also had a bladder injury compared to 89% of adults [1121].

3.18.3.1 Diagnostic evaluation

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and visible haematuria (95% of injuries). Patients with a pelvic fracture and visible haematuria present with a bladder rupture in up to 45% of cases [1122].

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or a CT scan. The best results can be achieved by retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury [1123].

Blunt injuries to the bladder are categorised as:

- contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation;
- ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children because of the bladder's exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

3.18.3.2 Management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

3.18.3.2.1 Intraperitoneal injuries

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair. Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion [1124]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

3.18.3.2.2 Extraperitoneal injuries

Non-operative management with catheter drainage for seven to ten days alone is the method of choice for extraperitoneal bladder rupture. However, if there are bone fragments within the bladder, these must be removed and the bladder must then be repaired and drained, according to the principles for treating intraperitoneal ruptures [1125].

3.18.3.3 Recommendations for the diagnosis and management of paediatric bladder injuries

Recommendations	Strength rating
Use retrograde cystography to diagnose suspected bladder injuries.	Strong
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	Strong
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Do not delay treatment of intra-peritoneal bladder ruptures by surgical exploration and repair as well as post-operative drainage for seven to ten days.	Strong

*3.18.4 **Paediatric urethral injuries***

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed otherwise by a diagnostic work-up.

3.18.4.1 Diagnostic evaluation

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury are blood at the meatus, visible haematuria, and pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum. A rectal examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate, as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [1126].

3.18.4.2 Disease management

Since many of these patients are unstable, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed.

A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous urethral or straddle injury and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding [1127].

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction.

The main goals in the surgical repair of posterior urethral injuries are:

- Providing a stricture-free urethra.
- Avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases [1128]. In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% [1129]. However, in children, there is much less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% [1130]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [1129]. A recently published follow-up study on 15 patients who underwent delayed urethroplasty for blunt urethral trauma during childhood reports high long-term success rates with a low rate of long-term urinary and sexual dysfunction in adulthood [1131].

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of fourteen children undergoing this procedure, this resulted in a stricture rate of 29% and incontinence in 7% of patients [1132].

3.18.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	Strength rating
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	Strong
Perform a rectal examination to determine the position of the prostate.	Strong
Manage bulbous urethral injuries conservatively with a transurethral catheter.	Strong
Manage posterior urethral disruption by either: • primary reconstruction; • primary drainage with a suprapubic catheter alone and delayed repair; • primary re-alignment with a transurethral catheter.	Weak

3.19 Post-operative fluid management

3.19.1 Epidemiology, aetiology and pathophysiology

Children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms, compared to adults [1133]. During development, children have a high metabolic rate and lower fat and nutrient stores which means they are more susceptible to metabolic disturbances caused by surgical stress [1134]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [1135].

3.19.2 Disease management

3.19.2.1 Pre-operative fasting

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. New regimens include a 30-60 minute limitation for clear liquids [1136, 1137] without increased risk of pulmonary aspiration [1138]. Several studies have shown that fasting times in clinical practice often exceed the guidelines with average fasting times of 6-10 hours [1137, 1139]. Compared to adults, children have a higher metabolic rate and low glycogen stores and impaired gluconeogenesis, which makes hypoglycaemia an important issue to consider, especially in children < 36 months old [1137]. Therefore, it is important to prevent too long fasting times. Clear-liquid carbohydrate drinks have been proposed to reduce these fasting times [1140].

Table 13 provides the current six, four and one hour guidelines for pre-operative fasting for elective surgery [1137, 1139].

Table 13: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	1
Breast milk	4
Light meal	6

3.19.2.2 Maintenance therapy and intra-operative fluid therapy

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid; this maintains adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents.

In recent years new strategies for maintenance and replacement fluid management have been developed and this has changed intra-operative fluid management significantly. The main goal of intra-operative fluid management is to maintain a normal extracellular fluid volume (EFV). During the intra-operative period fluid deficits may be induced by blood loss or pre-operative fasting. These fluid deficits can be replaced by balanced isotonic electrolyte solutions to restore a normal EFV. It is recommended that maintenance intravenuous (IV) fluids should consist of balanced isotonic solutions with appropriate potassium chloride

and dextrose in order to decrease the risk of hyponatremia development [1141]. No increased risk for hypernatremia, fluid overload with aedema and hypertension, and hyperchloremic acidosis was found, which was always feared for isotonic solutions [1141].

When children are clinically unstable due to third-space losses, these losses should be replaced with crystalloids (normal saline or Ringer's lactate). Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. When this fluid management is insufficient replacement management with colloids (albumin, gelatine and hydroxyethyl starch (HES) should be adopted, using a restrictive approach [1142].

Clinical guidelines have been proposed by Sümpelmann *et al.* [1142] regarding intra-operative fluid management (Table 14).

Table 14: Intra-operative fluid management

	Solution for infusion	**Initial/repeated dose**
Background infusion	Balanced isotonic solution + 1-2% glucose	10 mL/kg/h
Fluid therapy	Balanced isotonic solution	X 10-20 mL/kg
Volume therapy	Albumin, Gelatine, hydroxyethyl starch	X 5-10 mL/kg
Transfusion	Red blood cells, fresh frozen plasma, platelets	X 10 mL/kg

3.19.2.3 Post-operative feeding and fluid management

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 hours (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalemia.

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially due to the risk of polyuria as a result of post-obstructive diuresis [1143]. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes. If necessary, clinicians should not hesitate in consulting with a paediatric nephrologist.

In children who have undergone non-abdominal surgery, studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia [1144]. Early post-operative intake of fluid in children who have undergone minor or non-abdominal urological surgery is associated with reduced post-operative vomiting and lower opioid use [1145] and is therefore encouraged.

In abdominal surgery the enhanced recovery after surgery (ERAS) protocol has been implemented in the paediatric population following its success in adults [1140, 1146]. The ERAS protocol is a multimodal approach to prevent the post-operative effects of the surgical stress response. This protocol includes pre- and intra-operative element such as minimal pre-operative fasting and careful intra-operative fluid management, and also focuses on post-operative care. The post-operative ERAS protocol suggests starting clear fluid intake on the evening of surgery and a normal diet the day after surgery and thereby early discontinuation of IV fluids. Further focus is on early mobilisation, preventing epidurals and omitting or early removal of external tubes [1140, 1146]. The implementation of an ERAS protocol has resulted in shorter length of hospital stays, faster bowel recovery and opioid-free post-operative need [1140, 1146, 1147]. When implementing ERAS in children with neurological abnormalities special attention should be given to bowel management with pre-operative treatment of constipation and early post-operative continuation of routine bowel management.

3.19.3 Summary of evidence and recommendations for the management of post-operative fluid management

Summary of evidence	**LE**
Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.	2
During the intra-operative period balanced isotonic electrolyte solutions can be used to maintain a normal extracellular fluid volume.	1
Following abdominal surgery ERAS protocols can be used to reduce recovery times and complications.	1

Recommendations	Strength rating
Ensure shorter pre-operative fasting periods for elective surgeries (up to one hour for clear liquids).	Strong
Use ERAS protocols for abdominal surgery in children with normal bowel movement.	Strong
Use isotonic solutions in hospitalised children because they are at high risk of developing hyponatraemia.	Strong
Assess the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen since there is an increased risk of electrolyte abnormalities in children undergoing such surgery.	Strong
Start early oral fluid intake in all patients scheduled for minor surgical procedures.	Strong

3.20 Post-operative pain management: general information

*3.20.1 **Epidemiology, aetiology and pathophysiology***

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia [1148].

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain assessment methods and a knowledge of the clinical consequences of pain in neonates [1149, 1150]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic sequelae [1151, 1152]. Our current understanding of pain management in children depends fully on the belief that all children, irrespective of age, requires adequate pain treatment.

*3.20.2 **Diagnostic evaluation***

Assessment of pain is the first step in pain management. Several pain assessment tools have been validated according to the child's age, cultural background, mental status, communication skills and physiological reactions [1153]. Depending on the child's age, the 0-10 Numeric Rating Scale, Faces Revised Pain Scale or Colour Analog Scale, for example, can be used [1154]. One of the most important topics in paediatric pain management is informing and involving the child and caregivers during this process. Patient-family-controlled-analgesia is the preferred pain management in the hospital and at home if provided with the correct information [1154, 1155].

*3.20.3 **Disease management***

3.20.3.1 Drugs and route of administration

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [1156]. Regional anaesthesia are given intra-operatively which can include a regional nerve block, caudal blocks or local wound infiltration and has proven to reduce the need for post-operative analgesia [1157]. The WHO's 'pain ladder' is a useful tool for the pain management strategy [1158]. A three-level strategy seems practical for clinical use. Post-operative management should be based on sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block.
2. Paracetamol + NSAID.
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine).
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine).

The use of opioids in children has long held a standard role in the post-operative management of pain. Increased recognition of the adverse effects of opioids and prolonged opioid dependency demand a balanced intra-operative administration of opioids [1154, 1159]. Intra-operative adequate dosage of paracetamol and NSAIDs results in a decrease in opioid requirement in children [1160, 1161]. Furthermore, opioid awareness among physicians could reduce opioid use. When prescribing lower opioid dosage this did not increase pain scores in urological outpatient surgeries [1162]. Caution is necessary to take account of renal function when using NSAIDs. Paediatric dependent dosages for most common used pain medication can be found in this publication [1163].

3.20.3.2 Circumcision

Circumcision requires anaesthesia and proper pain management [1164]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), and sucrose preferably in combination [1157, 1163]. Caudal blockade methods have similar efficacy compared to DPNB. However, caregivers should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [1165]. Ultrasound guidance can be used [1163].

3.20.3.2.1 Penile, inguinal and scrotal surgery

Caudal blocks and peripheral nerve blocks (DPNB and pudendal) are commonly used methods for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used and shown to be adequate. Overall post-operative pain scores were lower with pudendal nerve blocks. No increase in post-operative complications was seen with these types of blocks [1157, 1166, 1167]. Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications. For inguinoscrotal surgery, various regional anaesthesia methods have been investigated, such as transversus abdominis plane block, ilioinguinal/iliohypogastric nerve blocks and caudal blocks. All have been shown to have adequate post-operative analgesic properties. Additional local anaesthetics such as clonidine or dexmedetomidine may improve results [1157].

3.20.3.3 Bladder and kidney surgery

Continuous local infusion reduces the need for post-operative opioids [1168-1170], as well as systemic (intravenous) application of analgesics [1171], has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs [1172, 1173]. Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter postoperative hospital stay and earlier return to oral intake and unrestricted daily activity [1174]. Caudal and paravertebral blocks continuous epidural analgesia, as well as rectus sheath and transversus abdominis plane blocks have decreased post-operative morphine requirement after abdominal and renal surgery [1175-1177]. For laparoscopic approaches, intra-peritoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [1178].

*3.20.4 **Summary of evidence and recommendations for the management of post-operative pain***

Summary of evidence	**LE**
Adequate paracetamol and NSAIDs use reduces opioid need post-operatively.	1
Pain may cause behavioural and somatic sequelae.	3
Every institute must develop their own well-structured strategy for post-operative analgesia.	4

Recommendations	**Strength rating**
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Inform patients and caregivers accurately.	Strong
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	Strong

3.21 Basic principles of laparoscopic surgery in children

*3.21.1 **Epidemiology, aetiology and pathophysiology***

The use of laparoscopy and robot-assisted laparoscopic surgery is rapidly increasing and has gained widespread acceptance for many urological surgeries in children. Diagnostic laparoscopy for undescended testis, nephrectomy, heminephrectomy, varicocelectomy, pyeloplasty and ureteral reimplantation are some of the indications which are commonly being performed. This expanding scope related to technological advancements allows surgeons to perform more complex procedures in a minimally invasive fashion even in infants and younger children. Generally, well established benefits of minimally invasive surgery are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery [708]. Additional advantages of robotic surgery over conventional laparoscopy include ergonomics, 3D vision, better manoeuvrability, decreased tremor and easy learning curve. Limitations to be considered are increased operative time, smaller working space at young age, cost and experience of the surgeon and anaesthesiologist. While the success and complication rates are comparable for nephrectomy and pyeloplasty (see chapter

3.12.3.2) advantages of laparoscopy and robotic surgery for ureteral reimplantation have not been proven and this can only be recommended for experienced centres (see chapter 3.13.3.2.3).

As worldwide experience increases, there is an accumulating awareness about the physiological consequences related to intra- and retroperitoneal carbon dioxide (CO_2) insufflation in children. In contrast to traditional open surgery pneumoperitoneum may have physiological responses which require close monitoring during surgery and should be taken seriously.

*3.21.2 **Technical considerations and physiological consequences***

3.21.2.1 Pre-operative evaluation

Laparoscopy in children requires specific anaesthetic precautions. Physiological effects of CO_2 pneumoperitoneum, positioning of the patient and in potentially increased operative time need to be considered by the anaesthesiology team. Therefore, a detailed medical examination and risk assessment is mandatory pre-operatively. Especially cardiac and pulmonary system should be assessed since increased intra-abdominal pressure may lead to decreased ventricular preload [1179].

3.21.2.2 Abdominal insufflation

Abdominal insufflation is the main principle of laparoscopic surgery to create working space for the surgeon. Carbon dioxide is the most commonly used insufflant in laparoscopic centres throughout the world. Other alternatives reported are nitrous oxide, helium, argon and air. However, CO_2 is considered to be the best available gas as it is colourless, cheap, has high solubility in the vascular system [1180] and is excreted by the pulmonary system making it the safest option. Smaller children and infants absorb more CO_2 than older children [1181], suggesting the need for more attention both during and early after laparoscopic surgery for these children.

Most complications of laparoscopy are attributable to gaining access to the abdominal cavity. One study reporting complications of > 5,400 paediatric laparoscopic surgeries showed that there was an overall complication rate of 5.3% of which 4.2% were related to problematic insufflation (subcutaneous emphysema, gas embolism, injury to the organs and vascular structures, mis-insufflation etc.) [1182]. There are two main and well-established techniques for initial access to the abdomen or retroperitoneum: open technique (Hasson) and Veress needle. Studies comparing these two different access techniques in paediatric laparoscopic urological procedures showed similar complication rates [1183]. The vast majority of the complications were minor and related to lack of surgical experience. Particularly in infants and smaller children the open access technique is recommended by the Panel to reduce the chance of complications.

Elasticity of the abdominal wall is age-related and is higher in infants and small children compared to older children [1184].

Pneumoperitoneal pressure (PnP in mmHg) is one of the critical points that needs to be carefully considered by laparoscopic surgeons. A recent RCT compared two different pneumoperitoneal pressure groups (6-8 mmHg vs. 9-10 mmHg) in infants less than 10 kg [1185]. It demonstrated that higher pressures were associated with more pronounced respiratory and hemodynamic changes as well as increased post-operative pain scores and prolonged time to resume feeding.

3.21.2.3 Pulmonary effects

After intra-abdominal insufflation the diaphragm is pushed upwards due to increased abdominal pressure. This leads to decreased total pulmonary compliance. Combined with CO_2 absorption this may lead to hypercarbia and acidosis, particularly in case of prolonged operative time or low pulmonary reserve such as in infants. Trendelenburg position may also aggravate the situation in operations in the pelvic region, such as anti-reflux or bladder neck surgeries. Several studies revealed increased end tidal CO_2 (ET CO_2) related to CO_2 absorption [1181, 1186, 1187]. One study showed a 33% increase in ET CO_2 in the majority of neonatal laparoscopic and thoracoscopic procedures [1187]. Shorter operative time and lower intra-abdominal pressures decrease the risk of increased ET CO_2. Hypoxemia is rarely seen, even in neonates and can easily be adjusted by increasing minute ventilation. These findings highlight the importance of close monitoring of the children.

3.21.2.4 Cardiovascular effects

Intra-abdominal pressure, CO_2 absorption and positioning may also affect the cardiovascular system. It has been shown in adults that after initiation of pneumoperitoneum, cardiac output and stroke volume decrease while mean arterial pressure, central venous pressure and systemic vascular resistance increase [1188]. Similar outcomes have been reported during paediatric laparoscopy with some nuances. Cardiac output was

30% decreased while blood pressure remained stable during laparoscopic orchidopexy with PnP of 10mmHg in children between 6-30 months old [1189]. When PnP was lowered from 12 mmHg to 6mmHg, cardiac index and other vascular parameters normalised [1190]. Using high intra-abdominal pressures in infants with congenital cardiac abnormalities may result in re-opening of cardiac shunts such as the foramen ovale and ductus arteriosus [1191]. Although cardiovascular effects of using high PnP are clinically measurable, they may not have a significant clinical impact on healthy children. However, it is clear that using lower pressures is safer especially in smaller children.

3.21.2.5 Effects on renal function

Although clinical studies in children are lacking, pneumoperitoneum may also have adverse effects on renal blood flow [1192]. High intra-abdominal pressures and reverse Trendelenburg position may cause decreased glomerular filtration rate and decreased urine output. One study has shown that 88% of infants and 14% of children more than one year old develop anuria within 45 minutes after initiation of PnP with 8 mmHg [1193]. However, urine output recovers with temporary polyuria after the operation. Although the clinical relevance of decreased urine output seems insignificant, it is important to monitor the fluid and electrolyte balance of the children during and after laparoscopic surgery.

3.21.2.6 Effects on neurological system

Another effect of pneumoperitoneum is increased intracranial pressure (ICP) which normalises after desufflation of the abdomen [1194]. Trendelenburg position, high PnP and hypoventilation are additional risk factors for increased ICP. Laparoscopy is therefore contraindicated in patients with intracranial space occupying lesions [1195]. Children with ventriculo-peritoneal (VP) shunts require precautions with regards to shunt drainage however laparoscopy is not contraindicated [1196].

*3.21.3 **Summary of evidence and recommendations for laparoscopy in children***

Summary of evidence	**LE**
Laparoscopy and robotic-assisted laparoscopic surgery can safely be performed in children	1
The general benefits of laparoscopy are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery.	1
Limitations to be considered are increased operative time, smaller working space with young age, cost, surgeon and anaesthesiologist experience.	1
Pneumoperitoneum may have physiological effects which require close monitoring during surgery and should be taken seriously.	2

Recommendations	**Strength rating**
Use lower intra-abdominal pressure (6-8 mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

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5. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/
References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Urological Trauma

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines Panel for Urological Trauma have prepared these guidelines in order to assist medical professionals in the management of urological trauma in adults. Paediatric trauma is addressed in the EAU Paediatric Urology Guidelines [1].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions – also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Trauma Guidelines Panel consists of an international group of urologists and an interventional radiologist, all with particular expertise in urological trauma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: http://uroweb.org/guideline/urological-trauma/?type=panel.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal, are also available [2-5]. All documents can be viewed through the EAU website: http://uroweb.org/guideline/urological-trauma/.

1.4 Publication history

The Urological Trauma Guidelines were first published in 2003. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. All sections of the 2020 Urological Trauma Guidelines have been fully updated.

2. METHODS

2.1 Evidence sources

For the 2020 Urological Trauma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Urological Trauma Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 31st 2018 and April 1st 2019. A total of 3,179 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/urological-trauma/?type=appendices-publications. The majority of identified publications were comprised of case reports and retrospective case series. The lack of high-powered randomised controlled trials (RCTs) makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

For each recommendation within the guidelines there is an accompanying online strength rating form the bases of which is a modified GRADE methodology [6, 7]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

The Urological trauma Guidelines was peer reviewed prior to publication in 2019.

3. EPIDEMIOLOGY, CLASSIFICATION & GENERAL MANAGEMNET PRINCIPALS

3.1 Definition and Epidemiology

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Trauma is the sixth leading cause of death worldwide, accounting for 10% of all mortalities. It accounts for approximately five million deaths each year and causes disability to millions more [10, 11].

About half of all deaths due to trauma are in people aged 15-45 years; trauma is the leading cause of death in this age group [12]. Death from injury is twice as common in males, especially in relation to motor vehicle accidents (MVAs) and interpersonal violence. Trauma is therefore a serious public health problem with significant social and economic costs. Significant variation exists in the causes and the effects of traumatic injuries between geographical areas, and between low, middle, and high-income countries. It should be noted that alcohol and drug abuse increase the rate of traumatic injuries by precipitating interpersonal violence, child and sexual abuse, and MVAs.

3.2 Classification of trauma

Traumatic injuries are classified by the World Health Organization (WHO) into intentional (either interpersonal violence related, war-related or self-inflicted injuries), and unintentional injuries (mainly MVAs, falls, and other domestic accidents). Intentional trauma accounts for approximately half of the trauma-related deaths worldwide [11]. A specific type of unintentional injury is iatrogenic injury which occurs during therapeutic or diagnostic procedures by healthcare personnel. Traumatic insults are classified according to the basic mechanism of the injury into penetrating, when an object pierces the skin, and blunt injuries. Penetrating trauma is further classified according to the velocity of the projectile into:

1. high-velocity projectiles (e.g. rifle bullets - 800-1,000 m/sec);
2. medium-velocity projectiles (e.g. handgun bullets - 200-300 m/sec);
3. low-velocity items (e.g. knife stab).

High-velocity weapons inflict greater damage due to a temporary expansive cavitation that causes destruction in a much larger area than the projectile tract itself. In lower velocity injuries, the damage is usually confined to the projectile tract. Blast injury is a complex cause of trauma which includes blunt and penetrating trauma and burns.

The most commonly used classification grading system is the AAST (American Association for the Surgery of Trauma) injury scoring scale [13]. It is useful for managing renal trauma, but for the other urological organs, the injuries are commonly described by their anatomical site and severity (partial/complete).

3.3 General management principals

3.3.1 The Initial evaluation

The initial emergency assessment of a trauma patient is beyond the focus of these guidelines. It is usually carried out by emergency medicine and trauma specialised personnel following ATLS principles. Detailed further assessment involves cross sectional imaging, laboratory analysis and specialist surgical input. The management of individual organ injury will follow in the sections below. Tetanus vaccine status should be assessed for all penetrating injuries.

3.3.2 ***Polytrauma managed in major trauma centres leads to improved survival***

Urological trauma is often associated with significant injuries in the polytraumatised patient [14]. Lessons from civilian trauma networks, military conflict, and mass casualty events have led to many advances in trauma care [15, 16]. These include the widespread acceptance of damage control principles and trauma centralisation to major trauma centres staffed by dedicated trauma teams. The re-organisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [15]. Urologists increasingly understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

3.3.3 ***Damage control***

Damage control is a life-saving strategy for severely injured patients that recognises the consequences of the lethal triad of trauma - hypothermia, coagulopathy and acidosis [17-19]. The first of a three phased approach consists of rapid control of haemorrhage and wound contamination. The second phase involves resuscitation in the intensive care unit (ICU), with the goal of restoring normal temperature, coagulation, and tissue oxygenation. The final stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilised patient [20]. Urological intervention needs to be mindful of the phase of management. Temporary abbreviated measures followed by later definitive surgery are required. Complex reconstructive procedures, including organ preservation, are not undertaken. The decision to enter damage control mode is taken by the lead trauma clinician following team discussion.

Urological examples include haemodynamically unstable patients due to suspected renal haemorrhage or pelvic fracture with associated urethral or bladder injury. The options of abdominal packing and temporary urinary drainage by ureteric, bladder or urethral catheterisation are valuable adjuncts to care.

3.3.4 ***Mass casualty events and Triage***

A mass casualty event is one in which the number of injured people and the severity of their injuries exceed the capability of the faculty and staff [21]. Triage, communication and preparedness are important components for a successful response.

Triage after mass casualty events involves difficult moral and ethical considerations. Disaster triage requires differentiation of the few critically injured individuals who can be saved by immediate intervention from the many others with non-life-threatening injuries for whom treatment can be delayed and from those whose injuries are so severe that survival is unlikely in the circumstances [22, 23].

3.3.5 ***The role of thromboprophylaxsis and bed rest***

Trauma patients are at high risk of deep venous thrombosis (DVT). Concerns with regard to secondary haemorrhage result in prolonged bed rest post-injury which effectively compounds this risk. Established prophylaxis measures reduce thrombosis and are recommended following systemic review [24]. However, the strength of evidence is not high and as yet there is no evidence to suggest that mortality or pulmonary embolism risk is reduced [25]. Compression stockings and low molecular weight heparins are favoured. The risk of secondary haemorrhage is thought to be low and the practice of strict bed rest has waned in patients who are able to mobilise.

3.3.6 ***Antibiotic stewardship***

Single-shot antibiotic doses are common in major trauma. The indication for continuing antibiotics is governed by injury grade, associated injuries and the need for intervention. Patients with urinary extravasation tend to be kept on antibiotics but there is no evidence base for this. Antibiotics should be avoided in lesser trauma e.g. Grade 1-3 renal trauma, and regular review undertaken for those continued on regular dosing.

3.3.7 ***Urinary catheterisation***

Prolonged catheterisation is required in all forms of bladder and urethral injury. Catheterisation is not necessary in stable patients with low-grade renal injury. Patients with heavy haematuria, who require monitoring or ureteric stenting, benefit from catheterisation. This can be removed once haematuria lightens and there is an improvement in the clinical situation. The shortest possible period of catheterisation is advised.

4. UROGENITAL TRAUMA GUIDELINES

4.1 Renal Trauma

*4.1.1 **Epidemiology, aetiology and pathophysiology***

Renal trauma is present in to up 5% of all trauma cases [26]. It is most common in young males and has an overall population incidence of 4.9 per 100,000 [27]. Most injuries can be managed non-operatively with successful organ preservation [28-31].

Blunt injuries result from MVAs, falls, sporting injuries, and assault [32]. The kidney and/or hilar structures are directly crushed as a result. Less commonly, sudden deceleration may result in an avulsion injury affecting the vascular structures of the hilum or the ureteropelvic junction (UPJ).

Penetrating injuries are due to stab and gunshot wounds. They tend to be more severe and less predictable than blunt trauma. The prevalence is higher in urban settings [33]. Penetrating injury produces direct tissue disruption of the parenchyma, vascular pedicles, or collecting system. High-velocity bullets or fragments have the potential for greatest parenchymal destruction and are most often associated with multiple-organ injuries [34].

The most commonly used classification system is that of the AAST [13]. It is validated and predicts morbidity and the need for intervention [35, 36]. This remains the most useful of urological trauma classifications; however, the majority of Grade 1 - 4 injuries are now managed conservatively and debate has centred around updating the classification of high-grade injury i.e. identifying the injuries most likely to benefit from early angiographic embolisation, repair or nephrectomy [29, 37].

Table 4.1.1: AAST renal injury grading scale

Grade*	Description of injury
1	Contusion or non-expanding sub-capsular haematoma No laceration
2	Non-expanding peri-renal haematoma Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation
4	Parenchymal laceration: through corticomedullary junction into collecting system *or* Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Parenchymal: shattered kidney *or* Vascular: renal pedicle or avulsion

**Advance one grade for bilateral injuries up to grade 3.*

*4.1.2 **Evaluation***

The evaluation of stable patients with renal trauma is now based on a trauma protocol computed tomography (CT) scan, often performed prior to involvement of a urologist [38, 39]. It is important to consider all parameters in the evaluation of the patient and to understand the indications for scanning when these are not absolute. Indicators of injury include a direct blow to the flank or rapid deceleration event (fall, high-speed MVAs). Special consideration should be given to pre-existing renal disease [40] or the injured solitary kidney [41]. Pre-existing abnormality e.g. hydronephrosis makes injury more likely following trauma [42].

Vital signs should be recorded throughout the initial evaluation and give the most reliable indication of the urgency of the situation. Physical examination may reveal flank bruising, stab wounds, or bullet entry or exit wounds and abdominal tenderness.

Urinalysis, haematocrit and baseline creatinine are required. Haematuria (visible or non-visible) is the key finding. However major injury such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and stab wounds may not have haematuria [43-45]. Haematuria that is out of proportion to the history of trauma may suggest pre-existing pathology [46]. Urine dipstick quickly evaluates for haematuria, but false-negative results can range from 3-10% [47]. An increased creatinine level usually reflects pre-existing renal pathology.

*4.1.3 **Imaging: criteria for radiographic assessment***

The goals of imaging are to grade the renal injury, document pre-existing renal pathology, demonstrate presence of the contralateral kidney and identify injuries to other organs. Haemodynamic status will determine the initial imaging pathway with unstable patients potentially requiring immediate intervention. The majority of patients with moderate to major trauma will have had a CT scan performed soon after presentation. In patients who have not had any imaging the indications for renal imaging are [32, 48-51]:

- visible haematuria;
- non-visible haematuria and one episode of hypotension;
- a history of rapid deceleration injury and/or significant associated injuries;
- penetrating trauma;
- clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.

4.1.3.1 Computed tomography

Computed tomography is the imaging modality of choice in stable patients. It is quick, widely available, and can accurately identify grade of renal injury [52], establish the presence of the contralateral kidney and demonstrate concurrent injuries to other organs. It is ideally performed as a three-phase study [53]:

1. The arterial phase assesses vascular injury and presence of active extravasation of contrast.
2. The nephrographic phase optimally demonstrates parenchymal contusions and lacerations.
3. The delayed phase imaging (5 minutes) identifies collecting system/ureteric injury [53].

In practice, trauma patients usually undergo standardised whole-body imaging protocols and delayed phase imaging of the renal tract is not routinely performed. If there is suspicion that renal injuries have not been fully evaluated, delayed phase imaging is recommended. The rates of contrast-induced nephropathy seen in trauma patients is low [54].

4.1.3.2 Ultrasonography (US)

In the primary survey of a critically injured patient, FAST (Focused Assessment Sonography in Trauma) is used to identify hemoperitoneum as cause of haemorrhage and hypovolemia. However, it is not routinely used for the assessment of solid organ injury as it is insensitive, operator dependant, does not define the injury well, and is inferior to CT. It is an option for follow-up [55-57].

4.1.3.3 Intravenous pyelography (IVP)

Intravenous pyelography has been superseded by cross-sectional imaging and should only be performed when CT is not available [49]. One-shot intra-operative IVP can be used to confirm the presence of a functioning contralateral kidney in patients too unstable to have had pre-operative imaging [58]. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after ten minutes. The quality of the resulting imaging is generally poor. Palpation of the contralateral (unaffected) kidney is a pragmatic surrogate of function [18].

4.1.3.4 Magnetic resonance imaging (MRI)

The diagnostic accuracy of MRI in renal trauma is similar to that of CT [59, 60]. However, the logistical challenges of MRI make this modality impractical in acute trauma.

4.1.3.5 Radionuclide scans

Radionuclide scans do not play a role in the immediate evaluation of renal trauma patients. In the longer term, follow-up scans can be used to identify areas of scarring, functional loss or obstruction [61].

*4.1.4 **Disease management***

4.1.4.1 Non-operative management

The non-operative management of renal trauma can be viewed as a “package of care”; a step-wise approach starting with conservative, followed by minimally invasive and/or surgical exploration, if necessary. It should be noted that an algorithm for “package of care” will vary in different centres according to available interventions; however, the importance of escalation in treatment interventions should be emphasised [29].

4.1.4.1.1 Blunt renal injuries

Haemodynamic stability is the primary criterion for the management of all renal injuries. Non-operative management has become the treatment of choice for most cases. In stable patients, this means a period of bed rest, serial blood tests, regular observation and re-imaging as indicated. Primary conservative management is associated with a lower rate of nephrectomies, and no increase in immediate or long-term morbidity [62].

Grade 1 - 3 injuries are managed non-operatively [63, 64]. Grade 4 injuries are also mostly treated conservatively, but the requirement for subsequent intervention is higher [65]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage [66].

Grade 5 injuries often present with haemodynamic instability and major associated injuries. There is thus a higher rate of exploration and nephrectomy [67, 68]. However several studies now support expectant management in patients with Grade 4 and 5 injuries [29, 30, 69-73]. Similarly, unilateral main arterial injuries or arterial thrombosis are normally managed non-operatively in haemodynamically stable patients with surgical repair reserved for bilateral artery injuries or injuries involving a solitary functional kidney [74]. Pre-hospital prolonged warm ischaemia usually results in irreparable damage and renal loss.

4.1.4.1.2 Penetrating renal injuries

Penetrating abdominal wounds have traditionally been managed surgically. However, selective non-operative management of penetrating abdominal wounds is now accepted following detailed assessment in stable patients [65, 75, 76].

For renal injuries, the site of the wound, haemodynamic stability, and diagnostic imaging are the main determinants for intervention. The majority of low-grade stab wounds posterior to the anterior axillary line can be managed non-operatively in stable patients [77]. Grade 3 or higher lesions due to stab wounds in stable patients can be managed expectantly, but warrant closer observation as the clinical course is more unpredictable and associated with a higher rate of delayed intervention [77, 78]. Overall, non-operative management of penetrating injuries in selected stable patients is associated with a successful outcome in up to 50% of stab wounds and up to 40% of gunshot wounds [30, 79-82].

4.1.4.1.3 Selective angioembolisation

Selective angioembolisation (AE) has a key role in the non-operative management of blunt renal trauma in haemodynamically stable patients [83-85]. Currently there are no validated criteria to identify patients who require AE and its use in renal trauma remains heterogeneous. Accepted CT findings indicating the need for AE are active extravasation of contrast, arteriovenous fistula (AVF) and pseudo-aneurysm [86]. The presence of both active extravasation of contrast and a large haematoma (> 25 mm depth) predict the need for AE with good accuracy [86, 87].

Angioembolisation has been utilised in the non-operative management of all grades of renal injury; however, it is likely to be most beneficial in the setting of high-grade renal trauma (AAST > 3) [83-85]. Non-operative management of high-grade renal trauma, where AE is included in the management algorithm, can be successful in up to 94.9% of Grade 3, 89% of Grade 4 and 52% of Grade 5 injuries [83, 84]. Increasing grade of renal injury is associated with increased risk of failed AE and need for repeat intervention [88].

Repeat embolisation prevents nephrectomy in 67% of patients. Open surgery after failed embolisation usually results in nephrectomy [88, 89]. Despite concerns regarding parenchymal infarction and the use of iodinated contrast media, AE does not appear to affect the occurrence or course of acute kidney injury following renal trauma [90]. In severe polytrauma or high operative risk, the main artery may be embolised, either as a definitive treatment or as a step to a more controlled nephrectomy.

The evidence supporting AE in penetrating renal trauma is sparse. One study found that AE is three times more likely to fail in penetrating trauma [75]. However, AE has been used successfully to treat acute haemorrhage, AVF and pseudo-aneurysms resulting from penetrating renal trauma [91].

4.1.4.1.4 Urinary catheterisation

Catheterisation is not necessary in stable patients with low-grade injury. Patients with severe visible haematuria, who require monitoring or stenting, benefit from catheterisation. A longer period of catheterisation is required if a stent is placed. Once the haematuria lightens and the patient is mobile, the catheter should be removed.

4.1.4.1.5 Repeat imaging (early)

Computed tomography scans should be performed on patients with fever, unexplained decreased haematocrit or significant flank pain. Repeat imaging is also recommended in high-grade injury and in penetrating trauma two to four days after trauma to minimise the risk of missed complications. Repeat imaging can be safely omitted for patients with Grade 1-3 injuries as long as they remain clinically well [92].

4.1.4.2 Surgical management

4.1.4.2.1 Indications for renal exploration

A non- or transient-response to initial fluid resuscitation is an absolute indication for exploration [75, 76]. There is a trend towards ongoing resuscitation and AE [93]. Exploration is influenced by aetiology and grade of injury, transfusion requirements, the need to explore associated abdominal injuries, and the discovery of

an expanding or pulsatile peri-renal haematoma at laparotomy [94]. Grade 5 vascular injury is an absolute indication for exploration [35].

4.1.4.2.2 Operative findings and reconstruction

The overall exploration rate for blunt trauma is low [95]. The goals of exploration following renal trauma are control of haemorrhage and renal salvage. Most series recommend the transperitoneal approach for surgery [96, 97]. Entering the retroperitoneum and leaving the confined haematoma undisturbed within the perinephric fascia is recommended; temporarily packing the fossa tightly with laparotomy pads can salvage the kidney in instances of intra-operative haemorrhage [98]. Access to the pedicle is obtained either through the posterior parietal peritoneum, which is incised over the aorta, just medial to the inferior mesenteric vein or by bluntly dissecting along the plane of the psoas muscle fascia, adjacent to the great vessels, and directly placing a vascular clamp on the hilum [98].

Stable haematomas detected during exploration for associated injuries should not be opened. Central or expanding haematomas indicate injuries of the renal pedicle, aorta, or vena cava and are potentially life-threatening and warrant further exploration [99].

Feasibility of renal reconstruction should be judged during the operation. The overall rate of patients who undergo a nephrectomy during exploration is approximately 30% [100]. Other intra-abdominal injuries also increase the likelihood of nephrectomy [101]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [102]. High velocity gunshot injuries make reconstruction difficult and nephrectomy is usually required [103].

Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system is desirable, although closing the parenchyma over the injured collecting system is acceptable.

The use of haemostatic agents and sealants in reconstruction is helpful [104]. In all cases, drainage of the ipsilateral retroperitoneum is recommended.

The repair of vascular injuries is seldom, if ever, effective [105]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [106]. Nephrectomy for main artery injury has outcomes similar to those of vascular repair and does not worsen post-treatment renal function in the short-term. Bleeding or dissection of the main renal artery may also be managed with a stent.

*4.1.5 **Follow-up***

The risk of complications relates to aetiology, injury grade, and mode of management [107, 108]. Follow-up includes physical examination, urinalysis, diagnostic imaging, blood pressure measurement and serum creatinine [67]. Potential complications are primarily identified by imaging; however, follow up imaging is not recommended in low-grade uncomplicated injury. Ultrasound can be used to define the post-injury anatomy avoiding further ionising radiation. Nuclear scans are useful for documenting functional recovery following renal injury and reconstruction [61]. Annual blood pressure monitoring is recommended to exclude renovascular hypertension [109].

4.1.5.1 Complications

Early (≤ 1 month) complications include bleeding, infection, perinephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation and urinoma. Delayed complications include bleeding, hydronephrosis, calculus formation, chronic pyelonephritis, hypertension, AVF, hydronephrosis and pseudo-aneurysms. Bleeding may be life-threatening with elective angiographic embolisation the preferred treatment [110]. Perinephric abscess formation is initially managed by percutaneous drainage [95].

Hypertension is rare [111, 112]. It may occur acutely as a result of external compression from peri-renal haematoma (Page kidney), chronically due to compressive scar formation, or as a result of renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), or AVF. Arteriography may be required. Treatment, including medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or nephrectomy, is indicated if hypertension persists [109].

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger fistulae may require surgery [113]. The development of pseudo-aneurysm is a rare complication following blunt trauma.

*4.1.6 **Iatrogenic renal injuries***

Iatrogenic renal trauma needs to be recognised and managed promptly to minimise morbidity and mortality. The most common causes of iatrogenic renal injuries are percutaneous access to kidney, stone surgery, cancer surgery (laparoscopic and open) and transplantation [3]. The diagnosis and management follow the same principles as outlined previously.

*4.1.7 **Summary of evidence and recommendations for evaluation and management of renal trauma***

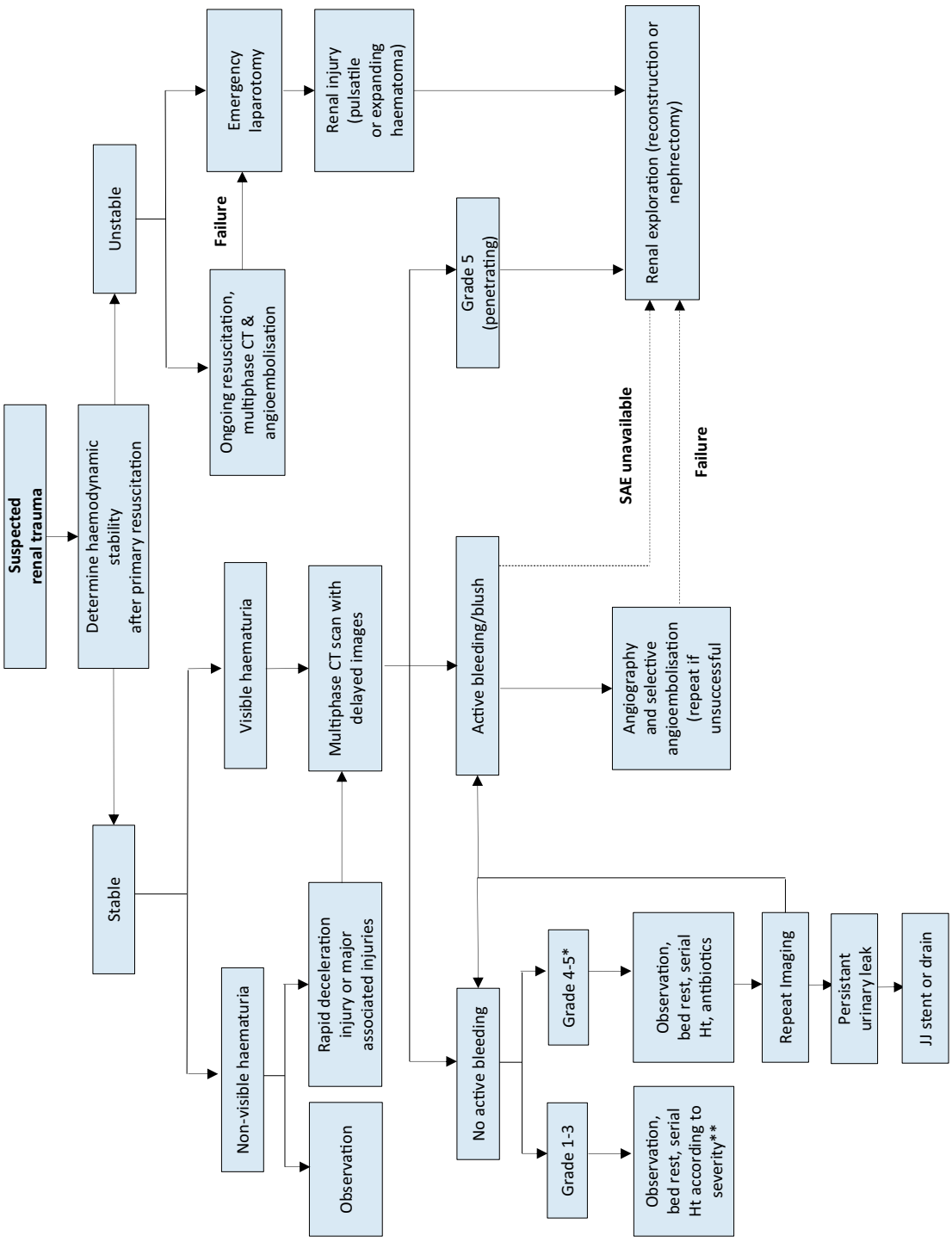
Summary of evidence	**LE**
Vital signs on admission give the most reliable indication of the urgency of the situation.	3
Special consideration should be given to patients with a solitary kidney and pre-existing renal disease.	4
Haematuria is a key finding following renal trauma; although, it may not be present in certain situations.	3
A multiphase CT scan is the best method for the diagnosis and staging of renal injuries in haemodynamically stable patients.	3
Haemodynamic stability is the primary criterion for selecting patients for non-operative management.	3
Selective angioembolisation is effective in patients with active bleeding from renal injury, without other indications for immediate abdominal operation.	3
Renal reconstruction should be attempted if haemorrhage is controlled and there is sufficient viable renal parenchyma.	3
Iatrogenic renal injuries are procedure-dependent (1.8-15%); the most common injuries are vascular.	3
Limited literature exists with regard to long-term consequences of renal trauma. Current follow-up includes physical examination, urinalysis, diagnostic imaging, serum creatinine, as well as annual blood pressure monitoring to diagnose renovascular hypertension.	4

Recommendations	**Strength rating**
Evaluation	
Assess haemodynamic stability upon admission.	Strong
Record past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, solitary kidney, lithiasis).	Strong
Test for haematuria in a patient with suspected renal injury.	Strong
Perform a multiphase computed tomography scan in trauma patients with: • visible haematuria; • non-visible haematuria and one episode of hypotension; • a history of rapid deceleration injury and/or significant associated injuries; • penetrating trauma; • clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.	Strong
Management	
Manage stable patients with blunt renal trauma non-operatively with close monitoring and re-imaging as required.	Strong
Manage isolated Grade 1-4 stab and low-velocity gunshot wounds in stable patients non-operatively.	Strong
Use selective angioembolisation for active renal bleeding if there are no other indications for immediate surgical exploration.	Strong
Proceed with renal exploration in the presence of: • persistent haemodynamic instability; • Grade 5 vascular or penetrating injury; • expanding or pulsatile peri-renal haematoma.	Strong
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	Weak
Repeat imaging in high-grade injuries and in cases of fever, worsening flank pain, or falling haematocrit.	Strong
Follow-up approximately three months after major renal injury with: • physical examination; • urinalysis; • individualised radiological investigation including nuclear scintigraphy; • blood pressure measurement; • renal function tests.	Weak
Measure blood pressure annually to diagnose renovascular hypertension.	Strong

4.1.8 ***Treatment algorithms***

Management of renal trauma

Figure 4.1.1 Management of renal trauma



** Excluding Grade 5 penetrating injuries.*

*** Antibiotics should be administered for all penetrating injuries.*

--- If haemodynamically unstable.

CT = computed tomography; Ht = haematocrit; SAE = selective angioembolisation.

4.2 Ureteral Trauma

*4.2.1 **Incidence***

Trauma to the ureters is relatively rare as they are protected from injury by their small size, mobility, and the adjacent vertebrae, bony pelvis and muscles. Iatrogenic trauma is the most common cause of ureteral injury (approximately 80%) [114]. It is seen in open, laparoscopic or endoscopic surgery and is often missed intra-operatively. Any trauma to the ureter may result in severe sequelae [115].

*4.2.2 **Epidemiology, aetiology, and pathophysiology***

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma [114, 116-118], with even higher rates in modern combat injuries [119]. Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military [114, 116, 120]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly MVAs [117, 118].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, as it occurs in 2-3% of cases [114]. It should also be suspected in blunt trauma with a deceleration mechanism, as the renal pelvis can be torn away from the ureter [114]. The distribution of external ureteral injuries along the ureter varies between series, but it is more common in the upper ureter [116-118].

Iatrogenic ureteral trauma can result from various mechanisms: ligation or kinking with a suture, crushing from a clamp, partial or complete transection, thermal injury, or ischaemia from devascularisation [120-122]. It usually involves the lower ureter [114, 120, 121, 123]. Gynaecological operations are the most common cause of iatrogenic trauma (Table 4.2.1), but it may also occur in colorectal operations, especially abdominoperineal resection and low anterior resection [124]. The incidence of urological iatrogenic trauma has decreased in the last twenty years due to improvements in technique, instruments and surgical experience [120, 125]. New methods such as robotic surgery in gynaecology have not further reduced the rate of ureteral injuries [126].

Ureteroscopy is a common cause of iatrogenic ureteric trauma. The post-ureteroscopic lesion scale (PULS) may standardise intra-operative traumatic findings during ureteroscopy [127].

Risk factors for iatrogenic trauma include conditions that alter the normal anatomy, e.g. advanced malignancy, prior surgery or irradiation, diverticulitis, endometriosis, anatomical abnormalities, and major haemorrhage [120, 124, 128, 129]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intra-operatively [115].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [123, 130, 131]	
Vaginal hysterectomy	0.02 – 0.5
Abdominal hysterectomy	0.03 – 2.0
Laparoscopic hysterectomy	0.2 – 6.0
Urogynaecological (anti-incontinence/prolapse)	1.7 – 3.0
Colorectal [122, 130, 132]	0.15 – 10
Ureteroscopy [125]	
Mucosal abrasion	0.3 – 4.1
Ureteral perforation	0.2 – 2.0
Intussusception/avulsion	0 – 0.3
Radical prostatectomy [133]	
Open retropubic	0.05 – 1.6
Robot-assisted	0.05 – 0.4

*4.2.3 **Diagnosis***

The diagnosis of ureteral trauma is challenging; therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intra-operatively during laparotomy [134], while it is delayed in most blunt trauma and iatrogenic cases [120, 123, 135].

4.2.3.1 Clinical diagnosis

External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spine injuries [117, 118]. Haematuria is an unreliable and poor indicator of ureteral injury, as it is present in only 50-75% of patients [114, 120, 136].

Iatrogenic injury may be noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. However, it is usually noticed later, when it is discovered by subsequent evidence of upper tract obstruction, urinary fistulae formation or sepsis. The following clinical signs are characteristic of delayed diagnosis flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever, uraemia or urinoma. When the diagnosis is missed, the complication rate increases [114, 119, 135]. Early recognition facilitates immediate repair and provides better outcome [131, 137].

4.2.3.2 Radiological diagnosis

Multi-phase CT is the mainstay imaging technique for trauma patients. Generally, it is widely available and allows for multi-phasic assessment of all of the structures in the pelvis and abdomen. Computed tomography urography (CTU) is the examination of choice when ureteral injuries are suspected [138]. Extravasation of contrast medium in the delayed phase is the hallmark sign of ureteral trauma. However, hydronephrosis, ascites, urinoma or mild ureteral dilation are often the only signs. In unclear cases, a retrograde or antegrade urography is the optimum standard for confirmation [120]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [114, 120].

4.2.4 ***Prevention of iatrogenic trauma***

The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intra-operative dissection in their proximity [120-122]. The use of prophylactic pre-operative ureteral stent insertion assists in visualisation and palpation and is used in complicated cases (about 4% in a large cohort) [139, 140].

It is probably also advantageous in making it easier to detect ureteral injury [121]; however, it does not decrease the rate of injury [141]. Apart from its evident disadvantages (potential complications and cost), a stent may alter the location of the ureter and diminish its flexibility [121, 132].

4.2.5 ***Management***

Management of ureteral trauma depends on many factors concerning the nature, severity and location of the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement. Partial injuries can be repaired immediately with a stent or urinary diversion by a nephrostomy tube. Stenting is helpful because it provides canalisation and may decrease the risk of stricture [120]. On the other hand, its insertion has to be weighed against potentially aggravating the severity of the ureteral injury. Immediate repair of complete ureteral injury is usually advisable. The ureter is mobilised on both ends and a spatulated end-to-end anastomosis is performed. However, in cases of unstable trauma patients, a ‘damage control’ approach is preferred with ligation of the ureter, diversion of the urine (e.g. by a nephrostomy), and a delayed definitive repair [142]. Injuries that are diagnosed late are usually managed first by a nephrostomy tube or a stent [120].

Endo-urological treatment of delayed-diagnosed ureteral injuries by internal stenting, with or without dilatation, is the first step in most cases. It is performed either retrogradely or antegradely through a percutaneous nephrostomy, and it has a variable success rate of 14-19% in published series [143-145]. An open or robot-assisted laparoscopic surgical repair is necessary in case of failure [146]. The basic principles for any surgical repair of a ureteral injury are outlined in Table 4.2.2. Wide debridement is highly recommended for gunshot wound injuries due to the ‘blast effect’ of the injury.

4.2.5.1 Proximal and mid-ureteral injury

Injuries shorter than 2-3 cm can usually be managed by a primary uretero-ureterostomy [114]. When this approach is not feasible, a uretero-calycostomy should be considered. In case of a large extra-renal pelvis and a stricture at the UPJ, a pelvic spiral flap according to Culp-DeWeerd is an option [147]. In extensive ureteral loss, a transuretero-ureterostomy is a valid option, where the proximal stump of the ureter is transposed across the midline and anastomosed to the contralateral ureter. The reported stenosis rate is 4% and intervention or revision occur in 10% of cases [148].

4.2.5.2 Distal ureteral injury

Distal injuries are best managed by ureteral re-implantation (uretero-neocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral re-implantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.

A psoas hitch between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. The contralateral superior vesical pedicle may be divided to improve bladder mobility. The reported success rate is very high (97%) [148]. In extensive mid-lower ureteral

injury, the large gap can be bridged with a tabularised L-shaped bladder flap (Boari flap). It is a time-consuming operation and not usually suitable in the acute setting. The success rate is reported to be 81-88% [149].

4.2.5.3 Long segment ureteral injury

A longer ureteral injury can be replaced using a segment of the intestines, usually the ileum (ileal interposition graft). This should be avoided in patients with impaired renal function or known intestinal disease. Follow-up should include serum chemistry to diagnose hyperchloremic metabolic acidosis [150]. The long-term complications include anastomotic stricture (3%) and fistulae (6%) [151]. In cases of extensive ureteral loss or after multiple attempts at ureteral repair, the kidney can be relocated to the pelvis (auto-transplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral re-implantation is performed [152, 153].

Buccal mucosa ureteroplasty is another option for long segment ureteral injury, especially after a previous failed reconstruction, as an alternative to auto-transplantation. The overall success rate is 90%, but experience is limited [154].

Table 4.2.2: Principles of surgical repair of ureteral injury

Debridement of necrotic tissue
Spatulation of ureteral ends
Watertight mucosa-to-mucosa anastomosis with absorbable sutures
Internal stenting
External drain
Isolation of injury with peritoneum or omentum

4.2.6 Summary of evidence and recommendations for the management of ureteral trauma

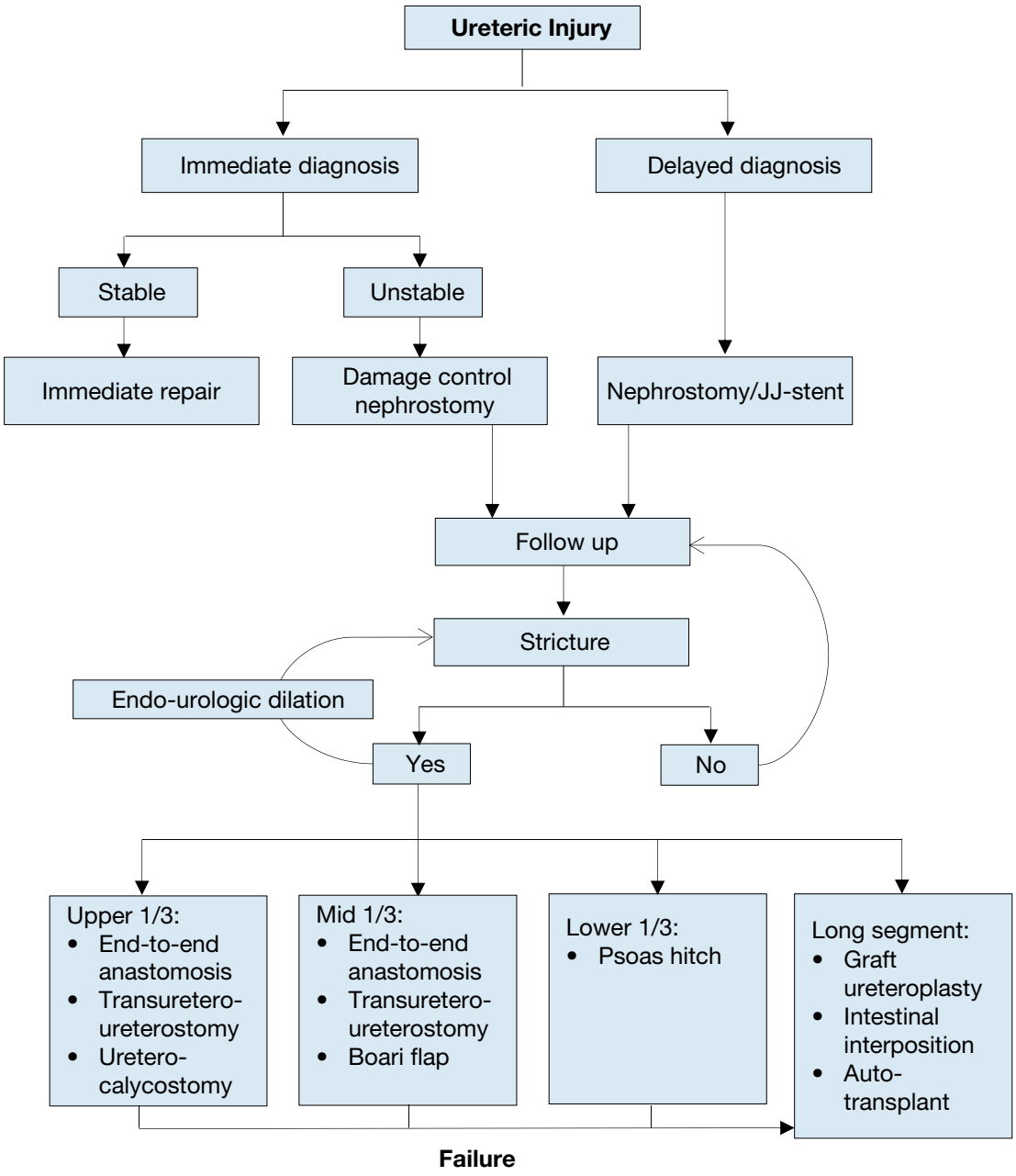
Summary of evidence	**LE**
Iatrogenic ureteral trauma is the most common cause of ureteral injury.	3
Gunshot wounds account for the majority of penetrating ureteral injuries, while MVAs account for most blunt injuries.	3
Ureteral trauma usually accompanies severe abdominal and pelvic injuries.	3
Haematuria is an unreliable and poor indicator of ureteral injury.	3
Pre-operative prophylactic stents do not prevent ureteral injury; however, they may assist in its detection.	2
Endo-urological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	**Strength rating**
Visually identify the ureters to prevent ureteral trauma during abdominal and pelvic surgery.	Strong
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	Strong
Use pre-operative prophylactic stents in high-risk cases.	Strong
Repair iatrogenic ureteral injuries recognised during surgery immediately.	Strong
Treat iatrogenic ureteral injuries with delayed diagnosis by nephrostomy tube/JJ stent urinary diversion.	Strong
Manage ureteral strictures by ureteral reconstruction according to the location and length of the affected segment.	Strong

*4.2.7 **Treatment algorithms***

Management of ureteric injuries

Figure 4.2.1: Management of ureteric injuries



4.3 Bladder Trauma

*4.3.1 **Classification***

Bladder trauma is primarily classified according to the location of the injury: **intraperitoneal, extraperitoneal,** and **combined** intra-extraperitoneal [155], as it guides further management [156]. Bladder trauma is categorised by aetiology: **non-iatrogenic** (blunt and penetrating) and **iatrogenic** (external and internal).

*4.3.2 **Epidemiology, aetiology and pathophysiology***

Motor vehicle accidents are the most common cause of blunt bladder injury, followed by falls and other accidents. The main mechanisms are pelvic crush and blows to the lower abdomen [117, 155, 157]. Most patients with blunt bladder injury have associated pelvic fractures (60-90%) and other intra-abdominal injuries (44-68.5%) [158, 159]. Pelvic fractures are associated with bladder injury in about 3% of cases [117, 160]; however, this can be as high as 26.5% in cases of severe pelvic injury [161]. Bladder injury is associated with urethral injury in 5-20% of cases [156, 159, 162].

The incidence of extraperitoneal (22.4-61.1%), and intraperitoneal (38.9-65.8%) injuries varies among series [163]. **Extraperitoneal injury** is almost always associated with pelvic fractures [157, 159]. It is usually caused by distortion of the pelvic ring, with shearing of the anterolateral bladder wall near the bladder base (at its fascial attachments), or by a contrecoup at the opposite side. The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm, and pubic rami fractures [117, 156]. An isolated acetabular fracture is not likely to be associated with bladder injury [156, 159, 164]. Occasionally, the bladder is directly perforated by a sharp bony fragment [156].

Intraperitoneal injury is caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures will usually occur there [156]. Penetrating injuries, mainly gunshot wounds, are rare except in conflict zones and violent urban areas [155, 165, 166]. Improvised explosive devices are the main cause of combat related bladder injuries in asymmetric warfare [167].

4.3.2.1 Iatrogenic bladder trauma (IBT)

The bladder is the urological organ that is most commonly affected by iatrogenic injury [168]. Table 4.3.2 shows the incidence of IBT during various procedures. **External IBT** occurs most often during obstetric and gynaecological procedures, followed by urological and general surgical operations [168]. Main risk factors are previous surgery, inflammation and malignancy [168]. Bladder perforations occur in up to 4.9% of mid-urethral sling (MUS) operations for stress urinary incontinence in women. This rate is significantly lower in the obturator route compared to the retropubic route [169].

Internal IBT mainly occurs during transurethral resection of the bladder (TURB). Reported risk factors are larger tumours, older age, pre-treated bladders (previous TURB, intravesical instillations) and location at the bladder dome [170, 171]. Tumours at the lateral wall pose a risk factor because of the obturator jerk [172, 173]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [171, 174], and perforations requiring intervention are rare (0.16-0.57%) [170].

Table 4.3.2: Incidence of iatrogenic bladder trauma during various procedures

Procedure	Percentage (%)
Obstetrics & Gynaecology	
Laparoscopic/Robotic radical hysterectomy (malignant) [175]	4.19-4.59
Abdominal radical hysterectomy (malignant) [175]	2.37
Laparoscopic/Abdominal hysterectomy (benign) [176, 177]	1-2.7
Vaginal hysterectomy (benign) [176, 177]	0.6-2.5
Caesarean delivery [178]	0.08-0.94
General surgery	
Abdominal cytoreductive surgery [179]	4.5
Rectal procedures [180]	0.27-0.41
Small/large bowel procedures [180]	0.12-0.14
Laparoscopic inguinal hernia repair [181]	0.04-0.14
Urology specific	
Transurethral resection of the bladder [182, 183]	3.5-58
Retropubic male sling [184]	8.0-19
Mid-urethral sling (retropubic route) [169, 185]	4.91-5.5
Transvaginal mesh surgery [186]	2.84
Pubovaginal sling [185]	2.8
Laparoscopic sacrocolpopexy [187]	1.9
Mid-urethral sling (transobturator route) [185]	1.61
Burch colposuspension [185, 188]	1.0-1.2
Native tissue colporrhaphy [186]	0.53

4.3.3 Diagnostic evaluation

The principal sign of bladder injury is visible haematuria [156, 157]. Absolute indications for bladder imaging include: visible haematuria and a pelvic fracture [156] or non-visible haematuria combined with high-risk pelvic fracture (disruption of the pelvic circle with displacement > 1 cm or diastasis of the pubic symphysis > 1 cm) or posterior urethral injury [156]. Bladder trauma should also be suspected in patients with blunt urethral trauma and high Injury Severity Score (ISS) [189]. In the absence of these absolute indications, further imaging is based on clinical signs and symptoms including [156, 157, 165, 190]:

- inability to void or inadequate urine output;
- abdominal tenderness or distension due to urinary ascites, or signs of urinary ascites in abdominal imaging;
- uraemia and elevated creatinine level due to intraperitoneal re-absorption;
- entry/exit wounds at lower abdomen, perineum or buttocks in penetrating injuries.

Intra-operative signs of external iatrogenic bladder injury include: extravasation of urine, visible laceration, visible bladder catheter, and blood and/or gas in the urine bag during laparoscopy [178]. Direct inspection is the most reliable method of assessing bladder integrity [168]. Intravesical instillation of dye helps to detect smaller lesions [191]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [168, 178].

Internal bladder injury is recognised by cystoscopic identification of fatty tissue, dark space, or bowel [182]. It may also be detected by the inability to distend the bladder, low return of irrigation fluid, or abdominal distension [192].

Post-operatively, missed bladder trauma is diagnosed by haematuria, abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, or increased serum creatinine [168, 178]. An IBT during hysterectomy or caesarean delivery can result in vesico-vaginal or vesico-uterine fistulae [178, 193].

4.3.3.1 Cystography

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected IBT in the post-operative setting [193, 194]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [157, 195]. However, CT cystography is superior in the identification of bony fragments in the bladder and bladder neck injuries, as well as concomitant abdominal injuries [156, 159].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material [194, 196]. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury [157]. Intraperitoneal extravasation is visualised by free contrast medium in the abdomen outlining bowel loops or abdominal viscera [197]. Extraperitoneal bladder injury is typically diagnosed by flame-shaped areas of contrast extravasation in the peri-vesical soft tissues. Contrast medium in the vagina is a sign of vesico-vaginal fistula [193].

4.3.3.2 Cystoscopy

Cystoscopy is the preferred method for detection of intra-operative bladder injuries as it may directly visualise the laceration and can localise the lesion in relation to the position of the trigone and ureteral orifices [197]. A lack of bladder distension during cystoscopy suggests a large perforation. Cystoscopy is recommended to detect perforation of the bladder (or urethra) following retropubic sub-urethral sling operations [169, 188]. Routine intra-operative cystoscopy during other gynaecologic procedures is not recommended [198], although the threshold to perform it should be low in any suspected bladder injury.

4.3.3.3 Ultrasound

Ultrasound alone is insufficient in the diagnosis of bladder trauma, although it can be used to visualise intraperitoneal fluid or an extraperitoneal collection of fluid.

4.3.4 ***Prevention***

The risk of bladder injury is reduced by emptying the bladder by urethral catheterisation in every procedure where the bladder is at risk [191, 199]. Furthermore, the catheter's balloon can aid in identification of the bladder [191]. For tumours at the lateral wall, obturator nerve block or general anaesthesia with adequate muscle relaxation can reduce the incidence of internal IBT during TURB [173]. There is conflicting evidence whether bipolar TURB can reduce the risk for an obturator jerk [172, 173]. The use of combat pelvic protection systems reduces the risk of bladder and other genitourinary injuries due to the blast mechanism of improvised explosive devices [167, 200].

4.3.5 ***Disease management***

4.3.5.1 Conservative management

Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis [171], is the standard treatment for an uncomplicated extraperitoneal injury due to blunt [156, 159, 162] or iatrogenic trauma [171].

Conservative treatment can also be chosen for uncomplicated intraperitoneal injury after TURB or other operations, but only in the absence of peritonitis and ileus [183, 197]. Placement of an intraperitoneal

drain is advocated, especially when the lesion is larger [192, 201]. Penetrating extraperitoneal bladder injuries (only if minor and isolated) can also be managed conservatively [163, 190, 202].

4.3.5.2 Surgical management

Bladder closure is performed with absorbable sutures [163, 168]. There is no evidence that two-layer is superior to watertight single-layer closure [159, 163].

4.3.5.2.1 Blunt non-iatrogenic trauma

Most extraperitoneal ruptures can be treated conservatively, however bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury or entrapment of the bladder wall necessitate surgical intervention [156]. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material. During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection [203]. Likewise, an extraperitoneal rupture should be sutured during surgical exploration for other injuries, in order to decrease the risk of complications and to reduce recovery time [162].

Intraperitoneal ruptures should always be managed by surgical repair [156, 159] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [158]. Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. Laparoscopic suturing of the intraperitoneal rupture is also possible [157].

4.3.5.2.2 Penetrating non-iatrogenic trauma

Penetrating bladder injury is managed by emergency exploration, debridement of devitalised bladder wall and primary bladder repair [165, 166]. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [163, 165]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, usually requiring faecal diversion [165, 190]. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for these two lesions [165]. As the penetrating agent (bullet, knife) is not sterile, antibiotic treatment is advised [166].

4.3.5.2.3 Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed [204]. Bladder injuries not recognised during surgery or internal injuries should be managed according to their location. The standard of care for intraperitoneal injuries is surgical exploration and repair [197]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [170]. For extraperitoneal injuries, exploration is only needed for perforations complicated by symptomatic extravesical collections. It requires drainage of the collection, with or without closure of the perforation [205]. If bladder perforation is encountered during mid-urethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (two to seven days) should be performed [206].

*4.3.6 **Follow-up***

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [168, 207]. Conservatively treated bladder injuries (traumatic or external IBT) are followed up by cystography to rule out extravasation and ensure proper bladder healing [156]. The first cystography is planned approximately ten days after injury [163]. In case of ongoing leakage, cystoscopy should be performed to rule out bony fragments in the bladder, and a second cystography is warranted one week later [156].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after five to ten days without cystography [207, 208]. In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g. steroids, malnutrition) cystography is advised [163, 207]. For conservatively treated internal IBT, catheter drainage, lasting five days for extraperitoneal and seven days for intraperitoneal perforations, is proposed [171, 174].

*4.3.7 **Summary of evidence and recommendations for bladder injury***

Summary of evidence	**LE**
The combination of pelvic fracture and visible haematuria is highly suggestive of bladder injury.	3
Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for suspected IBT in the post-operative setting.	3
Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury.	3

The risk of bladder perforation during mid-urethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route.	1a
Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis, is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma.	3
In extraperitoneal bladder injury with either bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury, or entrapment of the bladder wall, surgical intervention is necessary in order to decrease the risk of complications and to reduce recovery time.	3
Intraperitoneal bladder trauma is managed by surgical repair because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death.	3
Conservative treatment is suitable for uncomplicated intraperitoneal injury during endourological procedures, in the absence of peritonitis and ileus.	3
In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g. steroids, malnutrition) cystography is advised after bladder repair.	2a

Recommendations	Strength rating
Perform cystography in the presence of visible haematuria and pelvic fracture.	Strong
Perform cystography in case of suspected iatrogenic bladder injury in the post-operative setting.	Strong
Perform cystography with active retrograde filling of the bladder with dilute contrast (300-350 mL).	Strong
Perform cystoscopy to rule out bladder injury during retropubic sub-urethral sling procedures.	Strong
Manage uncomplicated blunt extraperitoneal bladder injuries conservatively.	Weak
Manage blunt extraperitoneal bladder injuries operatively in cases of bladder neck involvement and/or associated injuries that require surgical Intervention.	Strong
Manage blunt intraperitoneal injuries by surgical exploration and repair.	Strong
Manage small uncomplicated intraperitoneal bladder injuries during endoscopic procedures conservatively.	Weak
Perform cystography to assess bladder wall healing after repair of a complex injury or in case of risk factors for wound healing.	Strong

4.4 Urethral Trauma

*4.4.1 **Epidemiology, aetiology and pathophysiology***

4.4.1.1 Anterior male urethral injury

The bulbar urethra is the most common site affected by **blunt** trauma. In bulbar injuries, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at the site of compression [209]. Possible mechanisms are straddle injuries or kicks to the perineum. A penile fracture can be complicated by a urethral injury in approximately 15% of cases [210, 211]. Penetrating anterior injuries are rare and are usually caused by gunshot wounds, stab wounds, dog bites, impalement or penile amputations [209, 212]. Depending on the affected segment, **penetrating** injuries are usually associated with penile, testicular and/or pelvic injuries [212, 213]. Insertion of **foreign bodies** is another rare cause of anterior injury. It is usually a result of autoerotic stimulation or may be associated with psychiatric disorders [214].

Iatrogenic injury is the most common type of urethral trauma [215, 216]. The incidence of urethral injury during transurethral catheterisation is 6.7 per 1,000 catheters inserted [217], and can occur due to creation of a false passage by the tip of the catheter, inadvertent inflation of the anchoring balloon in the urethra or removal of the catheter with the anchoring balloon not fully deflated [217]. A strict indication for every urethral catheterisation is an important preventive measure [215]. The importance of catheter insertion training programmes, to prevent urethral injury during transurethral catheterisation, have been demonstrated [218, 219]. Preliminary data suggests that guidewire led catheter insertion, or use of a safety valve for balloon inflation may prevent urethral trauma in difficult catheterisation cases [220, 221]. Instrumentation of the urethra (TURP, cystoscopy, etc.) can traumatise all segments of it [215]. During penile prosthesis insertion (PPI), the risk of urethral perforation is 0.1-4%. Proximal urethral injuries are more common than distal ones [222].

4.4.1.2 Posterior male urethral injuries

Blunt posterior urethral injuries are almost exclusively related to pelvic fractures with disruption of the pelvic ring [215, 216]. These injuries are referred to as pelvic fracture urethral injuries (PFUI) [209, 223], and are mainly caused by MVAs [224]. Pelvic fracture urethral injuries are divided into partial or complete ruptures [224]. In complete ruptures, there is a gap between the disrupted ends of the urethra, which fills up with scar tissue.

There is no urethral wall in the scarred space and any lumen represents a fistulous tract between the urethral stumps [225]. Injuries of the bladder neck and prostate are rare and mostly occur at the anterior midline of both the bladder neck and prostatic urethra [226]. It is highly uncommon to find a complete transection of the bladder neck or an avulsion of the anterior part of the prostate [226]. Concomitant injuries to the head, thorax, abdomen and/or spine are frequent (up to 66%) [224].

Penetrating injuries of the pelvis, perineum or buttocks (mainly gunshot wounds) can also damage the posterior urethra, but are extremely rare in the civilian setting [227]. There is a high probability of associated injuries (80-90%), mainly intra-abdominal [165, 227].

The associated injuries which occur with both blunt and penetrating posterior urethral injuries can be life-threatening, and if so, will govern the patient's assessment and treatment [224]. Delayed morbidities of posterior urethral injuries include strictures, incontinence and erectile dysfunction, all of which may have a detrimental effect on the patient's quality of life [228]. The pooled estimate for the proportion of patients with erectile dysfunction following PIFU is 34% [229].

4.4.1.3 Female urethral injuries

Birth related injuries to the female urethra are rare and consist of minor (peri)urethral lacerations during vaginal delivery. Pelvic fractures are the main cause of **blunt** trauma [228, 230]; however, PFUIs in females are rare and less common than in males. This is usually attributed to the flexibility provided by the vagina and the greater inherent elasticity of the female urethra [228, 230], it may also be the result of less severe and more frequent stable pelvic fractures in females [156, 224]. In unstable pelvic fractures in females, a high suspicion for a urethral injury should be maintained [230]. Female urethral injuries are classified into two types: longitudinal or partial (most frequent) injuries and transverse or complete injuries [230]. Concomitant bladder or vaginal injury is possible; therefore, females are at risk of developing urinary incontinence and urethrovaginal fistula [224, 230].

Insertion of a synthetic sub-urethral sling for the treatment of female stress urinary incontinence is complicated by an intra-operative urethral injury in 0.2-2.5% of cases [231] and is an important cause of **iatrogenic** urethral injury.

*4.4.2 **Evaluation***

4.4.2.1 Clinical signs

Blood at the meatus is the cardinal sign, but the absence of it doesn't rule out a urethral injury [156, 224]. Inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture [224, 225]. Haematuria and pain on urination may be present in incomplete ruptures. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour) [225].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases), and may reveal a 'high-riding' prostate, which is an unreliable finding [156, 225]. Failure to detect a rectal injury can cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [156]. Another sign of urethral injury is difficulty or inability to pass a urethral catheter [156, 225].

A female urethral injury should be suspected from the combination of a (unstable) pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling, urinary retention or difficulties passing a urethral catheter [156, 228]. Vaginal examination is indicated to assess vaginal lacerations [156, 228].

4.4.2.2 Urethrography

Retrograde urethrography (RUG) is the standard in the early evaluation of a male urethral injury [156, 232] and is conducted by injecting 20-30 mL of contrast material while occluding the meatus. Films should be taken in a 30° oblique position. In patients with PFUI, it is important to move the X-ray beam to the 30° angle rather than the patient [224]. In an unstable patient, RUG should be postponed until the patient has been stabilised [156, 165].

During RUG, any extravasation outside the urethra is pathognomonic for urethral injury [225]. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling [224]. Although RUG is able to reliably identify the site of injury (anterior vs. posterior), the distinction between a complete and partial rupture is not always clear [223, 224]. Therefore, any proposed classification system based on RUG is not reliable [223, 224]. In females, the short urethra and vulvar oedema makes adequate urethrography nearly impossible [233].

Prior to deferred treatment, a combination of RUG and antegrade cysto-urethrography is the standard to evaluate site and extent of the urethral stenosis, and to evaluate the competence of the bladder neck [224].

4.4.2.3 Cysto-urethroscopy

Flexible cysto-urethroscopy is a valuable alternative to diagnose an acute urethral injury and may distinguish between complete and partial rupture [232]. Flexible cysto-urethroscopy is preferred to RUG in suspected penile fracture-associated urethral injury as RUG is associated with a high false-negative rate [234, 235]. In females, where the short urethra often precludes adequate radiological visualisation, cysto-urethroscopy and vaginoscopy are the diagnostic modalities of choice [156, 230]. If, prior to deferred treatment, the competence of the bladder neck is not clear upon antegrade cysto-urethrography, a suprapubic cystoscopy is advised [224].

4.4.2.4 Ultrasound and magnetic resonance imaging

In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter [224]. In complex PFUIs, MRI before deferred treatment provides valuable additional information, which can help to determine the most appropriate surgical strategy [236]. This information includes a better estimation of the length of the distraction defect, degree of prostatic displacement and presence/absence of a false passage [236].

4.4.3 ***Disease Management***

4.4.3.1 Male anterior urethral injuries

4.4.3.1.1 Immediate exploration and urethral reconstruction

This is indicated for penile fracture related injuries [211] and non-life threatening penetrating injuries [228]. Small lacerations can be repaired by simple closure [211]. Complete ruptures without extensive tissue loss are treated with anastomotic repair [211, 212]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation is needed [232].

Penetrating injuries require peri- and post-operative antibiotic treatment [237]. The role of immediate urethroplasty in blunt injuries is controversial. Patients (88.3% complete ruptures), who underwent immediate urethroplasty had a failure rate that was not significantly different compared to those who underwent delayed urethroplasty after initial suprapubic diversion (11.7% vs. 18.6%; p = 0.71). The time to spontaneous voiding was significantly shorter in the immediate urethroplasty group (27 vs. 192 days) [238]. A stricture rate of 14.4% following immediate repair has been reported based on 23 studies with a total of 591 patients [239]. An analysis of direct comparative studies showed a composite stricture rate of 20% for immediate repair vs. 44.2% for early endoscopic re-alignment, but at the expense of longer hospital stays and increased blood loss [239].

Perforation of the distal urethra during penile prosthesis insertion needs to be repaired over a catheter; in this instance the initial procedure should be abandoned [240].

4.4.3.1.2 Urinary diversion

Blunt anterior urethral injuries are associated with spongiosal contusion. Evaluation of the limits of urethral debridement in the acute phase might be difficult and as a consequence, it is reasonable to start with urinary diversion only [232]. If urinary diversion is performed, the therapeutic options are suprapubic diversion or a trial of early endoscopic re-alignment with transurethral catheterisation [232], there is conflicting evidence as to which intervention is superior [239, 241]. Urinary diversion is maintained for one to two weeks for partial ruptures and three weeks for complete ruptures [232, 241]. Satisfactory urethral luminal re-canalisation may occur in up to 68% after partial ruptures, but is rare (14%) after complete ruptures [241]. A review of 49 Chinese studies (1,015 patients), reported a 57% (range: 0-100%) success rate for endoscopic re-alignment of blunt anterior injuries [239]. The wide range in success rate most likely reflects a mix of partial and complete ruptures which was not further specified in the review. Transurethral or suprapubic urinary diversion are treatment options for iatrogenic or life-threatening penetrating injuries [228, 242]. Minor iatrogenic urethral injuries and urethral contusions do not require urinary diversion [3].

4.4.3.2 Male posterior urethral injuries

4.4.3.2.1 Emergency room management

As these injuries are usually associated with other severe injuries, resuscitation and immediate treatment of life-threatening injuries have absolute priority [224]. Penetrating injuries especially have a very high likelihood of associated injuries requiring immediate exploration [165, 227]. There is no urgency to treat the urethral injury and urinary diversion is not essential during the first hours after trauma [225]; however, it is preferable to establish early urinary diversion to:

- monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;

- treat symptomatic retention if the patient is still conscious;
- minimise urinary extravasation and its secondary effects, such as infection and fibrosis [224].

Insertion of a suprapubic catheter is an accepted practice in urgent situations [225, 227]. However, insertion of a suprapubic catheter is not without risk, especially in the unstable trauma patient where the bladder is often displaced by a pelvic haematoma or because of poor bladder filling due to haemodynamic shock or concomitant bladder injury. In these circumstances, an attempt at urethral catheterisation can be carried out by experienced personnel. It is extremely unlikely that the gentle passage of a urethral catheter will do any additional damage [224]. If there is any difficulty, a suprapubic catheter should be placed under US guidance or under direct vision, for example, during laparotomy for associated injuries [224]. Suprapubic catheter placement does not increase the risk of infectious complications in patients undergoing internal fixation to stabilise a pelvic fracture [243]. Therefore, the assertion that suprapubic catheter placement would increase the risk of orthopaedic hardware infection and subsequent explantation is not justified [243].

4.4.3.2.2 Early urethral management (less than six weeks after injury)

For partial injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries can heal without significant scarring or obstruction [225, 228]. A complete injury will not heal, and formation of an obliterated segment is inevitable in case of suprapubic diversion alone [225, 228]. To avoid this obliteration and a long period of suprapubic diversion followed by deferred urethroplasty, the urethral ends can be sutured (urethroplasty) or approximated over a transurethral catheter (re-alignment).

4.4.3.2.2.1 Immediate urethroplasty

Urethroplasty within 48 hours after injury is difficult because of poor visualisation and the inability to accurately assess the degree of urethral disruption, due to extensive swelling and ecchymosis, which may result in extensive unjustified urethral debridement. Another problem is the risk of severe bleeding (average 3 L) following entry into the pelvic haematoma [224]. In addition, with high rates of impotence (23%), incontinence (14%) and strictures (54%), urethroplasty within 48 hours is not indicated [224].

4.4.3.2.2.2 Early urethroplasty

Urethroplasty can be performed after two days and up to six weeks after the initial injury, if associated injuries have been stabilised, the distraction defect is short, the perineum is soft and the patient is able to lie down in the lithotomy position [244, 245]. This avoids a long period of suprapubic diversion with its discomfort and complications [244, 245]. As the results (complications, stricture recurrence, incontinence and impotence) are equivalent to delayed urethroplasty [245-247], early urethroplasty might be an option for patients fulfilling the above-mentioned criteria.

Lacerations (blunt or penetrating) at the bladder neck and prostatic urethra are a specific entity: they will never heal spontaneously, will cause local cavitation (presenting a source of infection) and compromise the intrinsic sphincter mechanism (with increased risk of urinary incontinence) [226]. They must be reconstructed as soon as possible [223, 227, 228]. For penetrating injuries with severe lesions to the prostate, prostatectomy (bladder neck sparing) must be performed [227].

4.4.3.2.2.3 Early re-alignment

Early re-alignment can be performed when a stable patient is on the operating table for other surgery or as a stand-alone procedure in the absence of concomitant injuries [165, 248]. In a partial injury, re-alignment, and transurethral catheterisation avoids extravasation of urine in the surrounding tissues reducing the inflammatory response. In complete injuries, the aim of re-alignment is to correct severe distraction injuries rather than to prevent a stricture [228, 249].

Re-alignment can be done by an open or endoscopic technique [249, 250]. The open technique is associated with longer operation times, more blood loss and longer hospital stays; as such, endoscopic re-alignment is now preferred [239]. Using a flexible/rigid cystoscope and biplanar fluoroscopy, a guidewire is placed inside the bladder under direct visual control, over this, a catheter is placed. If necessary, two cystoscopes can be used: one retrograde (per urethra) and one antegrade (suprapubic route through the bladder neck) [224]. The duration of catheterisation is three weeks for partial and six weeks for complete ruptures with voiding urethrography upon catheter removal [224]. It is important to avoid traction on the balloon catheter as it can damage the remaining sphincter mechanism at the bladder neck [224].

With contemporary endoscopic re-alignment procedures, stricture formation is reduced to 44-49% [249, 250] compared to a 89-94% stricture rate with suprapubic diversion [250, 251]. There is no evidence that early re-alignment increases the risk of urinary incontinence (4.7-5.8%) or erectile dysfunction (16.7-20.5%) [250, 251].

Another potential benefit of early re-alignment is that when a stricture occurs it will be shorter and therefore, easier to treat. For short, non-obliterative strictures following re-alignment, direct vision urethrotomy can be performed. Approximately 50% of strictures after endoscopic re-alignment can be treated endoscopically [249]. However, repetitive endoscopic procedures in case of stricture formation might delay the time to definitive cure and can increase the incidence of adverse events (false passage, abscess formation) [252, 253]. In light of this, repetitive endoscopic treatments after failed re-alignment are not recommended; instead, urethroplasty must be performed.

Koraitim *et. al*. found a shorter stricture length after early (open) re-alignment and as a consequence, a tendency for less complex manoeuvres to be needed to allow for a tension-free anastomosis during urethroplasty [254]. On the other hand, Tausch *et al*. reported an equal stricture length and no greater facilitation of urethroplasty after failed endoscopic re-alignment compared to suprapubic diversion only [252]. The proposed benefit is thus highly questionable. Furthermore, there is conflicting evidence as to whether failed early re-alignment jeopardises the success of definitive urethroplasty [224].

Differences between series in the rates of incontinence, impotence and re-stricture can be explained by differences in patient selection (severe vs. less severe trauma), a mix of partial and complete ruptures, and differences in follow-up duration. Furthermore, these differences make the comparison with other techniques difficult, especially with urethroplasty [156, 249].

4.4.3.2.3 Deferred management (greater than three months after injury)

The standard treatment remains deferred urethroplasty [13, 14]. In the case of a complete rupture, treated with an initial period of three months suprapubic diversion, obliteration of the posterior urethra is almost inevitable [225]. Endoscopic treatment of a complete obliteration is not successful [224]. After at least three months of suprapubic diversion, the pelvic haematoma is nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [244] and the patient is clinically stable and able to lie down in the lithotomy position [232, 244]. Associated life-threatening injuries often preclude early management of penetrating membranous urethral injuries. In those cases, suprapubic diversion with delayed urethroplasty is also advised [17, 25, 26]. Perineal anastomotic repair is the surgical technique of choice, but a combined abdominoperineal approach is necessary in rare cases of concomitant bladder neck injury or recto-urethral fistula [255].

The overall success rate for deferred urethroplasty is 86% [224]. Deferred urethroplasty does not significantly affect erectile function [256]. Although, a small proportion (< 7%) of patients report *de novo* erectile dysfunction after delayed urethroplasty, others (6-20%) have recovery of erectile dysfunction after delayed urethroplasty [224]. Incontinence is rare with deferred urethroplasty (approximately 5%), and is usually due to incompetence of the bladder neck [224]. The assessment of sexual function and the decision on definitive treatment (e.g. penile prosthesis), should be undertaken two years after the trauma because of the potential return of potency within that time [223, 257].

4.4.3.3 Female urethral injuries

Emergency room management of PFUIs in females is the same as in males (section 4.4.3.2.1); however, subsequent management differs. Treatment options are [230]:

- **Early repair (less than or equal to seven days):** Complication rate is the lowest with early repair; therefore, this strategy is preferred once the patient is hemodynamically stable [228, 230].
- **Delayed repair (greater than seven days):** Delayed repair often requires complex abdominal or combined abdominal-vaginal reconstruction with elevated risk of urinary incontinence and vaginal stenosis.

The approach (vaginal, abdominal or combined) for early repair depends on the location of the injury [230]. Proximal and mid-urethral disruptions require immediate exploration and primary repair using the retropubic and transvaginal routes, respectively, with primary suturing of the urethral ends or urethral laceration. Concomitant vaginal lacerations are repaired (two-layer closure) transvaginally at the same time [230]. Distal urethral injuries can be left hypospadiac since they do not disrupt the sphincter mechanism, but a concomitant vaginal laceration must be closed [156, 233]. In case of urethral injury during synthetic sub-urethral sling insertion, immediate repair is warranted with abortion of sling insertion [231].

Table 4.4.1: Complication rates for different treatment strategies for PFUIs in females [230]

Type of repair	Stricture (%)	Fistula (%)	Incontinence (%)	Vaginal stenosis (%)	Need for permanent urinary diversion (%)
Early realignment	59	13	0	0	0
Early repair	3	6	9	0	3
Delayed repair	3	4	31	4	7

4.4.4 Summary of evidence and recommendations for the evaluation and management of urethral trauma

Summary of evidence	LE
Implementing training programmes on urinary catheter insertion for personnel involved with urethral catheterisation significantly improves the rate of catheter-related complications.	2b
In males, a urethral injury is detected as contrast extravasation during urethrography or as a mucosal laceration during cysto-urethroscopy.	3
As opposed to cysto-urethroscopy, voiding cysto-urethrography will miss a female urethral injury in approximately 50% of cases.	3
Transurethral or suprapubic urinary diversion are the treatment options for iatrogenic injuries.	3
With urinary diversion (suprapubic or transurethral catheter) satisfactory urethral luminal re-canalisation may occur in up to 68% after partial blunt anterior urethral ruptures.	3
Complete blunt anterior urethral ruptures are unlikely to be fixed by urinary diversion alone, whereas immediate urethroplasty has an equal success rate compared to delayed urethroplasty.	3
If PFUIs are associated with life-threatening injuries, urethral management has no priority and urinary diversion with either urethral or suprapubic catheterisation is sufficient initially.	3
With early endoscopic re-alignment the stricture rate is reduced to 44-49% without increased risk of incontinence or erectile dysfunction.	3
Repetitive endoscopic treatments after failed re-alignment delay the time to definitive cure and increases the incidence of adverse events.	3
For partial posterior injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries might heal without significant scarring or obstruction.	3
Immediate urethroplasty (< 48 hours) in male PFUI is associated with a higher risk of bleeding and stricture, incontinence and impotence rates compared to delayed urethroplasty.	3
In selected patients for male PFUI early urethroplasty (two days to six weeks) is associated with similar stricture, incontinence and impotence rates compared to delayed urethroplasty.	3
Suprapubic diversion with delayed urethroplasty in male PFUI with complete urethral disruption is associated with a 86% stricture free success rate and with no significant impact on erectile function and urinary continence.	2a
Early repair in female PFUI has the lowest complication rate.	3

Recommendations	Strength rating
Provide appropriate training to reduce the risk of traumatic catheterisation.	Strong
Evaluate male urethral injuries with flexible cysto-urethroscopy and/or retrograde urethrography.	Strong
Evaluate female urethral injuries with cysto-urethroscopy and vaginoscopy.	Strong
Treat iatrogenic anterior urethral injuries by transurethral or suprapubic urinary diversion.	Strong
Treat partial blunt anterior urethral injuries by suprapubic or urethral catheterisation.	Strong
Treat complete blunt anterior urethral injuries in males by immediate urethroplasty.	Weak
Treat pelvic fracture urethral injuries (PFUIs) in hemodynamically unstable patients by transurethral or suprapubic catheterisation initially.	Strong
Perform early endoscopic re-alignment in male PFUIs when feasible.	Weak
Do not repeat endoscopic treatments after failed re-alignment for male PFUI.	Strong
Treat partial posterior urethral injuries initially by suprapubic or transurethral catheter.	Strong
Do not perform immediate urethroplasty (< 48 hours) in male PFUIs.	Strong
Perform early urethroplasty (two days to six weeks) for male PFUIs with complete disruption in selected patients (stable, short gap, soft perineum, lithotomy position possible).	Weak

Manage complete posterior urethral disruption in male PFUIs with suprapubic diversion and deferred (at least three months) urethroplasty.	Strong
Perform early repair (within seven days) for female PFUIs (not delayed repair or early re-alignment).	Strong

*4.4.5 **Treatment algorithms***

Management of anterior and posterior urethral injuries in men

Figure 4.4.1: Management of anterior urethral injuries in men

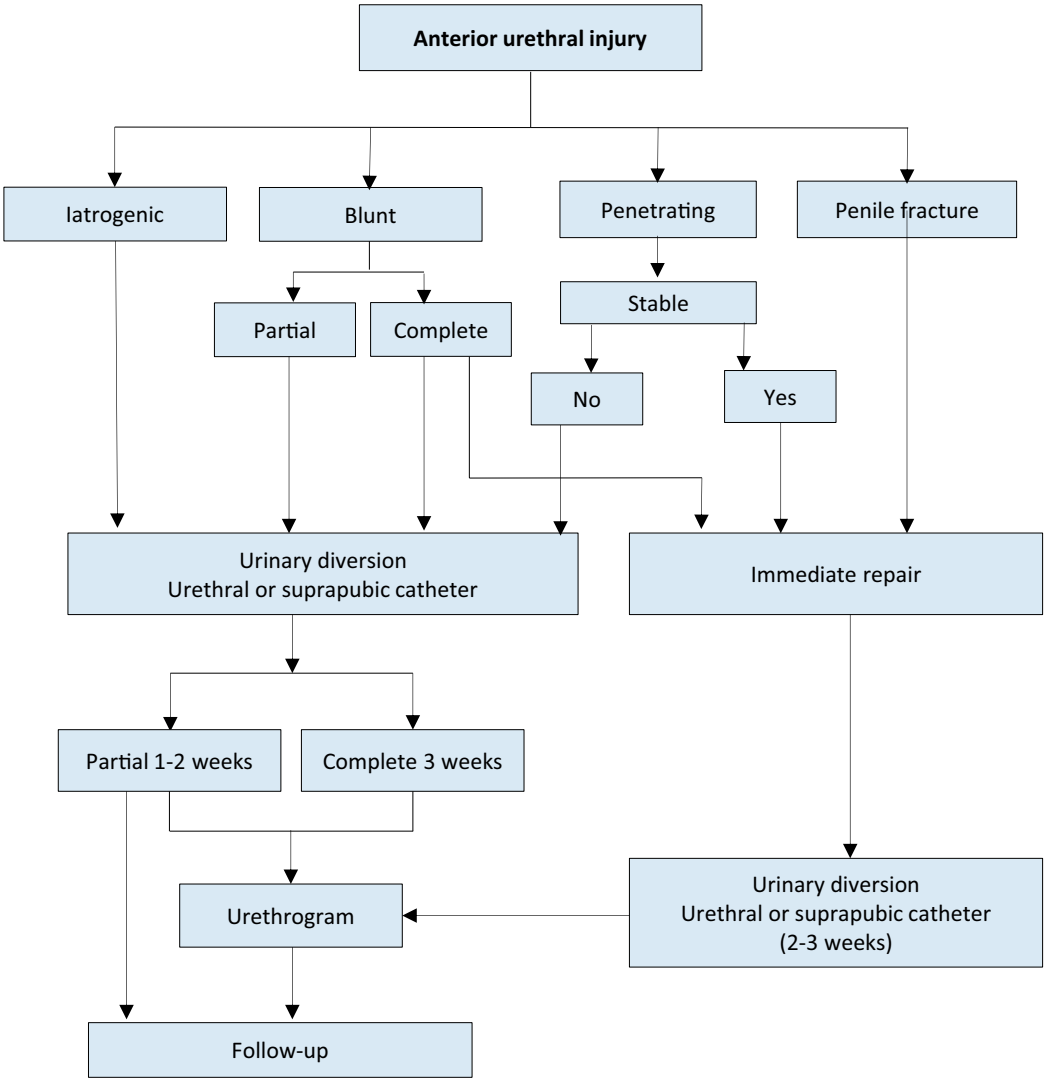
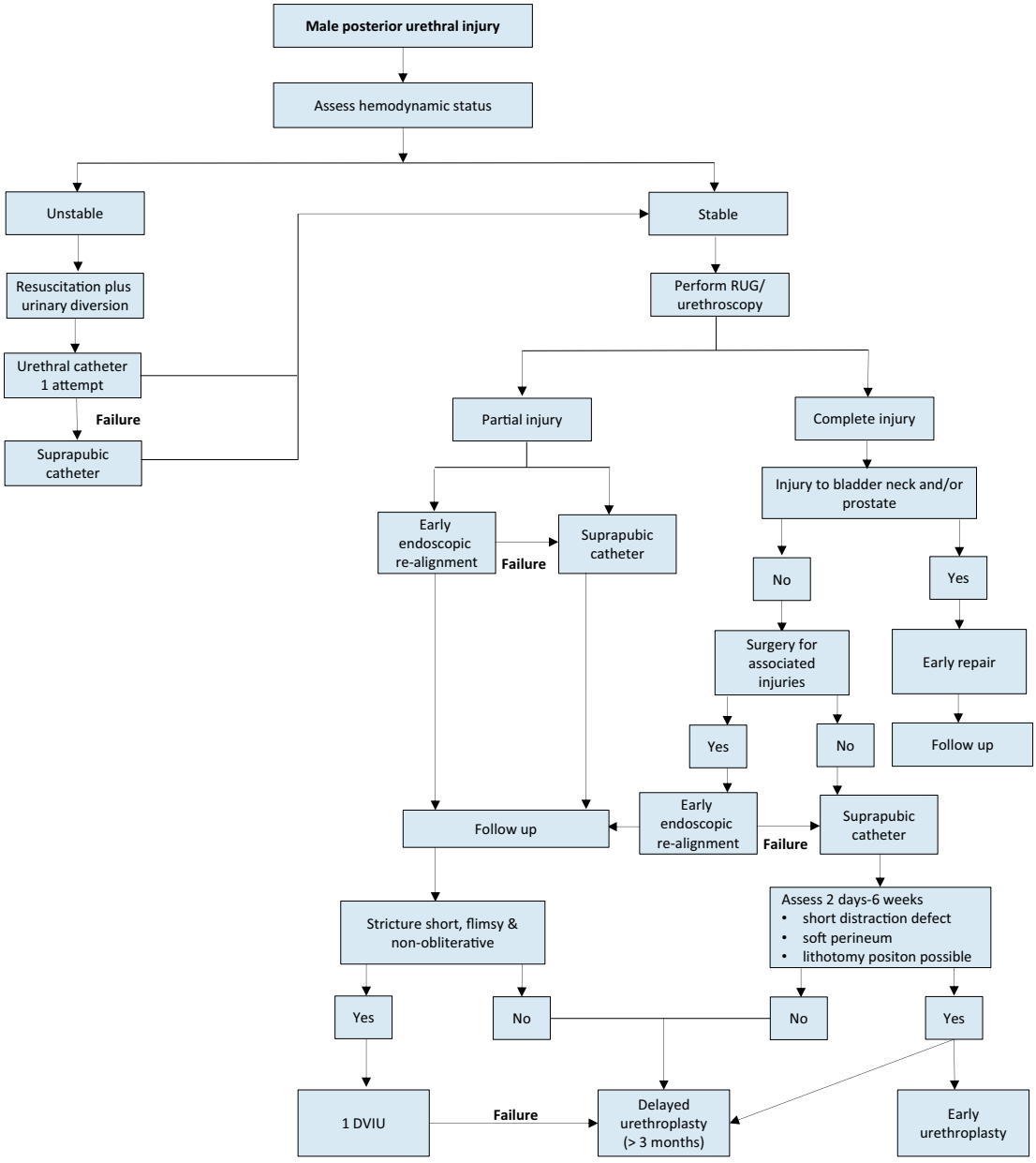


Figure 4.4.2: Management of posterior urethral injuries in men



RUG = retrograde urethrography; DVIU = direct visual internal urethrotomy.

4.5 Genital Trauma

4.5.1 Epidemiology, aetiology and pathophysiology

Of all urological injuries, 33-66% involve the external genitalia [258]. Genital trauma is much more common in males than in females, especially between the ages of 15 and 40 years. This is due to anatomical differences, increased frequency of MVAs and increased participation in physical sports, war and crime. The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum and bowel), after blunt trauma is higher in females than in males.

Genital trauma is commonly caused by blunt injuries (80%). In males, blunt genital trauma frequently occurs unilaterally with approximately 1% presenting as bilateral scrotal or testicular injuries [259]. Any kind of contact sport, without the use of protective aids, may be associated with genital trauma. Off-road cycling, motor biking (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities associated with blunt testicular trauma [260-263]. Penetrating injuries are most commonly caused by firearms (75.8%) [264].

Accidents during sexual intercourse can also cause genital trauma; men of younger age are the most affected. The major pathologies are penile fractures, strangulation and necrosis, and urethrovesical foreign bodies resulting from autoeroticism practices [265].

The most important presentation of blunt penile trauma is penile fracture. The most common causes are sexual intercourse, forced flexion (taqaandan), masturbation and rolling over in 46%, 21%, 18% and 8.2%, respectively [266]. The usual mechanism of injury is when the penis slips out of the vagina and strikes against the symphysis pubis or perineum. Sixty per cent of cases occur during consensual intercourse [267], with penile fracture more likely when the partner is on top. Penile fracture is caused by rupture of the cavernosal tunica albuginea, and may be associated with subcutaneous haematoma and lesions of the corpus spongiosum or urethra in 10-22% [268-270]. Genital injury is prevalent (42%) after sexual abuse [271].

Although animal bites are common, bites injuring the external genitalia are rare. Wounds are usually minor, but have a risk of wound infection.

Gunshot injuries to the external genitalia are relatively uncommon and are usually not life-threatening; however, they can have a significant impact on quality of life. About 40-60% of all penetrating genito-urinary lesions involve the external genitalia [213, 272], 35% of these are gunshot wounds [259]. In a series of wartime injuries, the majority were caused by improvised explosive devices and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [273]. In both males and females, penetrating injuries affect multiple organs in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases compared with 1% in blunt injuries [259, 274]. Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals [275]. Genital burns are rare in isolation and are usually due to industrial flames or chemicals [276]. Both male and female genital piercings increase the risk for unexpected genital trauma [277].

Traumatic dislocation of the testicle rarely occurs and is most common in victims of MVAs [278-281]. Bilateral dislocation of the testes has been reported in up to 25% of cases [279]. Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma [282, 283]. It may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea. A force of approximately 50 kg is necessary to cause testicular rupture [284]. Most penile avulsion injuries are self-inflicted, but some are a result of industrial accidents or assault.

Coital injury of the female genital tract can happen during consensual sexual intercourse. Up to 35% of all genital injuries in women are sustained during their first sexual contact. The most frequently found injuries are lacerations [285]. Blunt trauma to the vulva is rarely reported and usually presents as a large haematoma. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries [286]. The presence of a vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic or abdominal injuries [287, 288]. Blunt injuries of the vulva and vagina are associated with pelvic trauma in 30%, after consensual intercourse in 25%, following sexual assault in 20%, and other blunt trauma in 15% [289].

*4.5.2 **Diagnostic evaluation***

4.5.2.1 Patient history and physical examination

Penile fracture is associated with a sudden cracking or popping sound, pain and immediate detumescence. Local swelling of the penile shaft develops quickly, due to enlarging haematoma [210]. Bleeding may spread along the fascial layers of the penile shaft and extend to the lower abdominal wall if Buck's fascia is also ruptured. Sometimes, the rupture of the tunica may be palpable. Less severe penile injuries can be distinguished from penile fracture, as they are not usually associated with detumescence [266].

Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting. The hemiscrotum is tender, swollen, and ecchymotic. The testis itself may be difficult to palpate. **Blunt vulvar** or perineal trauma in women may be associated with bleeding, pain and voiding problems, bladder catheterisation is usually required.

In genital trauma, a urinalysis should be performed. The presence of visible haematuria requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy is recommended to exclude urethral and bladder injury [287, 289]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed [287].

*4.5.3 **Imaging***

In cases of suspected penile fracture cavernosography, US or MRI [266, 290-292] can identify lacerations of the tunica albuginea in unclear cases [293], or provide reassurance that the tunica is intact. Magnetic resonance imaging is superior to US in diagnosing penile fracture [294]. If a concomitant urethral injury is suspected, manage as outlined in section 4.4.

Ultrasound should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [283, 295-303]. However, the literature is contradictory as to the usefulness of US compared to clinical examination alone. Some studies have reported convincing findings with a specificity of up to 98.6% [304]. Heterogeneous echo pattern of the testicular parenchyma with the loss of contour definition is a highly sensitive and specific radiographic finding for testicular rupture [294]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocele, while accuracy is as low as 56% [296]. Colour Doppler-duplex US may provide useful information when used to evaluate testicular perfusion. If scrotal US is inconclusive, testicular CT or MRI may be helpful [305]; however, these techniques did not specifically increase the detection rates of testicular rupture.

*4.5.4 **Disease management***

4.5.4.1 Animal bites

Local wound management depends on the extent of tissue destruction. Antibiotics should be prescribed in accordance with local resistance patterns [306-308]. The possibility of rabies infection must be considered taking into account the geographical location, animal involved, specific nature of the wound and the type of attack (provoked/unprovoked). Elderly and immunosuppressed patients should be vaccinated with human rabies immunoglobulin and human diploid cell vaccine [309, 310].

4.5.4.2 Human bites

In cases of human bites, apart from wound management, infection should be considered since transmission of viral diseases may occur, Hepatitis B vaccine/immunoglobulin and/or immunodeficiency virus (HIV) post-exposure prophylaxis should be offered. For further details, see Guidelines for the Management of Human Bite Injuries [311].

4.5.4.3 Blunt penile trauma

Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. Subcutaneous haematoma after sexual intercourse, without associated rupture of the cavernosal tunica albuginea, does not require surgical intervention. In these cases, non-steroidal analgesics and ice-packs are recommended [312].

4.5.4.4 Penile fracture

The thickness of the tunica albuginea in the flaccid state (approximately 2 mm) decreases in erection to 0.25-0.5 mm, and is therefore more vulnerable to traumatic injury [304, 313]. When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended; it ensures the lowest rate of negative long-term sequelae and has no negative effect on the psychological wellbeing of the patient [314]. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables complete degloving of the penis. Increasingly, local longitudinal incisions centred on the area of fracture or ventral longitudinal approaches are currently used [234]. Further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven [210]. Surgical closure of the tunica should be carried out using absorbable sutures.

4.5.4.5 Penetrating penile trauma

In penetrating penile trauma non-operative management is recommended for small superficial injuries with intact Buck's fascia [213]. In more significant penetrating penile injuries, surgical exploration and debridement of necrotic tissue is recommended. Even in extended injuries of the penis, primary alignment of the disrupted tissues may allow for acceptable healing because of the robust penile blood supply [275].

The principles of care are debridement of devitalised tissue, with the preservation of as much viable tissues as possible, haemostasis, diversion of urine in selected cases and the removal of foreign bodies. Tissues of questionable viability may be left for subsequent definitive surgery. If a delayed repair is needed, depending on the type of injury and the extent of tissue damage, it usually takes place four to six weeks after the trauma has occurred.

The surgical approach depends upon the site and extent of the injury, but a subcoronal incision with penile degloving usually gives good exposure. Initially, a defect in the tunica albuginea should be closed after copious irrigation. If there has been too much tissue loss, the defect can be repaired either immediately or after delay with a patch (either from an autologous saphenous vein or xenograft).

The elasticity of genital skin means it is usually possible to manage the loss of a moderate amount of penile skin; however, management is more difficult in extensive injuries with significant skin loss. The tissue chosen for reconstruction following trauma needs to provide good coverage and must be suitable for reconstruction. Split-thickness skin grafting provides good coverage and a dependable take that is reproducible and durable. However, split-thickness grafts contract more than full-thickness grafts and their use on the penile shaft should be kept to a minimum. Skin grafts with thickness of at least 0.4 mm should be

used in order to reduce the risk of contraction [275]. Full-thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma during intercourse, when re-established [312]. The donor site may be taken from the abdomen, buttock, thigh or axilla and is chosen according to surgeon's preference and the pattern of injury. In cases of extensive destruction of deeper tissues, or if later prosthetic placement is being considered, skin flaps, with their secure vascular supply, can be used.

4.5.4.6 Penile avulsion injuries and amputation

Acute management involves resuscitation of the patient, and preparation for surgical re-implantation of the penis if it has been recovered and is not too badly damaged. Surgical re-implantation should be considered for all patients and should be performed within 24 hours of amputation [315].

The severed penis should be washed with sterile saline, wrapped in saline-soaked gauze, placed in a sterile bag and immersed in iced water. The penis must not come into direct contact with the ice. A pressure dressing or a tourniquet should be placed around the penile stump to prevent excessive blood loss. Re-attachment can be achieved in a non-microsurgical way, but gives higher rates of post-operative urethral stricture and more problems with loss of sensation [316]. When operating microscopically, the corpora cavernosa and urethra are firstly aligned and repaired. Subsequently, the dorsal penile arteries, the dorsal vein and the dorsal nerves are anastomosed. The cavernosal arteries are generally too small to anastomose. The fascia and skin are closed in layers and both a urethral and a suprapubic catheter are placed.

If the severed penis cannot be found, or is unsuitable for re-attachment, then the end should be closed as it is done in partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g. suspensory ligament division and V-Y plasty, pseudo-glans formation with split-thickness skin grafting, etc.). A delayed major reconstructive procedure, i.e. phalloplasty (either radial artery or pubic), is sometimes required for injuries which leave a very small or non-functioning penile stump [315].

4.5.4.7 Testicular dislocation

It can be either a subcutaneous dislocation with epifascial displacement of the testis or an internal dislocation. In the latter, the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

4.5.4.8 Haematocoele

Conservative management is recommended in haematoceles smaller than three times the size of the contralateral testis [317]. In large haematoceles, non-operative management can fail, and delayed surgery (more than three days) is often required. Patients with large haematoceles have a higher rate of orchiectomy than patients who undergo early surgery, even in non-ruptured testes [259, 275, 282, 318, 319]. Early surgical intervention results in preservation of the testis in more than 90% of cases compared to delayed surgeries which result in orchiectomy in 45-55% of patients [282]. In addition, non-operative management is also associated with prolonged hospital stays. Therefore, large haematoceles should be treated surgically, irrespective of the presence of testicular contusion or rupture. At the very least, the blood clot should be evacuated from the tunica vaginalis sac to relieve disability and hasten recovery.

4.5.4.9 Testicular rupture

It is essential to surgically explore equivocal patients whenever imaging studies cannot definitively exclude testicular rupture. This involves exploration with evacuation of blood clots and haematoma, excision of any necrotic testicular tubules and closure of the tunica albuginea, usually with running 3.0-absorbable sutures.

4.5.4.10 Penetrating scrotal trauma

Penetrating injuries to the scrotum require surgical exploration with debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In complete disruption of the spermatic cord, re-alignment without vaso-vasostomy may be considered if surgically feasible [320]. Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although only a few cases have been reported [320]. If there is extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure. If the patient is unstable or reconstruction cannot be achieved, orchiectomy is then indicated. Prophylactic antibiotics are recommended after scrotal penetrating trauma, although data to support this approach is lacking.

Extended laceration of scrotal skin requires surgical intervention for skin closure. Due to the elasticity of the scrotum, most defects can be primarily closed, even if the lacerated skin is only minimally attached to the scrotum [275]. Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence. In the case of extensive loss of genital tissue, e.g. improvised explosive device blast injury, complex and staged reconstructive surgical procedures are often required [273].

Table 4.5.1: Summary of key points for penile fracture and testicular trauma

Summary of key points:
Penile fracture
The most common causes of penile fracture are sexual intercourse, forced flexion, masturbation and rolling over.
Penile fracture is associated with a sudden cracking or popping sound, pain, immediate detumescence and local swelling.
Magnetic resonance imaging is superior to all other imaging techniques in diagnosing penile fracture.
Management of penile fracture is surgical intervention with closure of the tunica albuginea.
Testicular Trauma
Blunt testicular injury may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea.
Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting.
Scrotal ultrasound is the preferred imaging modality for the diagnosis of testicular trauma.
Surgical exploration in patients with testicular trauma ensures preservation of viable tissue when possible.

*4.5.5 **Complications***

The possibility of complications from genital trauma, including psychological effects, erectile dysfunction, urethral stricture, and infertility, is high. In patients with a history of penile fracture post-operative complications were reported in up to 20% of cases, development of plaques or nodules following surgery, post-operative curvature formation and erectile dysfunction occur in 13.9%, 2.8% and 1.9% of patients, respectively [266]. Conservative management of penile fracture increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [321]. Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% [267, 322].

Post-operative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma [213]. Despite good management and regular follow up of external genital gunshot wounds, such wounds are fraught with the possibility of complications such as erectile dysfunction, urethral stricture, and infertility. Delayed complications include chronic pain and testicular atrophy. Haematoceles initially treated non-operatively may eventually need delayed surgery if they develop infection or undue pain. Genital injuries are rarely life threatening, but fertility and testosterone production often become the male trauma patient's chief concern once acute issues are resolved [323].

*4.5.6 **Follow up***

In patients with genital trauma follow up should focus on diagnosis of and therapy for late complications. Erectile dysfunction, urethral stricture and assessment of fertility are the main concerns [270, 324].

*4.5.7 **Summary of evidence and recommendations for evaluation and management of genital trauma.***

Summary of evidence	LE
A concomitant urethral injury complicates penile fractures and requires specialised management.	3
Ultrasound can determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture with heterogeneous echo pattern parenchyma and loss of contour definition a highly sensitive and specific finding.	3
Surgical treatment of penile fracture ensures the lowest rate of negative long-term sequelae on functional and psychological wellbeing of the patient.	3
In patients with testicular rupture or equivocal imaging, surgical exploration can secure preservation of viable tissue.	3

Recommendations	Strength rating
Exclude urethral injury in the case of penile fracture.	Strong
Perform ultrasound (US) for the diagnosis of testis trauma.	Strong
Treat penile fractures surgically, with closure of tunica albuginea.	Strong
Explore the injured testis in all cases of testicular rupture and in those with inconclusive US findings.	Strong

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6. CONFLICT OF INTEREST

All members of the Urological Trauma Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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EAU Guidelines on

Chronic Pelvic Pain

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European Association of Urology

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1. INTRODUCTION

1.1 Aim

This guideline plays an important role in the process of consolidation and improvement of care for patients with abdominal and pelvic pain. From both literature and daily practice it has become clear that abdominal and pelvic pain are areas still under development. This guideline has been recognised as a cornerstone for important developments that have taken place in the past ten years.

This guideline aims to expand the awareness of caregivers in the field of abdominal and pelvic pain and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

It must be emphasised that guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. In 2016, a stepped information structure was made, in alignment with stepped care protocols, using new digital information sources like websites and apps to aid this process. Furthermore, the guideline was changed according to the template used in all other non-oncology guidelines of the EAU. It was recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. A multi-disciplinary approach is of utmost importance and demands a broad view. In 2016, the guideline was rewritten to be centred around pain instead of being organ-centred. It is partly theoretical to show the importance of using this pain-centred approach. The biggest part, however, deals with the practical approach to diagnostics, treatment and management of patients with abdominal and pelvic pain.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the CPP Guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 [3, 4]. Two chapters were added at that time: Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain’. In the 2014 edition minor revisions were made in Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 8 ‘Psychological aspects of chronic pelvic pain’.

For the 2015 edition the Panel critically reviewed the sub-chapter on bladder pain syndrome which is now a comprehensive part of the guideline. The fact that this part was so extensive shows that the roots of talking about abdominal and pelvic pain lies in the bladder, where Interstitial Cystitis was one of the first subjects addressed talking about pain in urology. The Panel has illustrated this in the publication in European Urology in 2013 [5].

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and android devices. These are abridged versions which may require consultation together with the full text version. This reference document follows the updating cycle of the underlying large texts.

All available material can be viewed at the EAU website. The EAU website also includes a selection of EAU Guideline articles as well as translations produced by national urological associations: uroweb.org/guideline/chronicpelvicpain/.

1.4 Panel composition

The panel of experts responsible for this document include four urologists, (one of which has a sub-specialisation in neuro-urology and one is a sexologist), two consultants in pain medicine, a uro-gynaecologist, a psychologist, a gastroenterologist and a pelvic physiotherapist, health scientist and (clinical) epidemiologist.

The Panel is also grateful to Ms. J. Birch for her expertise, time and diligence in undertaking a review of these guidelines from a patient perspective.

1.5 Terminology

Definitions of CPP terminology

Classification

Much debate over the classification of CPP has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition: phenotyping, terminology and taxonomy.

Phenotyping

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's ulcers and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for irritable bowel syndrome (IBS), which may be sub-divided into that associated primarily with diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, auto-immune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint.

Terminology

Terminology is the words that are used within classification, both to name the phenotype and within the definition of the phenotype. Examples of names for phenotypes associated with the bladder include interstitial cystitis, painful bladder syndrome or bladder pain syndrome (BPS). The EAU, the International Society for the study of BPS (known as ESSIC), the International Association for the Study of Pain (IASP) and several other groups now prefer the term bladder pain syndrome. In the pain syndromes, the role of the nervous system in generating the sensations is thought to be pivotal, but the term syndrome is also comprehensive and takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in "itis" in particular should be avoided unless infection and or inflammation is proven and considered to be the cause of the pain [6]. It must be appreciated that end-organ inflammation may be secondary and neurogenic in origin and not a primary cause of the pain.

Taxonomy

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach sub-divides CPP into conditions that are pain syndromes and those that are non-pain syndromes. The latter are conditions that have well-recognised pathology (e.g., infection, neuropathy or inflammation), whereas the former syndromes do not and pain as a disease process is the mechanism. Other terms for the non-pain syndromes include "classical conditions", "well-defined conditions" and "confusable diseases". Although the EAU approach deals primarily with urological conditions, this approach to classification can be applied to all conditions associated with pain perception within the pelvis; the classification has been developed to include non-urological pain and was accepted by the IASP for publication in January 2012.

Classification of CPP syndromes

Importance of classification

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying CPP go far beyond that.

Clues to the mechanism

As a result of systematic phenotypic and taxonomic classifications, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows one to compare disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

Guidelines for best treatment options

As conditions become better defined, more specific treatment approaches can be adopted. In particular, there

will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal anti-inflammatory drugs for the "-itis" conditions). Generic treatments aimed at groups of conditions will be more commonplace and based upon research evidence.

Research platform
Only by clearly defining the phenotype being investigated can research be valued or applied to the clinical situation.

Patient needs
A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as in self-management. However, it may also lead to accessing information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about appropriateness of treatment.

IASP definitions
Sub-dividing pain syndromes
There is much debate on the sub-divisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows [2]:

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence of infection or inflammation. Investigations by end-organ specialists should therefore be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A sub-division phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic pelvic pain syndrome (CPPS) should be used. If the pain can be localised to an organ, then a more specific term, such as rectal pain syndrome, may be used. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPS should once again be considered. As well as defining the patient by a specific end-organ phenotype, there are several other more general descriptors that need to be considered. These are primarily psychological (e.g., cognitive or emotional), sexual, behavioural and functional. Psychological and behavioural factors are well-established factors which relate to quality of life (QoL) issues and prognosis. In North America a research programme, the MAPP program (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or auto-immune disorders.
3. In 2004 the panel introduced the concept of managing the polysymptomatic nature of CPP, since then others have developed their own schemes, such as Nickel's UPOINT [7], modified by Magri *et al.* [8]. In light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to sub-dividing the pain syndromes remains ongoing. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPP conditions (e.g., bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. Only time and good research will determine whether this is appropriate. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

The classification has been set up according to the axis system used by IASP.

Table 1: EAU classification of chronic pelvic pain syndromes

Axis I Region		Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix		Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Specific disease associated pelvic pain OR Pelvic pain syndrome	Urological	Prostate		Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalegesie SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
				Bladder					
				Scrotal Testicular Epididymal					
				Penile Urethral					
				Post-vasectomy					
		Gynaecological	Vulvar Vestibular Clitoral						
				Endometriosis associated					
				CPPS with cyclical exacerbations					
				Dysmenorrhoea					
		Gastrointestinal	Irritable bowel						
				Chronic anal					
				Intermittent chronic anal					
		Peripheral nerves	Pudendal pain syndrome						
		Sexological	Dyspareunia						
				Pelvic pain with sexual dysfunction					
		Psychological	Any pelvic organ						
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal						
				Coccyx					

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

Pain syndromes

The original EAU classification [2] was inspired by the IASP classification [9] and much work around what has become known as "pain as a disease" and its associated psychological, behavioural, sexual and functional correlates. After ten years of work developing the initial ideas, an updated version was accepted by the IASP Council for publication in January 2012.

Definition of chronic pelvic pain

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction.
[*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being discerned in a specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least six months. That is, it can be cyclical over a six-month period, such as the cyclical pain of dysmenorrhoea. Although arbitrary, six months was chosen because three months was not considered long enough if cyclical pain conditions are included. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period. Cyclical pain is included in the classification and hence dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be sub-divided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term "specific disease-associated pelvic pain" is proposed for the former, and "chronic pelvic pain syndrome" for the latter. The following classification only deals with CPPS.

Definition of chronic pelvic pain syndrome

Chronic pelvic pain syndrome is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Chronic Pelvic Pain Syndrome is a sub-division of CPP.

Further subdivision of CPPS

Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end organ term such as Bladder Pain Syndrome (Table 2). The use of such a phrase with the terminology "syndrome" indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the term CPPS should be used. Many, including some of the panel members never sub-divide by anatomy and prefer to refer to patients with pain perceived within the pelvis, and no specific disease process, as suffering from CPPS, sub-divided by psychological and functional symptoms.

Psychological considerations for classification

Many CPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships. Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients' symptoms. It is important to note that many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for any one individual suffering from CPPS. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable characteristics of the syndrome).

Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and therefore bowel control is abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype.

Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

Multi-system sub-division

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective and accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multi-systemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the panel have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS.

Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically sub-divided into superficial and deep.

Perineal pain syndrome

Perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Perineal pain syndrome should be distinguished from pudendal neuralgia which is a specific disease associated with pelvic pain that is caused by nerve damage.

Table 2: Chronic Pelvic Pain Syndromes

Urological Pain Syndromes	
Prostate pain syndrome	Prostate pain syndrome (PPS) is the occurrence of persistent or recurrent episodic pain (which is convincingly reproduced by prostate palpation). There is no proven infection or other obvious local pathology. Prostate pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term “chronic prostatitis” continues to be equated with that of PPS. In the authors’ and others’ opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The National Institutes of Health (NIH) consensus [10] includes infection (types I and II), which the authors feel should not be considered under PPS, but as specific disease-associated pelvic pain. The term prostadynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPS of the male is used instead of PPS, which has been agreed by the majority.

Bladder pain syndrome	Bladder pain syndrome is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Bladder pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of sub-classifications [11] to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”. These terms are no longer recommended.
Scrotal pain syndrome	Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.
Testicular pain syndrome	Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended
Epididymal pain syndrome	Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences.
Penile pain syndrome	Penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, in the absence of proven infection or other obvious local pathology. Penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.
Urethral pain syndrome	Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.
Post-vasectomy scrotal pain syndrome	Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Post-vasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Post-vasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and for that reason it is considered a special form of scrotal pain syndrome.

Gynaecological Pain Syndromes: external genitalia	
Vulvar pain syndrome	Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain. There is no proven infection or other local obvious pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Although pain perceived in the vulva was included under sexual disorders in the DSM-IV-R manual for classifying psychiatric disorders, there is no scientific basis for this classification, and pain perceived in the vulva is best understood as a pain problem that usually has psychological consequences. There is no evidence for its classification as a psychiatric disorder. The International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we use the term vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder". If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g. provoked or unprovoked). The following definitions are based on that approach.
Generalised vulvar pain syndrome	Generalised vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localised by point-pressure mapping via probing with a cotton-tipped applicator or similar instrument. Rather, the pain is diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included "dysesthetic vulvodynia" and "essential vulvodynia", but these are no longer recommended.
Localised vulvar pain syndrome	Localised vulvar pain syndrome refers to pain that can be consistently and precisely localised by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction). Localised vulvar pain syndrome can be sub-divided into vestibular pain syndrome and clitoral pain syndrome.
Vestibular pain syndrome	Vestibular pain syndrome refers to pain that can be localised by point-pressure mapping to the vestibule or is well perceived in the area of the vestibule.
Clitoral pain syndrome	Clitoral pain syndrome refers to pain that can be localised by point-pressure mapping to the clitoris or is well-perceived in the area of the clitoris.
Gynaecological system: internal pelvic pain syndromes	
Endometriosis associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end-organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
Chronic pelvic pain syndrome with cyclical exacerbations	Chronic pelvic pain syndrome with cyclical exacerbations covers the nongynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or BPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Dysmenorrhoea	Dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.
Gastrointestinal Pelvic Pain Syndromes	

Irritable bowel syndrome	Irritable bowel syndrome is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. Irritable bowel syndrome is often associated with worry and pre-occupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria [12]: three months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> three bowel movements per day or < three per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
Chronic anal pain syndrome	Chronic anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction.
Intermittent chronic anal pain syndrome	Intermittent chronic anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a sub-group of the chronic anal pain syndromes. It was previously known as “proctalgia fugax” but this term is no longer recommended.
Musculoskeletal System	
Pelvic floor muscle pain syndrome	Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with over-activity of, or trigger points within, the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.
Coccyx pain syndrome	Coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. The term “coccydynia” was used but is no longer recommended.

2. METHODOLOGY

2.1 Methods

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [13, 14]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [15];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [16]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

The 2012 full text update was based on a systematic review of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycINFO and Bandolier databases to identify the best evidence from randomised controlled trials (RCTs) (Level of Evidence 1 [LE: 1]) according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence. Where no LE: 1 literature could be identified the search was moved down to the next lower level on the rating scale. Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 to July 2011 and were restricted to English language publications. In 2017, a scoping search for the previous five years was performed and the guideline was updated accordingly.

For the 2020 print, a scoping search was performed, covering all areas of the guideline starting from the last cut-off date of May 2018 with a cut-off date of May 2019. Embase, Medline, the Cochrane Central Register of Controlled Trials and Cumulative Index of Nursing and Allied Health Literature databases were searched and were restricted to English language publications. A detailed search strategy is available online: https://uroweb.org/guideline/chronic-pelvic-pain/.

2.2 Review

This document was subject to peer review prior to publication in 2015 and will be reviewed after publication in 2020.

2.3 Future goals

1. The results of ongoing and new systematic reviews will be included in the 2021 update of the Chronic Pelvic Pain Guidelines. An ongoing systematic review is:

    - What are the benefits and harms of Botulinum Toxin A vs. best clinical practice or no treatment or sham or placebo in CPP? [17].

2. The Panel's classification system was first published in 2004. The International Classification of Diseases 11th Revision (ICD 11) has now been released by the World Health Organization (WHO) with significant overlap with the Panel's system. The Panel now needs to consider whether changes to its classification to reflect ICD 11 are required and this will part of the work programme for 2020.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

3.1 Chronic visceral pain

Definition of pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP Taxonomy).

Introduction to chronic pelvic pain syndromes

Over the years much of the focus for CPP has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of the mechanisms for the CPPSs are based within the CNS. Although a peripheral stimulus such as infection may initiate the start of a CPP condition, the condition may become self-perpetuating as a result of CNS modulation. As well as pain, these central mechanisms are associated with several other sensory, functional,

behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and each individual phenomenon needs to be addressed in its own right through multi-specialty and multi-disciplinary care. Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPPSs in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage.

*3.1.1 **Incidence***

No adequate data on incidence were found.

*3.1.2 **Prevalence***

In a large European study undertaken in 2004 [18], it was found that chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of their social and working lives. There are some differences between countries but not much spread is seen. A more recent study in the UK found a prevalence of CPP of 14.8% in women over 25 years [19].

*3.1.3 **Influence on Quality of Life***

Assessing QoL in pelvic pain patients is challenging due to the complex pathology, the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes [20, 21].

Pelvic pain syndromes have an impact in terms of QoL [22, 23], depression, anxiety, impaired emotional functioning, insomnia and fatigue [22, 24]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve. Addressing comorbidities will help in further improving QoL [25]. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial and emotional tools, using standardised and validated instruments [23].

The impact of pain on QoL has been assessed in a large European study [18]. Of the 4,839 respondents with chronic pain (about 300 per country), 66% had moderate pain and 34% had severe pain; 46% had constant pain and 54% had intermittent pain. Twenty-one percent had been diagnosed with depression because of pain, and almost all had reduced their work hours or stopped working altogether. Sixty per cent had visited their doctor about their pain two to nine times in the last six months, but only 2% were currently treated by a pain management specialist.

*3.1.4 **Costs***

No adequate data on costs were found.

*3.1.5 **Risk Factors and underlying causes***

3.1.5.1 Risk factors

Risk factors include many different factors from various areas, including genetic, psychological state, recurrent physical trauma and endocrine factors.

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Up-regulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g. IBS and BPS. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception. Stress can also produce long-term biological changes which may form the relation between chronic pain syndromes and significant early life and adverse life events [26]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [27, 28].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred to be more prone to apparent chronic pain state. A range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that developmental, environmental and social factors also influence the situation. Evidence that BPS may have a genetic component has been presented in several identical twin studies, but genetics may contribute to less than one third of total variation in susceptibility to BPS [29, 30].

Studies about integrating the psychological factors of CPPSs are few but the quality is high. Psychological factors are consistently found to be relevant in the maintenance of persistent pelvic and urogenital [31]. Beliefs about pain contribute to the experience of pain [32] and symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [33], and catastrophic thinking about pain and perceived stress predict worsening of urological chronic pain over a year [31, 34]. Central sensitisation has been demonstrated in symptomatic endometriosis [35] and central changes are evident in association with dysmenorrhoea and increasingly recognised as a risk for female pelvic pain [36]. The various mechanisms of CNS facilitation, amplification and failure of inhibition, mean that there is no simple relationship between physical findings, pain experienced and resulting distress and restriction of activities. Division of aetiology into organic vs. psychogenic is unscientific. Diagnoses that assign women's pain to psychological origins due to scepticism about the reality or severity of their pain [37, 38] undermines any therapeutic relationship [39]. Pelvic pain and distress may be related [40] in both men and women [41]; as are painful bladder and distress [34]. In a large population based study of men, CPPS was associated with prior anxiety disorder [42]. The only systematic review [43] of risk factors for chronic non-cyclical pelvic pain in women included, as well as medical variables: sexual or physical abuse (Odds Ratio (OR) 1.51 to 3.49); psychological problems such as anxiety (OR: 2.28, 95% Confidence Interval (CI): 1.41- 3.70) and depression (OR: 2.69, 95% CI: 1.86-3.88); multiple somatic problems (OR: 4.83, 95% CI: 2.50-9.33 and OR: 8.01, 95% CI: 5.16-12.44).

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, particularly in women with pelvic pain [44]. It is hard to establish a causal role for sexual abuse or trauma history, anxiety or depression in women with CPP [45-47], the attribution of current pain to past sexual or physical abuse is associated both with current depression [48] and with current overall physical health [49]. There is some evidence for a specific relationship between rape and CPP (and with fibromyalgia and functional gastrointestinal disorders) [50]; and, recent sexual assault may prompt presentation of pelvic pain [44, 51]. Few studies have been found of sexual or physical abuse in childhood and pelvic pain in men, although it has known adverse effects on health [50], but men who reported having experienced sexual, physical or emotional abuse had increased odds (3.3 compared to 1.7) for symptoms suggestive of CPP [52]. Both sexes should be screened for sexual abuse when presenting with symptoms suggestive of CPP, and clinicians should inquire about pelvic pain in patients who have experienced abuse [52].

3.1.5.2 Underlying causes

The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1. Ongoing acute pain mechanisms [53] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [6].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [54-56].

Symptoms and signs of neuropathic pain appear to be common in CPP patients and assessment of neuropathic pain should be considered in that group of patients. The presence or absence of endometriosis does not seem to change this [57].

Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in men with chronic prostatitis/CPPS [58].

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. These underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

	Visceral pain	Somatic pain
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised but well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A∂ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases, afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on.	These fibres are very important in the central sensitisation process. Silent afferents present, but form a lower percentage.
Central mechanisms	Play an important part in the hyperalgesia, viscero-visceral, viscero-muscular and musculo-visceral hyperalgesia.	Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm.
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

Ongoing peripheral pain mechanisms in visceral pain

In most cases of CPP, ongoing tissue trauma, inflammation or infection is absent [59, 60]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. For example, out of a large cohort with acute bacterial prostatitis, 10.5% ended up with a state of CPPS [61]. It is for this reason that the early stages of assessment include looking for these pathologies [11]. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur; therefore, magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [62].

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility:

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulate the receptors of the transducers [63].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 is to lower the threshold and the effect of 3 is to increase responsiveness to external stimuli. Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the positive and inhibitory loops [64, 65].

Central sensitisation as a mechanism in visceral pain

It is important to appreciate that nociception is the process of transmitting information to centres involved in perception of a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. The brain may affect the modulation of pain pathways at the spinal cord level.

Central sensitisation is responsible for a decrease in threshold and an increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signalling to the CNS and amplifies what we perceive from a peripheral stimulus. For example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally sub-threshold and not usually perceived, may be perceived. For instance, with central sensitisation, stimuli that are normally sub-threshold may result in a sensation of fullness and a need to void or to defecate. Non-noxious stimuli may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of BPS and IBS may be explained by central sensitisation. A similar explanation exists for the muscle pain in FM.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [66]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main ones are the opioids, 5-hydroxytryptamine and noradrenaline.

The autonomic nervous system also plays a role in sensitisation. There is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly in the dorsal horns. In visceral pain, the efferent output of the CNS may be influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on QoL and must be managed as appropriate.

Psychological mechanisms in visceral pain

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex.

Various psychological processes affect pain neuromodulation at a higher level. Inhibiting or facilitating both the strength of the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal, will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels. Functional magnetic resonance imaging (fMRI) has indicated that the psychological modulation of visceral pain probably involves multiple pathways. For instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain [67].

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation [68] may occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to perceiving sensations that would not normally be experienced as painful.

An important review [26] of CPP in women dismantles the notion that women without relevant physical findings differ in psychological characteristics from women with relevant physical findings. It argues for better methodology, and for greater use of idiographic methods. Women with pelvic pain often have other non-pain somatic symptoms and current or lifetime anxiety and depression disorder [19]; they may have a

history of physical or sexual abuse in childhood of unclear significance. Studies that describe these non-pain somatic symptoms as 'medically unexplained' or 'psychosomatic' or 'somatoform' disorders are unhelpful, misinterpreting absence of physical finding to indicate psychological origins of the complaint. Pain studies describe multiple processes by which pain may spread from one site to another, or in time, including central sensitisation (see previous section), viscero-visceral cross sensitisation in relation to multiple pain sites [69], activation of the hypothalamic-pituitary axis and dysregulation of serotonergic pathways [70] that can render pain levels sensitive to stress. Some pain problems which affect sexual activity are diagnosed as sexual problems (e.g. 'dyspareunia') when pain is the central problem and not contingent on sexual activity alone [71]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed, building on a biopsychosocial formulation [72, 73].

The term psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process. Medical and surgical history may also be important [74]. There have been a few studies of maintenance of, or recovery from, pelvic pain in relation to psychologica factors of importance in pain. Those that described pelvic pain as medically unexplained or psychosomatic, due to the lack of physical findings, have been discarded, because such a distinction is inconsistent with known pain mechanisms.

Understanding the psychological components of pain

Psychological processes of emotions, thought and behaviour involve distributed networks, whose interactions with pain processing are complex, producing inhibition and facilitation of signal processing, appraisal, and response. Models that integrate psychological factors involved in maintaining persistent pelvic and urogenital pain with current neurobiological understanding of pain are few, but the quality is high (see 3.1.5.1).

There is no evidence that women with CPP without physical findings are primarily presenting a psychological problem [26]. Anxiety and post-traumatic stress symptoms are common in some women with CPP [38, 75] and with vulvar pain [76], and may account for substantial variance in health status, treatment use and treatment outcome; for instance, women's expectations about vulvar pain on penetration predicted pain, sexual function and sexual satisfaction [77]. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [78, 79] and anxiety often focuses on what might be 'wrong'. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with pain, assessment of anxiety and distress requires questions about the patient's beliefs about the cause of pain, the hope that diagnosis will validate pain, the struggle with unpredictability, and the implications of pain for everyday life [80, 81]. Reference to the studies of the IMMPACT group [82] is recommended for guidance on outcome measures suitable for pain trials.

Stress can modify the nervous system to produce long-term biological changes. These structural changes may be responsible for significant early life and adverse life events which are associated with chronic pain syndromes [28]. The patient should be asked about adverse life events that may produce these biological responses and affect a patient's general psychological well-being [28, 83].

3.1.5.3 Clinical paradigms in visceral pain

Referred pain

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal [62].

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infections. Vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscero-somatic neurons. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

Muscles and pelvic pain

In the urogenital pain syndromes, muscle tenderness and trigger points may be implicated as a source of pain. Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but it is more often associated with classical referral patterns. As well as trigger points, inflammation of the attachments to the bones (enthesitis) and of the bursa (bursitis) may be found [84]. Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect [26].

Visceral hyperalgesia

The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, BPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation. Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

3.2 Pelvic Pain

*3.2.1 **Incidence***

No adequate data on incidence were found.

*3.2.2 **Prevalence***

3.2.2.1 Prostate Pain syndrome

There is only limited information on the true prevalence of PPS in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostatic enlargement and BPS), purely symptom based case definitions may not reflect the true prevalence of PPS [85, 86]. In the literature, population-based prevalence of prostatitis symptoms ranges from 1 to 14.2% [87, 88]. The risk of prostatitis increases with age (men aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

3.2.2.2 Bladder Pain syndrome

Reports of BPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06% to 30% [89-98]. There is a female predominance of about 10:1 [95] but possibly no difference in race or ethnicity [85, 99, 100]. The relative proportions of classic and non-lesion disease are unclear. Incidence in studies has ranged from 5 to 50% [101-104]. There is increasing evidence that children under eighteen may also be affected, although prevalence figures are low; therefore, BPS cannot be excluded on the basis of age [105].

3.2.2.3 Sexual pain syndrome

In the 1980s an association between CPP and sexual dysfunction was postulated. In a review the relationship between PPS and health status, with influence on sexual activity, was addressed [106]. In a Chinese study of men with CPP, 1,768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with evaluation tools and populations [107, 108]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [109], 15.2% among Turkish men (significantly higher than in the control group) [110] and 43% among Finnish men with PPS [111]. The prevalence of ED was found to be higher in young men with PPS than in the general population. According to other studies men with pelvic pain had a higher chance of suffering from ED [112]. Recently, a significant correlation between “chronic prostatitis”, CPP symptoms (measured by NIH-CPSI) and ED (measured by International Index of Erectile Function [IIEF]) was confirmed [113], while other studies using the same questionnaires were not able to confirm such a correlation [73, 114]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [107, 108, 115, 116].

In community-based studies in the UK [117], New Zealand [118] and Australia [119], a substantially larger proportion of the women with CPP reported dyspareunia (varying between 29% and 42%) than women without CPP (varying between 11% and 14%). Only a few studies have investigated sexual problems within clinical populations [120]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with CPP than in women without CPP [120] In line with the results of community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP [120, 121]. One study of

patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [122].

3.2.2.4 Myofascial pain syndromes

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [123]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [124, 125]. The vast majority (92.2%) of men visiting a tertiary centre for pelvic pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) [126]. This relationship has been found in chronic prostatitis [127], BPS [128] and vulvar pain [129]. Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up with a diminished length, leading to restrictions even when it is in a relaxed state.

*3.2.3 **Influence on QoL***

Data on the influence on QoL will be included in the next version of the guidelines.

*3.2.4 **Costs***

No adequate data on costs were found.

*3.2.5 **Risk factors and underlying causes***

The risk factors are unspecific for most of the pain syndromes in the pelvic area. They are described in 3.1.5.1. The underlying causes, including the mechanisms for the different clinical pain syndromes are described here.

3.2.5.1 Prostate Pain Syndrome

Pain is the main symptom in PPS. As a common feature of chronic pain syndromes, no single aetiological explanation has been found. One explanation is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological, inflammatory state and/or neurogenic injury, creating acute and then chronic pain. One recent study showed that chronic but not acute histological inflammation of the prostate was significantly associated with symptomatic progression [130]. Based on the peripheral and the central nervous system, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state [131]. This could also explain why tissue damage is not usually found in PPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPS and anxiety appears to be a risk factor for its development [42].

3.2.5.2 Bladder Pain syndrome

An initial unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain is thought to be the cause of BPS. However, BPS might be a local manifestation of a systemic disorder. No infection has as yet been implicated. Nevertheless, urinary infection is significantly more frequent during childhood and adolescence, in patients with BPS in adulthood [132]. Experimental induction of CPP by O-antigen deficient bacterial strains reinstates the bacterial hypothesis [133]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of BPS type 3 C [134], but is scant in non-lesion BPS [28, 67, 135, 136]. Cystoscopic and biopsy findings in both lesion and non-lesion BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [137-143] and a consequent cytotoxic effect [144, 145]. Basic and clinical studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in BPS [146, 147].

An association has been reported between BPS and non-bladder syndromes such as FM, CFS, IBS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [148-152].

Risk of BPS correlates with a number of non-bladder syndromes in each patient [153]. Recent work showing non-lesion BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than BPS type 3 C patients, emphasises the need for subtyping [154].

3.2.5.3 Scrotal Pain Syndrome

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens. The ilioinguinal, genitofemoral and the pudendal nerves innervate the scrotum [155]. Any

pathology or intervention at the origin or along the course of the nerves may result in pain perceived in the scrotum [156].

Two special forms of scrotal pain syndrome can be described. The first is post-vasectomy scrotal pain syndrome which occurs following vasectomy. The mechanisms are poorly understood, and it is for that reason considered a special form of scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all men who have undergone a vasectomy [157]. In men with post-vasectomy pain, 2-6% have a Visual Analogue Scale (VAS) score > 5 [158]. In a large cohort study of 625 men, the likelihood of scrotal pain after six months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of post-vasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. the scalpel group 18.8%) [159].

The second special form of scrotal pain is post-inguinal hernia repair pain. It is seen as a complication of hernia repair, but in trials it is seldom reported, or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group [156, 160]. In one particular study, there was no difference at one year but after five years, the open group had far fewer patients with scrotal pain [161].

3.2.5.4 Urethral Pain Syndrome

Some mechanisms for the development of urethral pain syndrome have been proposed. The intimate relationship of the urethra with the bladder (both covered with urothelium) suggests that urethral pain syndrome may be a form of BPS. Mechanisms thought to be basic for BPS may also apply to the urethra. This means that the specific testing with potassium has been used to support the theory of epithelial leakage [162, 163]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection [164]. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multi-parity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [165].

3.2.5.5 Vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma, as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for more than six months, it can be diagnosed as vulvar pain syndrome previously known as “vulvodynia” or “chronic vaginal pain” with no known cause. It is still a poorly understood condition, and therefore difficult to treat.

There are two main sub-types of vulvar pain syndrome: generalised, where the pain occurs in different areas of the vulva at different times; and focal, where the pain is at the entrance of the vagina. In generalised vulvar pain syndrome, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In focal vulvar pain syndrome, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The possible causes of vulvar pain syndrome are many and include:

- history of sexual abuse;
- history of chronic antibiotic use;
- hypersensitivity to yeast infections, allergies to chemicals or other substances;
- abnormal inflammatory response (genetic and non-genetic) to infection and trauma;
- nerve or muscle injury or irritation;
- hormonal changes.

3.2.5.6 Chronic Pelvic Pain and Prolapse/Incontinence Mesh

Continence and prolapse mesh implants were developed as simple flexible polypropylene plastic acting as a scaffold to treat urinary stress incontinence (USI) and uterovaginal prolapse, respectively. They were deemed easy to insert, but no credence was given as to how safe they were, whether they could be removed should they cause complications, or what to do should they not be effective [166-168]. Most meshes took less than an hour to implant surgically and most patients were treated as day cases, allowing women to leave hospital quickly and get on with their lives. Therefore, rather than undergo complex traditional surgery, women were offered permanent mesh implants, particularly in the treatment of USI where they were considered to be the gold standard [169, 170]. However, over the last few years the insertion of mesh has come with significant ‘health and safety warnings’ [171, 172].

For many, mesh was initially seen not just as an effective treatment but as a permanent one. Complications were thought not be a significant issue and the figure of 1-3% was often quoted. However, we now know the complication rate was closer to 10% [173]. They included chronic pain [174, 175], as well as chronic infections [176], erosion into the surrounding organs including the vagina, urethra and bladder, as well as nerve and musculo-skeletal damage affecting mobility [174, 177-179]. All had a significant impact on the patients' QoL.

It is as a result of severely debilitating complications following mesh implantation [174], that the field of mesh removal medicine and surgery has emerged.

Early recognition of possible mesh complications is very important. It is normal to wake up in some degree of discomfort after any surgery. However, if the pain after the operation is very severe and much more than expected after this type of surgery, it can be a sign that there was added trauma to the surrounding organs during the procedure. Most pain is often managed with analgesia, but some women might not fully respond to therapy. If the pain is difficult to treat and does not improve over time, it may become necessary to remove the mesh. Leaving a painful mesh in the pelvis, can lead to CPP. The precise mechanism is unknown but it is thought to be a 'neuro-inflammatory' process [180], as has been proposed in hernia mesh neuralgia [181]. The impact of the mesh, regardless of site, appears to be similar.

3.2.5.7 Associated conditions in pelvic pain syndromes

Nerve damage

Spinal pathology and any pathology along the course of the nerve involved may result in neuropathic pain in the distribution of these nerves. Neoplastic disease, infection and trauma, surgical incisions and post-operative scarring may result in nerve injury [182].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may pre-dispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [183, 184].

The pudendal nerve may be damaged at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinal/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.

The site of injury determines the site of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

The clinical presentation depends on different factors. There is a wide age range, as one would expect with a condition that has so many potential causes. There is a suggestion that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem [185-187]. Six out of ten cases are observed in women. Some special situations can be listed:

- In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage [188, 189]. The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous fixation is clearly associated with pudendal nerve damage in some cases [190, 191]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
- Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.
- Tumours in the pre-sacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [192].
- The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life. This is more difficult to be certain about [193].
- Child birth and repeated abdominal straining associated with chronic constipation [194] are thought to pre-dispose elderly women to post-menopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor. In Urogenital Pain Management Centres, the commonest associations with pudendal neuralgia appear to be: history of

pelvic surgery; prolonged sitting (especially young men working with computer technology); and post-menopausal older women.

Sexual dysfunction

Chronic pelvic pain is a clinical condition that results from the complex interactions of physiological and psychological factors and has a direct impact on the social, marital and professional lives of men and women.

Men

Chronic pain and its treatment can impair our ability to express sexuality. In a study in England, 73% of patients with chronic pain had some degree of sexual problems as a result of the pain [122]. These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin re-uptake inhibitors [SSRIs]) can also decrease libido [195] and delay ejaculation. The number of studies on the effects of CPP on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At present, the most commonly used tool is the IIEF questionnaire [114].

The presence of pelvic pain may increase the risk for ED independent of age [196]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [197]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms suggestive of a more severe inflammatory condition [116]. These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression and more failure anticipation thoughts [106-108, 197-199]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the patients' relationships. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with CPP have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [106, 200]. Prostate Pain Syndrome patients reported greater sexual and relationship problems [106, 200]. On the other hand, it was found that men with PPS did not report significantly decreased sexual satisfaction compared to controls [201]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain are of relevance in relation to changes in sexual function. Also intimacy and having sex can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

Women

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [118, 202-204]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with CPP reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. Patients with CPP reported more sexual problems than women with any other type of chronic pain problem [206]. The quality of intimate relationships is closely connected with sexual function [207]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [208]. In addition sexual dissatisfaction is related to sexual dysfunction. When one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning [208].

Approximately two-thirds of patients in another study reported reduced frequency in their sexual relations as a result of CPP [209]. One study demonstrated that CPP patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without CPP [210]. In an interview with 50 chronic pain sufferers and their spouses, 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life [211]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [122]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Using the FSFI, women with CPP reported worse sexual function in all subscales and total score than women without CPP. The largest differences between women with CPP and without CPP were seen for the domains of pain and arousal. The total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPP. The FSFI also showed good ability to discriminate between women with and without CPP [210].

Myofascial pain

Chronic pelvic pain can simply be a form of myalgia, due to the muscles being used in an abnormal way, in this case, the pelvic floor muscles. Studies in the field of chronic prostatitis support the idea that patients with CPP have more muscle spasm and increased muscle tone and report pain when the pelvic floor muscles are palpated [212]. Muscle relaxation can diminish spasm and pain [213]. Repeated or chronic muscular overload can activate trigger points in the muscle. A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPP group [127].

In 1999, the first ideas about the neurological aspects of the pelvic floor muscles in relation to CPP were published. The probability of CNS breakdown in the regulation of pelvic floor function was suggested as a mechanism for development of CPP. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor function [126]. Basic studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them [214].

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyper-irritable spots within a taut band. Other criteria for trigger points are recognition of the pain as 'familiar', and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and iliopsoas muscles. Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions (e.g., pain related to voiding or defecation).

3.3 Abdominal aspects of pelvic pain

3.3.1 ***Incidence***

Epidemiological data on IBS and CPP are scarce [215]. Chronic Pelvic Pain has been shown to be one of the most common functional disorders in women of reproductive age. The monthly incidence rate of CPP published by Zondervan *et al.* was 1.58/1000 [216].

3.3.2 ***Prevalence***

Using a vague definition of continuous or episodic pain situated below the umbilicus over six months, one study reported that CPP was one of the most common diagnoses in primary care units in Great Britain [216]. The monthly prevalence rate of CPP in this study was 21.5/1,000, with an annual prevalence of 38.3/1,000. The prevalence rates increase significantly with older age and vary significantly between regions in the UK. The overall prevalence of anorectal pain in a sample of USA householders was 6.6% and was more common in women [217]. Irritable Bowel Syndrome is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [218]. Fifty per cent of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPP had symptoms of IBS [219]. In a survey from Olmsted county 20% of women reported CPP and 40% of those met criteria for IBS [20]. This overlap of CPP and IBS was associated with an increased incidence of somatisation. Not gynaecological surgical procedures but only psychosocial variables predict pain development without a different incidence of IBS in a prospective and controlled study [220]. Clinical features of pelvic floor dysfunction, gynaecological and psychological features are related to disordered anorectal function in IBS patients but do not predict physiological anorectal testing.

3.3.3 ***Influence on QOL***

There is little known on health related quality of life (HRQoL) in patients with CPP. There is a need to develop validated disease specific HRQoL instruments for CPP in addition to sound measurement properties. More data are available in patients with IBS treated at referral centres who have comparable HRQoL scores as patients with other common disorders such as diabetes, end-stage renal disease, and inflammatory bowel disease [221]. Sub-groups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multi-variate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

*3.3.4 **Costs***

Costs combine direct health-care costs and societal costs (productivity loss) such as under-performance and absenteeism from work. The annual costs to society can be calculated by using the average population earnings. In Germany direct care costs are estimated at € 791 and societal costs € 995 per patient with IBS per year which may be comparable to patients with CPP [222].

*3.3.5 **Risk factors & underlying causes***

Risk factors are covered in Section 3.1.5.

3.4 Summary of evidence and recommendations: CPP and mechanisms

Summary of evidence	LE
CPP mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1
End-organ function can also be altered by the mechanisms of neuroplasticity so that symptoms of function can also occur.	1
The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multi-specialty and multi-disciplinary care.	2

Recommendations	Strength rating
All of those involved in the management of Chronic Pelvic Pain (CPP) should have knowledge of peripheral and central pain mechanisms.	Strong
The early assessment of patients with CPP should involve investigations aimed at specific disease-associated pelvic pain.	Strong
The early assessment of patients with CPP should involve assessment of functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation.	Strong
Manage CPPS patients in a multi-specialty and multi-disciplinary environment with consideration of all their symptoms.	Strong

4. DIAGNOSTIC EVALUATION

4.1 General Evaluation

*4.1.1 **History***

History is very important for the evaluation of patients with CPP. Pain syndromes are symptomatic diagnoses, which are derived from a history of pain perceived in the region of the pelvis, and absence of other pathology, for a minimum of three out of the past six months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, drug-induced pathology (e.g. ketamine use) [223], primary anatomical or functional disease of the pelvic organs, and neurogenic disease must be ruled out.

4.1.1.1 Anxiety, depression, and overall function

Distress is best understood in the context of pain and of the meaning of pain to the individual and is best assessed ideographically rather than normatively. Almost all diagnostic measures and standardised instruments of anxiety and depression are designed for people without significant physical problems, so are hard to interpret in CPP [224].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain [32], or to uncertainties about treatment and prognosis. These can drive healthcare seeking behaviour. The question: “What do you believe or fear is the cause of your pain?” has been suggested [225]. Anxiety may also concern urinary urgency and frequency that are problematic in social settings.

Depression or depressed mood are common in chronic pain [226] e.g, often related to losses consequent to chronic pain (work, leisure activities, social relationships, etc.). Due to the lack of suitable assessment instruments, it is better to ask a simple question such as “How does the pain affect you emotionally?” If the

answer gives cause for concern about the patient's emotional state, further assessment should be undertaken by an appropriately qualified colleague.

Most measures of restricted function are designed primarily for musculoskeletal pain and may emphasise mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. A promising specific measure, UPOINT, was introduced and in a later version the sexological aspects were added [227]. However, it may under-assess relevant psychological variables [41]. Generic QoL measures are helpful. If such an instrument is not already used in the clinic, the Brief Pain Inventory [228] provides a broad and economical assessment of interference of pain with various aspects of life in multiple languages. (For further suggested instruments see [229]). In a study, more pain, pain-contingent rest, and urinary symptoms were associated with poorer function [56].

4.1.1.2 Urological aspects

Pain may be associated with urological symptoms. A detailed history of lower urinary tract functions should be taken. Dysfunctions of the lower urinary tract may exacerbate symptoms, as pain may interfere with the function of the lower urinary tract. Micturition in all its aspects should be addressed. Special attention should be paid to the influence of micturition on the experience of pain.

Prostate pain syndrome

Prostate pain syndrome is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other lower urinary tract pathology, for a minimum of three out of the past six months. As mentioned above, specific disease-associated pelvic pain must be ruled out. A thorough history is an important first step in the evaluation of PPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen [48]. In addition, associated lower urinary tract symptoms, sexual function, psychological, social and economic factors should be addressed. Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument (see section 4.2.3). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

Bladder pain syndrome

Bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 4) [11].

The nature of pain is key to disease definition:

1. pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content;
2. located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum;
3. relieved by voiding but soon returns [230, 231];
4. aggravated by food or drink [231].

Bladder pain syndrome type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

4.1.1.3 Gynaecological aspects

A detailed medical history outlining the nature, frequency and site of pain; its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma is mandatory as well as up to date cervical cancer screening. A history of obstetric and/or gynaecological surgery is also warranted, particularly if devices such as synthetic mesh were used.

4.1.1.4 Gastrointestinal aspects

The predominant symptoms that patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III criteria for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

Diagnostic criteria for chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching, episodes last at least 20 minutes and exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and coccygodynia. These criteria should be fulfilled for the past three months with symptom onset at least six months before diagnosis [232, 233].

The chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle (previously called "Levator Ani Syndrome"). Pathophysiology of pain is thought to be due to over-activity of the pelvic floor muscles.

Intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for three months: recurrent episodes of pain localised to the anus or lower rectum, episodes last from several seconds to minutes and there is no anorectal pain between episodes. Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 minutes. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients.

4.1.1.5 Peripheral nerve aspects

A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather that the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pain developing in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any type of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well-tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts of urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they

often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with CPP are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also due to the lack of afferent perception.

4.1.1.6 Myofascial aspects

When taking a history from a patient with pelvic pain, it is important to address the function of all the organs in the pelvic area. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psychosocial aspects. One cannot state that there is a pelvic floor dysfunction based only on the history. But there is a suspicion of pelvic floor muscle dysfunction when two or more pelvic organs show dysfunction, for instance a combination of micturition and defecation problems.

4.1.2 ***Physical Evaluation***

The clinical examination often serves to confirm or refute the initial impressions gained from a good history. The examination should be aimed at specific questions where the outcome of the examination may change management. Prior to an examination, best practice requires the medical practitioner to explain what will happen and what the aims of the examination are to the patient. Consent to the examination should occur during that discussion and should cover an explanation around the aim to maintain modesty as appropriate and, if necessary, why there is a need for rectal and/or vaginal examination. Finally, the risk of exacerbating the pain should form a part of that request. A record of the discussion should be noted. The possibility of the presence of a chaperone should be discussed with the patient. As well as a local examination, a general musculoskeletal and neurological examination should be considered an integral part of the assessment and undertaken if appropriate. Following the examination, it is good practice to ask the patient if they had any concerns relating to the conduct of the examination and that discussion should be noted.

There is no specific diagnostic test for CPPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Abdominal and pelvic examination to exclude gross pelvic pathology, as well as to demonstrate the site of tenderness is essential. Abnormalities in muscle function should also be sought. Examination of the external genitalia is a part of the evaluation. In patients with scrotal pain, gentle palpation of each component of the scrotum is performed to search for masses and painful spots. The penis and urethra may be palpated in a similar way. Many authors recommend that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3), and the degree of tenderness should be recorded. The bulbocavernosus reflex in the male may also provide useful information concerning the intactness of the pudendal nerves. Clinical pelvic examination should be a single digit examination if possible. The usual bi-manual examination can generate severe pain so the examiner must proceed with caution. A rectal examination is done to look for prostate abnormalities in male patients including pain on palpation and to examine the rectum and the pelvic floor muscles regarding muscle tenderness and trigger points.

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched for thoroughly in patients with anal pain. Rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the Levator Ani Syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and unspecified.

Functional Anorectal Pain is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during combined rectal and vaginal examination to diagnose pelvic organ prolapse.

A full clinical examination of the spinal, muscular, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischial spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger

points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominus or paraspinal muscles).

4.2 Supplemental evaluation

If history is suggestive of lower urinary tract, gynaecological, anorectal or other known aetiology disease, diagnostic work-up should follow respective guidelines.

*4.2.1 **Assessing pain and related symptoms***

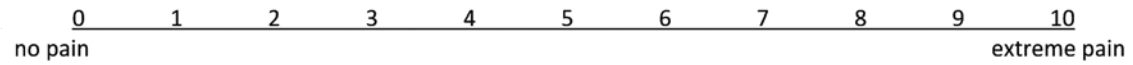
Determination of the severity of disease, its progression and treatment response can be assessed only by means of a reliable symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed (see below) to identify progression and treatment response. As well as doing this in the clinic, the patient can keep a daily record (pain diary). This may need to include other relevant variables such as voiding, sexual activity, activity levels, or analgesic use.

Increased attention to patient reported outcomes gives prominence to patients' views on their disease and pain diaries, in patients' own environments, improve data quality.

Quality of life should also be measured because it can be very poor compared to other chronic diseases [234, 235]. In a study more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale) [56].

Where the primary outcome of treatment is pain relief, it is useful before starting treatment to agree a clinically useful level of relief [236]. The most reliable methods are:

- a five point verbal scale: none, mild, moderate, severe, very severe pain;
- a VAS score from one to ten;
- an eleven point numerical scale.



Pain assessment ratings are not independent of cognitive and emotional variables [55]. Target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. When the primary outcome is pain its meaning should be anchored in discussion of clinically important difference [236].

Prostate pain syndrome

Reliable, valid indices of symptoms and QoL are the NIH-CPSI [237] and the International Prostate Symptom Score (I-PSS) [238].

Bladder pain syndrome

Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) was validated in a large study [239].

Gastrointestinal questionnaire

Functional anorectal pain disorders (anorectal pelvic pain) are defined and characterised by duration, frequency, and quality of pain. More complex questionnaires are used in the setting of IBS. The validated IBS-Symptom Severity Scale (IBS-SSS) includes the broadest measurement of pain-related aspects [240, 241]. However, as different instruments measure different endpoints of chronic abdominal pain in IBS, a comparison of published studies is often impossible.

Sexual function assessment

In males the most frequent effects on sexual function are ED and premature ejaculation. These can be evaluated by proper questionnaires namely IIEF and PEDT (Premature Ejaculation Diagnostic Tool). In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. The FSFI has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The corresponding evidence in men is lacking.

*4.2.2 **Focused myofascial evaluation***

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor by a physiotherapist is a good alternative. A vaginal or rectal examination is performed to assess the function of the pelvic floor muscles, according to the International Continence Society (ICS) report. This assessment has been tested and shows satisfactory face validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [242]. Rectal examination is a good way to test the pelvic floor function in men [243]. There is a growing number of reports on the use of ultrasound (US) in establishing the function of the pelvic floor muscles. The exact place in the diagnostic setting needs to be addressed in the future [244]. In a cohort study of 72 men with CPP, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis (74%), perineum (65%) and rectum (46%) [245]. In addition, a broad musculoskeletal (tender point) evaluation, including muscles outside the pelvis, helps to diagnose the myofascial pain aspects of the pelvic pain in phenotyping pelvic pain patients [246, 247].

*4.2.3 **Neurological***

Injections

An injection of local anaesthetic and steroid at the site of nerve injury may be diagnostic. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [248, 249]. Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

Electrophysiological studies

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [185, 188, 250-252]. However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal.

*4.2.4 **Imaging***

Ancillary studies should be performed according to appropriate guidelines for exclusion of diseases with known aetiology presenting with symptoms identical to those of CPP. Once the latter diagnosis is established studies can be useful to assess functional abnormalities and phenotype conditions such as BPS, and chronic anal pain syndrome.

Ultrasound

Has limited value but may reassure patients. However, over-investigating may be detrimental.

MRI

Magnetic resonance neurography has been increasingly used in specialised centres for the diagnosis of the location (proximal vs. peripheral) and degree (total vs. partial) of nerve injury in the peripheral nervous system, earlier and with higher specificity than conduction studies.

MR defecating proctogram

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. Magnetic resonance imaging studies simultaneously outline the anatomy of the pelvic floor and visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., US gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and thereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of intussusception.

Functional neuroimaging
Functional neuroimaging, functional magnetic resonance imaging (fMRI) is currently being re-evaluated as a research tool and some groups have raised issues around over interpretation [253]. With regards to pain, fMRI findings may represent a pain matrix or may represent non-specific threat processing [254]. Currently this panel cannot recommend fMRI as a clinical tool.

*4.2.5 **Laboratory Tests***

Microbiology tests
Prostate pain syndrome
Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation [255]. Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10^3 cfu/mL of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [256, 257]. Overall, these tests help only a little in the diagnosis of PPS, because 8% of patients with suggested PPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic men [258].

Bladder pain syndrome
Urine dipstick and urine culture (including culture for Tuberculosis if sterile pyuria) are recommended in all patients suspected of having BPS. Urine cytology is also recommended in risk groups.

Gynaecological aspects of chronic pelvic pain
Vaginal and endocervical swabs to exclude infection are recommended. In specific cases, imaging may be required to help rule out a defined pathology such as sacral neuropathy in endometriosis [259].

*4.2.6 **Invasive tests***

Anorectal pain
Anorectal manometry with sensory testing (pressure volume measurement: barostat) may be useful to diagnose dyssynergic defecation and hypersensitivity of the rectum which are typical for patients with CPP and IBS. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain to rule out coincidental colorectal pathology.

Laparoscopy for females
Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [260, 261] and to assist in the differential diagnosis of CPP in women [262]. Often, it is combined with cystoscopy [263, 264] and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy
Three very different studies of laparoscopy suggest that it can improve pain through resolving concerns about serious disease [265], although showing women the photograph of their pelvic contents did not improve pain on explanation alone [266]. Integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain is helpful [267].

Cystoscopy and bladder biopsy
Despite controversy on the diagnostic and follow-up value of cystoscopy in BPS [268-272], the panel believes that objective findings are important for diagnosis, prognosis and ruling out other treatable conditions (a standardised scheme of diagnostic criteria will also contribute to uniformity and comparability of different studies) [273]. Endoscopically, BPS type 3 displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the Hunner lesion [230]. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between BPS type 3 and reduced bladder capacity under anaesthesia [274]. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign although they can be observed without BPS [275]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [138, 162, 273, 276, 277]. Important differential diagnoses to exclude, by histological examination, are carcinoma *in situ* and tuberculous cystitis.

Table 4: ESSIC classification of BPS types according to results of cystoscopy with hydrodistension and biopsies [11]

	Cystoscopy with hydrodistension			
	Not done	**Normal**	**Glomerulations[a]**	**Hunner's lesion[b]**
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

[a]*Cystoscopy: glomerulations grade 2-3.*

[b]*Lesion per Fall's definition with/without glomerulations.*

[c]*Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.*

4.3 Diagnostic algorithm

Figure 1: Diagnosing chronic pelvic pain

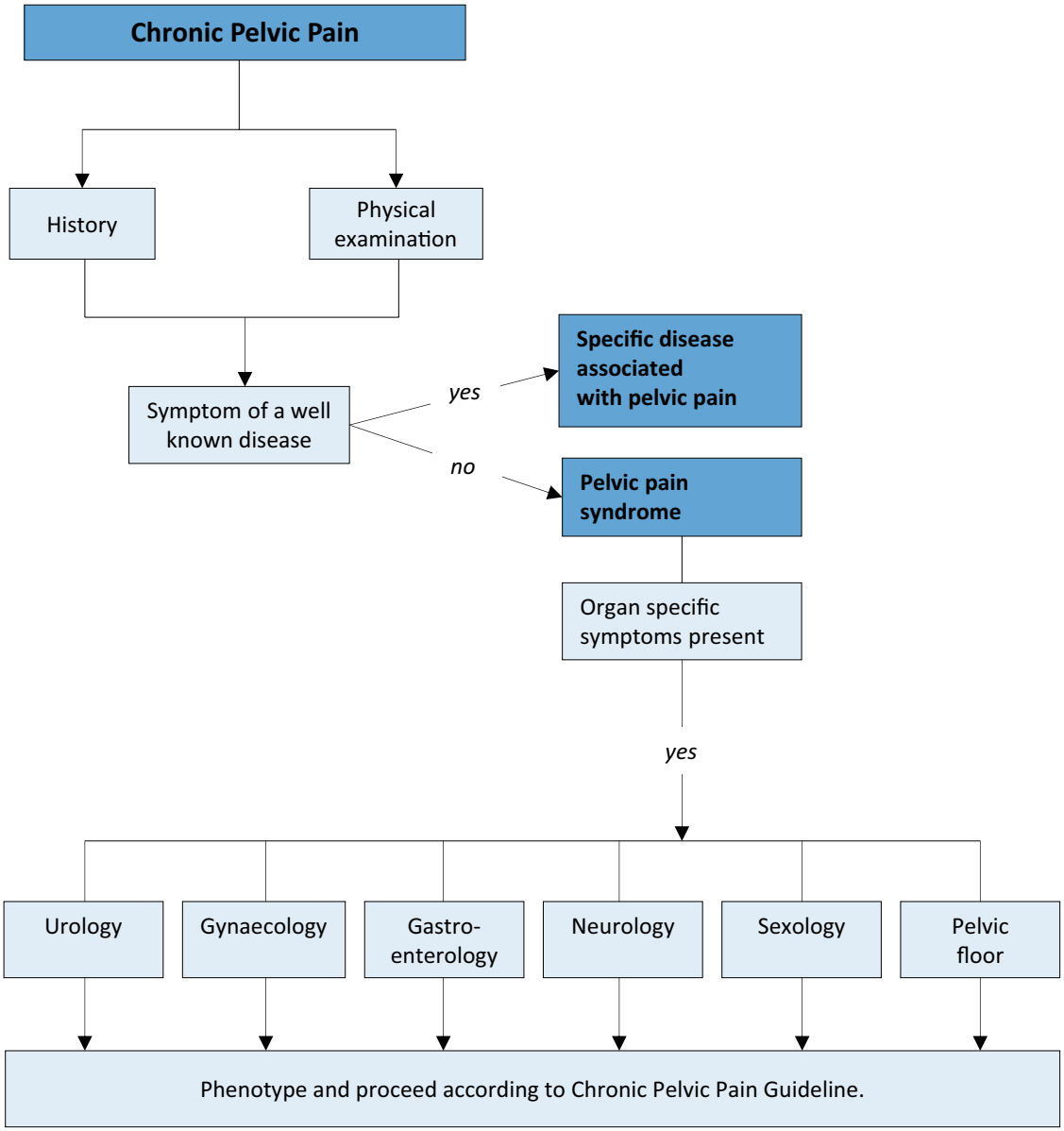


Figure 2: Phenotyping of pelvic pain - UPOINT classification

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry.
Psychology	Anxiety about pain, depression and loss of function, history of negative sexual experiences.
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints. Gynaecological examination, rectal examination.
Infection	Semen culture and urine culture, vaginal swab, stool culture.
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function.
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles.
Sexological	Erectile function, ejaculatory function, post-orgasmic pain.

4.4 Other painful conditions without a urological cause

Dysmenorrhoea

Menstrual pain or 'dysmenorrhoea' may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [262]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [261], adenomyosis or pelvic infection, which need to be excluded.

Infection

In pre-menopausal women, a history of Pelvic Inflammatory Disease (PID) must be excluded. A patient's sexual history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [278], as they can cause severe pelvic/vaginal/vulvar pain [279] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [280]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnoses is endometriosis.

Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. It has widespread impact on women's lives [281], with pain more important than physical findings in determining QoL [282]. The precise aetiology is unknown, but an association with infertility is recognised [283]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [284-287]. Adenomyosis is associated with augmented pain during menses [288]. It is diagnosed by an US scan of the uterus, which often shows cystic dilatation of the myometrium [289].

Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread.

Injuries related to childbirth

Trauma occurring at the time of childbirth may lead to CPP related to the site of injury [287]. Female sexual dysfunction is perhaps the commonest presenting problem [290], though increasingly women are reporting other symptoms such as pelvic girdle pain and other genito-pelvic pain of different aetiology [291]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor can similarly compound the situation [292].

Pain associated with pelvic organ prolapse and prolapse surgery

Pelvic organ prolapse is often asymptomatic, unless it is so marked that it causes back strain, vaginal pain and skin excoriation [293]. Prolapse is often a disease of older women, and it is often associated with post-menopausal oestrogen deficiency, which may lead to pain associated with intercourse. Prolapse surgery has entailed the use of non-absorbable mesh (usually in the form of "mesh kits"). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [294] and neuropathy [295]. Patients need to be fully evaluated and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis of the possible cause of the pain [296-299].

Haemorrhoids

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anti-coagulation therapy, or those with clotting disorders.

Anal fissure

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond six weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn's disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures.

Proctitis

Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids.

Irritable bowel syndrome

Although IBS can be associated with pelvic pain, the panel consider a full discussion of this topic beyond the scope of these guidelines. A number of high quality clinical guidelines address this topic [232, 300].

4.5 Summary of evidence and recommendations: diagnostic evaluation

*4.5.1 **Diagnostic evaluation of PPS***

Summary of evidence	LE
Prostate pain syndrome is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
Prostate pain syndrome has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
Prostate pain syndrome has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	Strength rating
Adapt diagnostic procedures to the patient. Exclude specific diseases with similar symptoms.	Strong
Use a validated symptom and quality of life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	Strong
Assess prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	Strong

4.5.2 *Diagnostic evaluation of BPS*

Summary of evidence	LE
BPS has no known single aetiology.	3
Pain in BPS does not correlate with bladder cystoscopic or histologic findings.	2a
BPS Type 3 C can only be confirmed by cystoscopy and histology.	2a
Lesion/non-lesion disease ratios of BPS are highly variable between studies.	2a
The prevalence of BPS-like symptoms is high in population-based studies.	2a
BPS occurs at a level higher than chance with other pain syndromes.	2a
BPS has an adverse impact on QoL.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	Strength rating
Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease.	Strong
Diagnose patients with symptoms according to the EAU definition, after primary exclusion of specific diseases, with bladder pain syndrome (BPS) by subtype and phenotype.	Strong
Assess BPS associated non-bladder diseases systematically.	Strong
Assess BPS associated negative cognitive, behavioural, sexual, or emotional consequences.	Strong
Use a validated symptom and quality of life scoring instrument for initial assessment and follow-up.	Strong

4.5.3 *Diagnostic evaluation of scrotal pain syndrome*

Summary of evidence	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal contents does not aid in diagnosis or treatment of scrotal pain.	2b
Post-vasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b

4.5.4 *Diagnostic evaluation of urethral pain syndrome*

Summary of evidence	LE
Urethral pain syndrome may be a part of BPS.	2a
Urethral pain involves mechanisms of neuroplasticity and neuropathic pain.	2b

4.5.5 *Diagnostic evaluation of gynaecological aspects chronic pelvic pain*

Summary of evidence	LE
Clinical history and examination are mandatory when making a diagnosis.	2a
Laparoscopy is well-tolerated and does not appear to have negative psychological effects.	1b

Recommendations	Strength rating
Take a full history and evaluate to rule out a treatable cause (e.g. endometriosis) in all women with chronic pelvic pain.	Strong
Take a full uro-gynaecological history in those who have had a continence or prolapse non-absorbable mesh inserted and consider specialised imaging of the mesh.	Strong
Refer to a gynaecologist if clinical suspicion of a gynaecological cause for pain following complete urological evaluation. Laparoscopy should be undertaken in accordance with gynaecological guidelines.	Strong

4.5.6 *Diagnostic evaluation of anorectal pain syndrome*

Summary of evidence	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a

Recommendation	Strength rating
Anorectal function tests are recommended in patients with anorectal pain.	Strong

4.5.7 *Diagnostic evaluation of pudendal neuralgia*

Summary of evidence	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1

Recommendations	Strength rating
Rule out confusable diseases, such as neoplastic disease, infection, trauma and spinal pathology.	Strong
If a peripheral nerve pain syndrome is suspected, refer early to an expert in the field, working within a multidisciplinary team environment.	Weak
Imaging and neurophysiology help diagnosis but image and nerve locator guided local anaesthetic injection is preferable.	Weak

4.5.8 *Diagnostic evaluation of sexological aspects in CPP*

Summary of evidence	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.	2b
Sexual dysfunctions are prevalent in patients with PPS.	2b
In men with PPS the most prevalent sexual complaints are ED and ejaculatory dysfunction.	3
In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.	3
Vulvar pain syndrome is associated with BPS.	2a
Women with BPS suffer significantly more from fear of pain, dyspareunia and decreased desire.	3
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	2a
Chronic pain can cause disturbances in each of the sexual response cycle phases.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b

Recommendation	Strength rating
Screen patients presenting with symptoms suggestive for chronic pelvic pain syndrome for abuse, without suggesting a causal relation with the pain.	Weak

4.5.9 *Diagnostic evaluation of psychological aspects of CPP*

Summary of evidence	LE
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse are possible contributory factors in pelvic pain.	2a

Recommendations	Strength rating
Assess patient psychological distress in relation to their pain.	Strong
Ask patients what they think is the cause of their pain to allow the opportunity to inform and reassure.	Strong

*4.5.10 **Diagnostic evaluation of pelvic floor function***

Summary of evidence	LE
The ICS classification is suitable for clinical practice.	2a
Over-activity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Over-activity of the pelvic floor muscles is an input to the CNS causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3

Recommendations	Strength rating
Use the International Continence Society classification on pelvic floor muscle function and dysfunction.	Strong
In patients with chronic pelvic pain syndrome it is recommended to actively look for the presence of myofascial trigger points.	Weak

5. MANAGEMENT

The philosophy for the management of CPP is based on a bio-psychosocial model. This is a holistic approach with the patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy.

The management strategy may well have elements of self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and end points. These may well include: psychology, physiotherapy, drugs and more invasive interventions.

Treatment philosophy
Providing information that is personalised and responsive to the patient's problems, conveying belief and concern, is a powerful way to allay anxiety [301]. Additional written information or direction to reliable sources of information is useful; practitioners tend to rely on locally produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients [302].

5.1 Conservative management

*5.1.1 **Pain education***
It is always valuable to include education about the causes of pain, including eliciting from patients their anxieties about undiscovered pathology and addressing them. Information improves adherence to treatment and underpins self-management, as shown in many other painful and non-painful disorders but not specifically in pelvic and abdominal pain except by a small qualitative study [303].

*5.1.2 **Physical therapy***
The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome. In most studies that have been done looking at the effect of physiotherapy in pelvic pain, the treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [304]. The review found six RCTs, of which three showed level 1b evidence with low-risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after one year follow-

up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with cognitive behaviour therapy (CBT) [305].

Pelvic floor muscle pain

Treating pelvic floor over-activity and myofascial trigger points should be considered in the management of CPP. Treatment should be done by specialised physiotherapists who are trained not only in the musculo-skeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

For patients with CPP and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general massage was carried out in patients with prostate or bladder pain. The global response rate to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two treatment arms. In the bladder pain group, myofascial treatment did significantly better than massage. Massage only improved complaints in the prostate pain group. The fact that gender distribution was different in each group is mentioned as a possible confounding factor [306].

Myofascial trigger point release

Treatment of myofascial trigger points can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods. There is no evidence that manual techniques are more effective than no treatment [307]. Most studies of dry needling have compared with wet needling. Different systematic reviews have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo [308].

Physiotherapy in BPS

Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in BPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [309]. The role of specific levator ani trigger point injections in women with CPP has been studied [310]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy-two percent of women improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with BPS; global response assessment (GRA) rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and symptoms decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in women with BPS [311].

Anal Pain Syndrome

An RCT demonstrated that biofeedback treatment was superior to electrogalvanic stimulation and massage for treating chronic anal pain syndrome [124]. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. In patients with tenderness of the puborectalis muscle (Rome II: Highly likely Levator Ani Syndrome), 87% reported adequate relief after one month of biofeedback vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at twelve months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: Highly likely and Possible Levator Ani Syndrome), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50 mL water filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [124]. The pathophysiology of the chronic anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

Treatment of sexual dysfunctions and CPP

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [312]. It needs to be remembered that sexual difficulties will arise as a result of pelvic pain syndromes as well as those disorders potentially being primary. Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting the activity

to less than that causes pain. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of post-coital flares. The corresponding evidence in men is lacking, but similar principles would apply. Other behavioural changes involve pre- and post-coital voiding, application of ice packs to the genital or suprapubic area [312, 313], and use of vaginal dilators, fingers or sex toys. Lubricants can also be used and women with signs of vulvovaginal atrophy may benefit from oestrogen cream [314]. Optimising the pelvic floor muscle is indicated when dysfunction is present and will relief the pain [315-317].

Other physical therapy interventions

Electromagnetic therapy. A small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a one-year period for CPPS [318].

Microwave thermotherapy. In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [319, 320].

Extracorporeal shockwave therapy. A small sham-controlled double-blind study of four times weekly perineal extracorporeal shockwave therapy (n=30) in men with chronic pelvic pain syndrome showed significant improvement in pain, QoL, and voiding compared to the control group (n=30) over twelve weeks [321]. Two other randomised sham-controlled studies, have been published more recently, one comparing ten treatment sessions over two weeks (n=40 vs. n=40) [322], another with four times weekly treatments (n=20 vs. n=20) [323]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at twelve weeks. Unfortunately, no long term effects at 24 weeks could be shown in a published follow-up study of the second [324]. A recent Cochrane review of non-pharmacological interventions for CPP reported a reduction in symptoms following treatment compared with control and concluded that extracorporeal shockwave therapy may improve symptoms without an increase in adverse events [325].

Acupuncture. In a small three-arm randomised trial of CPPS in men, electro-acupuncture was superior to sham treatment and advice and exercise alone [326]. Another more recent randomised study comparing acupuncture (n=50) vs. sham-controlled (n=50) once weekly treatment for six weeks showed significant long lasting improvement at 24 weeks in terms of response rate and overall symptom scores [327]. Another RCT showed a significant effect for a follow-up of 32 weeks [328]. Two systematic reviews and meta-analyses were published in 2016 analysing seven randomised-controlled studies on a total of 471 participants comparing acupuncture to sham control or oral medical treatment [329, 330]. Both came to the conclusion that acupuncture was effective and safe, significantly reducing total NIH-CPSI scores compared to sham or medical treatment, and should be considered as a treatment option. This is in line with the conclusion of a recent Cochrane systematic review [325] on non-pharmacological treatment options. However, the durability of this effect is not known.

Posterior tibial nerve stimulation. See section 5.3.2, Neuromodulation.

Transcutaneous electrical nerve stimulation. See section 5.3.2, Neuromodulation.

5.1.3 Psychological therapy

Psychological interventions may be directed at pain itself or at adjustment to pain in terms of function and mood and reduced health-care use, with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [331, 332] but these have been neglected in pelvic pain. Two systematic reviews and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [333, 334] found some short-term benefits for pain, of around 50%, comparable to that from pharmacotherapy, but this was not sustained at follow-up. Exposure to pain-related fears in women with chronic pelvic pain proved superior to manual therapy in reducing those fears and overall pain disability, albeit assessed only by self-report [335]. More standard multi-component psychologically-based programmes are in the pilot stages [336]. One that combined mixed psychological therapies with acupuncture for endometriosis-related pain, reported significant pain reduction at two year follow-up [337]. Indeed acupuncture is the only complementary treatment to have alleviated pain in this group [338]. Three more standard multicomponent (including psychological) treatments for pain [267, 305, 339] did not provide pain or symptom relief. Another RCT of multi-component treatment showed no effect on pain but benefits for distress [340], as did an RCT of mindfulness meditation for women with bladder pain [341]. The importance of multi-disciplinary treatment is emphasised by several reviews [41, 342, 343]. For less disabled and distressed patients, this can be delivered in part over the internet [344].

5.1.4 Dietary treatment

Scientific data are limited and dietary restriction alone does not produce significant symptomatic relief; however, consider the involvement of a dietician.

5.2 Pharmacological management

*5.2.1 **Drugs for chronic pelvic pain syndrome***

In this section the evidence available for specific CPPSs is presented. Where there is no evidence the reader is directed to the section on analgesics below (5.2.2) where more generic use is discussed. There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of for example PPS, one reason for treatment failure in some large randomised placebo-controlled trials may be the heterogeneity of the patient population. One strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for PPS has shown significant improvement of symptoms and QoL [345]. Monotherapeutic strategies for the treatment of PPS may fail [346], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past ten years, results from RCTs have led to advances in standard and novel treatment options.

5.2.1.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drugs headings below.

5.2.1.2 Comparisons of agents used in pelvic pain syndromes

Prostate Pain Syndrome (PPS)

Anti-inflammatory drugs

For non-steroidal anti-inflammatory agents (NSAIDs), a trial with celecoxib reported that the pain sub-score, QoL sub-score, and total NIH-CPSI score were in favour of the treatment arm vs. placebo, but effects were limited to the duration of therapy [347]. In a meta-analysis, two studies of NSAIDs [258, 347] and one with prednisolone [348] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. In an updated network meta-analysis with more restrictive inclusion criteria regarding documented outcome measures but a wider spectrum of drugs (including glycosaminoglycans, phytotherapy and tanezumab) a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

α-blockers

Positive results from RCTs of α-blockers, i.e. terazosin [349, 350], alfuzosin [351], doxazosin [352, 353], tamsulosin [354, 355], and silodosin [356] have led to widespread use of α-antagonists in the treatment of PPS in recent years. Whereas one systematic review and meta-analysis has not reported a relevant effect of α-blockers due to study heterogeneity [357], another network meta-analysis of α-blockers [358] has shown significant improvement in total symptoms, pain, voiding, and QoL scores. In addition, they had a higher rate of favourable response compared to placebo [relative risk (RR) 1.4, 95% CI 1.1-1.8, p=0.013]. However, treatment responsiveness, i.e. clinically perceptive or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, α-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients [359]. Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g. patients with PPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

Antibiotic therapy

Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for four to six weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS [360], and prostate biopsy culture findings do not differ from those of healthy controls [361]. The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [362], levofloxacin (six weeks) [363], and tetracycline hydrochloride (twelve weeks) [364]. The studies have been analysed in meta-analyses [358, 365]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with α-blockers has shown even better outcomes in network meta-analysis. Despite significant improvement in symptom scores, antibiotic therapy did not lead to statistically significant higher response rates [365]. In addition, the sample sizes of the studies were relatively small and treatment effects only modest and most of the time below clinical significance. It may be speculated that patients profiting from treatment have had some unrecognised uropathogens. If antibiotics are used, other

therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over six weeks.

5-α-reductase inhibitors
Although a few small pilot studies with 5-α-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first RCT published in a peer-reviewed journal did not support this, but the study lacked power [366]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a one-year period, but lacked a placebo-control arm [367]. A six-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power [368]. The NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [369]. Patients (n=427, age 50 to 75, elevated prostate-specific antigen [PSA]) were included if they had significant "prostatitis-like" symptoms at baseline. Based on the evidence, 5-α-reductase inhibitors cannot be recommended for use in PPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [369].

Phytotherapy
Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of a pollen extract (Cernilton) showed clinically significant symptom improvement over a twelve-week period in inflammatory PPS patients (NIH Cat. IIIA) [370]. The effect was mainly based on a significant effect on pain. Another pollen extract (DEPROX 500) has been shown to significantly improve total symptoms, pain and QoL compared to ibuprofen [371]. A SR and meta-analysis of pollen extract for the treatment of PPS showed significant improvement in overall QoL [372]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [373]. In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a one-year period [367]. In a SR and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [358]. In addition, overall response rate in network meta-analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

Pregabalin is an anti-epileptic drug that has been approved for use in neuropathic pain. In an adequately powered randomised placebo-controlled study, which was the only report included in a recently published Cochrane review [374], a six-week course of pregabalin (n=218) compared to placebo (n=106) did not result in a significant reduction of NIH-CPSI total score [375].

Pentosane polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3 x 300 mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in men with PPS, suggesting a possible common aetiology [376].

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been few prospective clinical trials to support these claims. In one RCT, a triple combination of a muscle relaxant (thiocolchicoside), an anti-inflammatory drug (ibuprofen) and an α-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an α-blocker alone [353].

Botulinum toxin type A (BTX-A) showed some effect in the global response assessment and the NIH-CPSI pain subdomain score in a small randomised placebo-controlled study of perineal skeletal muscle injection (100 U). However, patient numbers were low (thirteen in the BTX-A group and sixteen in the placebo group), and follow-up was too short to draw definitive conclusions. Side-effects are unclear [377]. In another randomised-controlled study of intraprostatic injection of BTX-A (100 or 200 U depending on prostate volume) vs. placebo (n=30 in both groups) a significant improvement of total NIH-CPSI and subdomain scores could be shown at six months [378]. However, no real placebo effect could be demonstrated, which suggests unblinding. No definitive conclusion can be drawn.

Zafirlukast, a leukotriene antagonist, and prednisone in two low-power placebo-controlled studies failed to show a benefit [348, 379]. More recently, a placebo-controlled phase II study of tanezumab, a humanised monoclonal antibody against the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [380].

Tanezumab is a humanised monoclonal antibody that specifically inhibits nerve growth factor (NGF), and should only be used in clinical trials.

Allopurinol
There is insufficient evidence for the use of allopurinol in PPS [381, 382].

Bladder Pain Syndrome

Treatments of significant value for BPS

Anti-histamines
Mast cells may play a role in BPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 [383] and H2 [384] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [385].

Amitriptyline
Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of BPS symptoms after oral amitriptyline [386]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [387]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosane polysulphate
Is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [388, 389]. Pentosane polysulphate had a more favourable effect in BPS type 3 C than in non-lesion disease [390]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy showed a response rate of 40% compared to 13% with placebo. For patients with an initial minor response to pentosane polysulphate, additional subcutaneous heparin was helpful [391, 392].

Immunosuppressants
Azathioprine treatment has resulted in disappearance of pain and urinary frequency [393]. Initial evaluation of cyclosporin A (CyA) [394] and methotrexate [395] showed good analgesic effect but limited efficacy for urgency and frequency. Corticosteroids are not recommended in the management of patients with BPS because of a lack of evidence.

Intravesical Treatments
Intravesical drugs are administered due to poor oral bio-availability establishing high drug concentrations within the bladder, with few systemic side-effects. Disadvantages include the need for intermittent catheterisation which can be painful in BPS patients, cost and risk of infection [396].

- **Local anaesthetics**

There are sporadic reports of successful treatment of BPS with intravesical lidocaine [397, 398]. Alkalisation of lidocaine improves its pharmacokinetics [399]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% [400]. Intravesical instillation of alkalised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [401].

- **Hyaluronic acid and chondroitin sulphate**

These are described to repair defects in the GAG layer. Despite the fact that intravesical GAG replenishment has been in use for about twenty years for BPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. A recent RCT seems to reinforce the case for GAG layer replenishment, however it lacks a placebo arm [402]. A meta-analysis confirms usefulness of GAG layer replenishment. However most retrieved studies are non-randomised and with scarce numbers [403].

- **Intravesical heparin**

Bladder pain syndrome patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after one year of therapy [404]. Kuo reported another trial of intravesical heparin for three months in women with frequency-urgency syndrome and a positive potassium test. Symptomatic improvement was reported in 80% of BPS patients [405]. Intravesical heparin plus peripheral neuromodulation in patients with refractory BPS was studied and it was shown that voiding

frequency, pain score and maximum cystometric capacity were significantly better after two and twelve months [406].

- **Hyperbaric oxygen**

This has a moderate effect on a small subgroup of BPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [391].

Treatments of limited value for BPS

Cimetidine

There is limited data to suggest that cimetidine improves symptoms of BPS in the short-term . Compared with placebo for three months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [407].

Prostaglandins

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, 14 out of 25 patients had significantly improved, with twelve showing a sustained response after a further six months [408]. The incidence of adverse drug effects was 64%.

L-Arginine

Oral treatment with the nitric oxide (NO) synthase substrate L-arginine decreases BPS-related symptoms [409-411]. Nitric oxide is elevated in patients with BPS [412]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [413, 414].

Oxybutynin is an anti-cholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [415]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-noradrenaline re-uptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of BPS [416]. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended for treatment of BPS.

Scrotal Pain Syndrome

Treatment of scrotal pain syndrome is based on the principles of treating chronic pain syndromes, as described throughout these guidelines .

Chronic gynaecological pain

It is difficult to compare the wide variation of drugs from an efficacy and safety perspective as they have such diverse uses/indications.

In those gynaecological patients where CPP is unrelated to any of the well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multi-disciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens [333]. Though efficacious, physicians need to be knowledgeable with progestogenic side effects (e.g. weight gain, bloatedness - the most common adverse effects) which can stop some patients from accepting such medication. Gonadotrophins, such as goserelin, are also thought to help such pain. However, when compared with progestogens, their efficacy remains limited. The quality of evidence is generally low and is drawn from single studies [333].

Gonadotropin-releasing hormone (GnRH) on the other hand binds to specific receptors on pituitary gonadotrophs, leading to desensitisation and consequently to suppressed gonadotropin secretion. By contrast, GnRH antagonists compete with GnRH for receptors thus gonadotrophin secretion, which may be beneficial in certain clinical applications, such as reducing the size of fibroids, endometrial bleeding and endometriosis [417].

Pelvic Floor, Abdominal and Chronic Anal Pain

Botulinum toxin type A (pelvic floor)

Botulinum toxin type A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [418]. Reviews do not support the injection of BTX-A into trigger points [419].

Pelvic floor muscle over-activity plays a role in CPP. Botulinum toxin type A, as a muscle relaxant, can be used to reduce the resting pressure in the pelvic floor muscles. In women with high resting pressure in the pelvic floor muscles, it has been found that BTX-A lowers this pressure significantly. The magnitude of reduction was significantly higher than that in the placebo group. On the VAS pain score, no intergroup differences were found in this relatively small randomised study [420]. Botulinum toxin type A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates bladder problems and secondarily the spasm. In a cohort study of thirteen patients with CPP, BTX-A was injected into the external urethral sphincter. Subjectively, eleven patients reported a substantial change in pain symptoms, from a score of 7.2 to 1.6 on a VAS [421].

Botulinum toxin type A (chronic anal pain syndrome)
In CPP associated with spasm of the levator ani muscles, treatment of the puborectalis and pubococcygeus muscle by BTX-A appears to be promising in some women, as shown in a pilot study (n=12). The inclusion criteria were dependent only on vaginal manometry with over-activity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H_2O. Although dyspareunia and dysmenorrhoea improved, non-menstrual pelvic pain scores were not significantly altered [422]. In the following double-blinded, randomised, placebo-controlled trial, the same group defined pelvic floor myalgia according to the two criteria of tenderness on contraction and hypertension (> 40 cm H_2O) and included 60 women. In this larger study, non-menstrual pelvic pain was significantly improved compared to those treated with placebo (VAS score 51 vs. 22; p=0.009). It was concluded therefore that BTX-A is effective at reducing pelvic floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence [420]. However, recently, a small RCT failed to show any benefit of BTX-A [423].

Intermittent chronic anal pain syndrome
Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled β-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [424]. Other treatment options are topic diltiazem and BTX-A [425]. However, there is still some controversy regarding the duration of pain of intermittent chronic and chronic anal pain syndrome. Randomised controlled trials often use different definitions, extending the pain duration (with a shift to chronic pain) in order to include more patients and to better evaluate the study-drug action.

Abdominal pain associated with Irritable Bowel Syndrome
Linaclotide, a minimally absorbed peptide guanylate cyclase-C agonist at a dose of 290 µg once daily significantly improved abdominal pain (48.9% vs. 34.5% placebo-treated) and bowel symptoms associated with IBS with constipation over 26 weeks of treatment [426]. Diarrhoea was the most common adverse event in patients treated with linaclotide (4.5%). Although it is known to overlap with IBS pelvic pain, effect on the latter was not assessed in this study.

Delta-9-tetrahydrocannabinol (THC) shows only equivocal evidence of analgesic effects in chronic abdominal pain. In a recently published phase II trial no difference was found between THC tablet and a placebo tablet in reducing pain outcome in patients with chronic abdominal pain [427].

*5.2.2 **Analgesics***

If the use of simple analgesics fails to provide adequate benefit, then consider using neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain. Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous sections. The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPP [428], therefore, a wider look at the literature has been undertaken and further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents. They may also allow lower individual dosages and thus minimise side-effects. The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the use of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent does not exclude potential benefit of an alternative. If the benefit is limited by side-effects, then the lowest effective dose should be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side-effects.

5.2.2.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drug headings below.

5.2.2.2 Comparisons within and between groups in terms of efficacy and safety

Paracetamol (acetaminophen)
Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central mechanism of action [429]. It is often available over the counter without prescription. A review questions its routine use as a first-line analgesic based on inadequate evidence of efficacy in many pain conditions including dysmenorrhoea [430]. It will not be effective for all patients and individual responses should be reviewed when deciding on longer term use.

Non-steroidal anti-inflammatory agents (NSAIDs)
These agents are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain; many are available over the counter and are usually well tolerated. There is insufficient evidence to suggest one NSAID over another for pelvic pain. Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side-effects than paracetamol, including indigestion, headaches and drowsiness.

The evidence for their benefit in CPP is weak or non-existent and are often limited by side-effects. For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [431], NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side-effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis [432], then the evidence is lacking for NSAIDs despite their common use.

At a practical level, if NSAIDs are considered for use, they should be tried (having regard for the cautions and contraindications) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or side-effects are limiting, then they should be withdrawn.

Neuromodulators
These are agents that are not simple analgesics but used to modulate neuropathic or centrally mediated pain. There are several classes commonly used with recognised benefits in pain medicine. They are taken on a regular basis and all have side-effects that may limit their use. In the UK, the National Institute for Health and Clinical Excellence (NICE) has reviewed the pharmacological management of neuropathic pain [433]. Not all the agents are licensed for use in pain management but there is a history and evidence to demonstrate their benefit. The evidence for treatment of CPP is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side-effects. The aim is for patients to have an improvement in their QoL, which is often best assessed by alterations in their function. It is common to use these agents in combination but studies comparing different agents against each other, or in combination, are lacking. Some of these agents are also used for specific conditions. Early identification of neuropathic pain with a simple questionnaire could facilitate targeted therapy with neuromodulators [57].

Antidepressants
Tricyclic antidepressants
The tricyclic antidepressants (TCAs) have multiple mechanisms of action including, blockade of acetylcholine receptors, inhibition of serotonin and noradrenaline re-uptake, and blockade of histamine H1 receptors. They also have anxiolytic affects [434] and are frequently limited by their side-effects. Tricyclic antidepressants have a long history of use in pain medicine and have been subjected to a Cochrane review [435], suggesting that they are effective for neuropathic pain. Amitriptyline is the most commonly used at doses from 10 to 75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and can be taken at night [433]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants
Duloxetine is a serotonin-noradrenaline re-uptake inhibitor (SNRI) antidepressant licensed for use in depression, urinary stress incontinence and neuropathic pain. There is moderately strong evidence of benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [436]. Side-effects are common and may result in its discontinuation.

Selective serotonin re-uptake inhibitors are antidepressants with fewer side-effects. They are effective for depression, but there have been insufficient studies to demonstrate their benefit in pelvic or neuropathic pain [435-437].

Anticonvulsants

Anticonvulsants are commonly used in the management of neuropathic pain. There are general studies and some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Guidelines [433].

There is a growing awareness and evidence of the risk for dependence and misuse of gabapentionids [438]. A formal assessment of efficacy against benefit and side-effects (both pain and quality of life) is required with the patient in order to determine the lowest effective dose and if longer-term treatment is to be used.

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [439]. Trials trend to be of short duration, showing only moderate benefit. There are side-effects; some of which may be serious. It is no longer a first choice agent. Other anticonvulsant agents are available with fewer serious side-effects.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed [440]. It provides good quality relief with number needed to treat (NNT) of approximately six. Side-effects are common, notably drowsiness, dizziness and peripheral oedema. For higher dose levels, reference should be made to local formularies, and many clinicians do not routinely exceed 2.4 g/day in divided doses (most commonly three times daily). One study of women with CPP has suggested that gabapentin alone or in combination with amitriptyline provides better analgesia than amitriptyline alone [441]. A more recent pilot study suggests that gabapentin is beneficial and tolerable; a larger study is required to provide a definitive result [442].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions but the NNT varies depending on the condition [443]. The dose for benefit is in the range of 300 to 600 mg/day. The same SR found that doses less than 150 mg/day are unlikely to provide benefit. A review for CPPS (prostate) only found a single reviewable study that does not show overall symptom improvement but suggests individual symptoms may improve (e.g. pain, QoL) and side-effects were common demonstrating the need for further robust studies [374]. As with gabapentin, side-effects are common and may not be tolerated by patients. A formal assessment of efficacy against side-effects is required with the patient in order to determine longer-term treatment. Other anticonvulsants are available but not commonly used for managing pain. Other agents can be used in the management of neuropathic pain but they are best administered only by specialists in the management of pain and familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive multidimensional management plan.

Opioids

Opioids have been used extensively for managing chronic non-cancer pain. There is increasing evidence that their role is limited in this patient population but may be beneficial for a small number of patients. There is clear evidence of harm and significant professional, public, political and press coverage on this matter.

Often patients will stop taking oral opioids due to side-effects or insufficient analgesic effect [444]. There is a growing understanding of opioid-induced hyperalgesia; a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli [445]. There is little guidance on the best method for tapering the dose of opioids with the aim of stopping them or finding the lowest effective dose [446].

Opioids should only be used in conjunction with a management plan with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician.

There are well-established guidelines for the use of opioids in pain management as well as considering the potential risks [445]. There is also information available online for patients [445]. Opioids Aware is a web-based resource for patients and healthcare professionals, jointly produced by the Faculty of Pain Medicine of Royal College of Anaesthetists and Public Health England, to support prescribing of opioid medicines for pain. https://fpm.ac.uk/opioids-aware.

Cannabinoids

There has been increasing interest and changes in national regulations regarding the use of cannabinoids for medicinal use. Regarding pain the evidence base is weak [447, 448] and further well conducted clinical trials are required. This is an area where further guidance and research is likely in the coming years.

5.3 Further management

5.3.1 ***Nerve blocks***

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [449]. They may have a diagnostic or therapeutic role. Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately. Diagnostic blocks can be difficult to interpret due to the complex mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., radiofrequency procedures). There is a weak evidence base for these interventions for chronic non-malignant pain [450].

Pudendal Neuralgia

The role of injections may be divided into two. First, an injection of local anaesthetic and steroid at the sight of nerve injury may produce a therapeutic action. The possible reasons for this are related to the fact that steroids may reduce any inflammation and swelling at the site of nerve irritation, but also because steroids may block sodium channels and reduce irritable firing from the nerve [451]. However, a recent paper by Labat *et al.* challenges this [452]. The second possible benefit is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [249, 453-460].

Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, CT guidance, or the use of US, the latter avoids any radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Pulsed radio frequency stimulation has also been suggested as a treatment [461]. Pulsed Radio frequency lesioning for pudendal neuralgia is being developed with a paper demonstrating potential benefit. Follow-up is short term and further research is required to better elucidate its place in management [462].

5.3.2 ***Neuromodulation***

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are used as part of a broader management plan and require regular follow-up. The research base is developing and the techniques broadening (e.g., spinal cord stimulation (SCS), sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventional techniques for patients refractory to other therapies. Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence but more detailed, high quality research is required [463]. Its role in overactive bladder and faecal incontinence is more robust but is limited for pain. Two recent systematic reviews have evaluated neuromodulation techniques for CPP [464, 465]. Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with CPP however studies were of a low quality and long-term results were needed.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous Electrical Nerve Stimulation (TENS) is a non-invasive technique used in many pain conditions. A SR identified twelve studies of TENS in CPP conditions including four RCTs [464]. All RCTs demonstrated a significant reduction in pain following twelve weeks of treatment for pain conditions including dysmenorrhoea and CPP. Pain was also found to improve following TENS for provoked vestibulodynia. There was conflicting data with regard to improvement of QoL following TENS; where validated questionnaires were used, no significant improvement was found, whereas in trialist-defined studies, an improvement was seen in TENS for dysmenorrhea and CPP. The beneficial effects of a course of TENS may be sustained; one study demonstrating a persistent benefit at 43 months in 73% of men with CPP and another demonstrating a prolonged significant improvement in women with provoked vestibulodynia at ten months post-treatment. Where reported there were no adverse events recorded. TENS could offer an effective non- invasive treatment option for patients with CPP.

Percutaneous Tibial Nerve Stimulation

Percutaneous Tibial Nerve Stimulation (PTNS) is a minimally invasive technique that can be use in an outpatient setting. Two SRs have shown that PTNS is effective in reducing pain in patients with CPP [464, 465].

Three RCTs identified showed a significant improvement in pain scores and QoL as measured by validated questionnaires. Where recorded, adverse events were rare and minor including temporary slight pain at application site and haematoma.

Sacral Nerve Stimulation

Sacral nerve stimulation is an invasive technique requiring sedation or general anaesthesia for implantation of a device following trial stimulation. A SR identified ten studies of SNS in CPP, either retrospective case series or prospective cohort studies and no RCTs. Where reported, a mean of 69% of participants progressed to implantation of device following test stimulation (range 52-91%). All studies reported an improvement in pain, statistically significant in five studies. QoL was measured in three studies and a significant improvement demonstrated in two of three studies. There was a large variation in adverse events reported ranging from 0-50%. Those not requiring reoperation included pain, failure of device, wound infection and seroma. Re-operation rate ranged between 11-50% for complications including lead migration, systemic infection, intrathecal implantation, loss of efficacy and erosion. In clinical practice, a patient should be appropriately counselled regarding the need for a period of trial stimulation and whilst there may be an improvement in symptoms, this should be weighed against a notable complication rate.

Other neuromodulation techniques

A variety of other techniques of neuromodulation for patients with CPP were identified by a recent systematic review [464]. These techniques include intravaginal electrical stimulation for women with CPP, pudendal nerve stimulation for CPP, spinal cord stimulation for pudendal neuralgia, transcutaneous interferential electrical stimulation for irritable bowel syndrome, electrical acupuncture for dysmenorrhoea and electrical stimulation/ biofeedback and electromagnetic stimulation for men with CPP. Whilst an improvement in pain has been reported in these studies it is noted that they are largely of low quality and further work is needed in this area to enable robust clinical recommendations to be made.

*5.3.3 **Surgery***

Bladder Pain Syndrome (BPS)

Bladder distension

Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scarce. It can be part of the diagnostic evaluation, but has limited therapeutic role.

Hydrodistension and Botulinum toxin type A

Botulinum toxin type A may have an antinociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [466]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [467]. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, VAS score and functional and cystometric bladder capacity improved at three months. Botulinum toxin type A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after three months follow-up [468]. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated. Adverse effects of BTX-A administration for IC/BPS were significantly less than for overactive bladder syndrome, namely in increased post-void residual volumes and decreased voiding efficiency [469]. Recent RCTs have confirmed benefits and long efficacy of BTX-A administration [470-474]. The American Urological Association (AUA) guidelines panel has upgraded BTX-A treatment from fifth to a fourth line treatment [475].

Transurethral resection (TUR), coagulation and laser

Endourological destruction of bladder tissue aims to eliminate urothelial, mostly Hunner lesions. Since the 1970s resection and fulguration have been reported to achieve symptom relief, often for more than three years [476, 477]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [478].

Open Surgery for BPS

Bladder pain syndrome is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence that it relieves pain. Surgery for refractory BPS is only appropriate as a last resort for patients with refractory end-stage disease. Major surgery should be preceded by thorough pre-operative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery

is considered, the panel's advice is to refer the patient to a specialist centre experienced in managing CPP with a multi-disciplinary team approach.

Four major techniques are common:

1. Urinary diversion without cystectomy is performed to minimise the duration and complexity of surgery, but complications related to the retained bladder commonly occur. Reports that un-resected BPS bladders cease to induce symptoms after loss of contact with urine are scarce [102, 479].

2. Supratrigonal cystectomy with bladder augmentation represents the most favoured continence-preserving surgical technique particularly in younger patients [480]. Various intestinal segments have been used [481-483]. After orthotopic bladder augmentation, bladder emptying may be incomplete so intermittent self-catheterisation may be required. A study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients and improvement in sexual function items in women who remained sexually active [484]. Pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [485].

3. Subtrigonal or simple cystectomy refers to removal of the entire bladder at the level of the bladder neck. This approach has the benefit of removing the trigone as a possible disease site, but at the cost of requiring ureteric re-implantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [486], especially in patients with non-ulcer type disease [487, 488]. However, in a previous study all patients were rendered symptom-free by supratrigonal resection compared to 82% of those undergoing subtrigonal cystectomy. Voiding dysfunction is most likely to occur following trigonal resection and patients considering augmentation and especially substitution procedures must be capable of accepting, performing and tolerating self-catheterisation [489].

4. Cystectomy with formation of an ileal conduit is considered for patients with BPS who develop recurrent pain in the augmented bladder, continent pouch after enterocystoplasty or continent urinary diversion, re-tubularisation of a previously used bowel segment to form a urinary conduit has been recommended [490].

Prostate Pain Syndrome

There is no evidence for surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate or, in particular, radical prostatectomy in the management of chronic pain in patients with PPS. Recently, a large Chinese randomised-controlled trial of circumcision combined with a triple oral therapy (ciprofloxacin, ibuprofen, tamsulosin) vs. oral therapy alone has been published for patients with PPS (total n=774) [491]. It is hypothesised that there may be some immunological interaction via pathogenic antigen presenting cells in the foreskin with CD4+ T cells causing auto-immunity to the prostate gland. They reported an improvement in total NIH-CPSI score and subdomain scores at twelve weeks. However, despite a large cohort, the study results are questionable because of the weak theoretical background, and a potential large placebo effect lacking a sham control. In addition, no long-term effectiveness has been reported. Before having an impact on recommendations, the results of this study have to be independently confirmed and the treatment effect must persist.

Testicular Pain Syndrome

Microsurgical denervation of the spermatic cord can be offered to patients with testicular pain. In a long-term follow-up study, patients who had a positive result on blocking the spermatic cord were found to have a good result following denervation [492, 493].

Chronic Anal and Abdominal Pain Syndrome

Chronic anal pain syndrome after stapled procedures, such as hemorrhoidopexy (PPH) or stapled transanal rectal resection (STARR) may respond to excision of the scarred staple line as shown in 21 consecutive patients with an overall improvement of pain in 85.7% of patients undergoing scar excision surgery [494]. An early scar excision before three to six months after pain onset was associated with better pain relief. Adhesiolysis is still in discussion in the pain management after laparotomy/laparascopy for different surgical indications in the pelvis and entire abdomen. A recent study has shown, that adhesiolysis is associated with an increased risk of operative complications, and additional operations and increased health care costs as compared to laparoscopy alone [495].

Urethral Pain Syndrome

There is no specific treatment that can be advised. Management should be multi-disciplinary and multi-modal [496]. Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment [497]. The majority of publications on treatment of urethral pain syndrome have come from psychologists [164].

Presumed intra-abdominal adhesions

In gynaecological patients with CPP and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [498].

Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief after the removal of early extensive endometriosis compared to sham surgery [261, 499]. In patients with adenomyosis, the only curative surgery is hysterectomy but patients can benefit from hormonal therapy and analgesics (see 5.2.2).

Pudendal Neuralgia and surgery

Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is transgluteal; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery [187, 249, 500-503]. Currently, there has been only one prospective randomised study (transgluteal approach) [502]. This study suggests that, if the patient has had the pain for less than six years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for more than six years). Surgery is not the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut; most patients were grateful to have undergone surgery but many still have symptoms that need management.

Chronic Pelvic Pain and Prolapse/Incontinence Mesh

Removing an existing mesh is a complex procedure [504]. Each patient is approached on an individual basis depending on the type of mesh and extent of complications [505]. The complexity of surgery often involves removal of dense scar tissue, reformation of inflamed vaginal skin and surgical reconstruction of the urethra and bladder [506]. Such surgery requires specialist skills, often provided with a multidisciplinary tertiary setting. Possible complications as a result of this surgical removal include bleeding, infection, damage to surrounding organs as well as lower urinary tract symptoms, chronic pain and recurrent urinary stress incontinence, which occurs after mesh removal [507].

Removal of mesh, whilst complex, does have beneficial outcomes generally, which are also durable particularly in chronic pain [508]. However, the long-term consequences after the mesh is removed still can include chronic persistent pain but also autoimmune responses and complex neuropathies affecting the pelvis and the lower limbs [509, 510]. Some of these can be treated effectively using a multi-disciplinary pain medicine approach [511]. In other cases, the residual symptoms may require the input of an immunologist, rheumatologist or other symptom-defined specialist.

The alternative to continence and prolapse mesh surgery is dependent on the clinical findings at the time. They include behavioural change, physiotherapy (for USI and Grade I-II uterovaginal prolapse) or traditional surgical techniques. Studies have shown that over 70% who committed to physiotherapy for stress urinary incontinence often did not need any further intervention [512]. Many clinicians are reverting to conservative measures first, before re-considering surgery. Clinicians are also now retraining in traditional continence surgical techniques, which existed in the pre-mesh era, such as the Burch colposuspension and autologous fascial sling; as well as traditional utero-vaginal prolapse techniques such as vaginal hysterectomy, sacrospinous fixation and fascial repair of vaginal wall prolapse.

5.4 Summary of evidence and recommendations: management

*5.4.1 **Management of PPS***

Summary of evidence	LE
Phenotypically directed treatment may improve treatment success.	3
α-blockers have moderate treatment effect regarding total pain, voiding, and QoL scores in PPS.	1a
Antimicrobial therapy has a moderate effect on total pain, voiding, and QoL scores in PPS.	1a
NSAIDs have moderate overall treatment effects on PPS.	1a
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.	1a
Pentosane polysulphate improves global assessment and QoL score in PPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPS.	2b
Pregabalin is not effective for the treatment of PPS.	1b
BTX-A injection into the pelvic floor (or prostate) may have a modest effect in PPS.	2b
Acupuncture is superior to sham acupuncture in improving symptoms and QoL.	1a
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	1b
Extracorporeal shock wave therapy is probably effective over the short term.	1b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPS.	3
Cognitive behavioural therapy designed for PPS may improve pain and QoL.	3

Recommendations	Strength rating
Offer multimodal and phenotypically directed treatment options for Prostate Pain Syndrome (PPS).	Weak
Use antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks in treatment-naïve patients with a duration of PPS less than one year.	Strong
Use α-blockers for patients with a duration of PPS less than one year.	Strong
Offer high-dose oral pentosane polysulphate in PPS.	Weak
Offer acupuncture in PPS.	Strong
Offer non-steroidal anti-inflammatory drugs (NSAIDs) in PPS, but long-term side-effects have to be considered.	Weak

*5.4.2 **Management of BPS***

Summary of evidence	LE
There is insufficient data for the long-term use of corticosteroids.	3
Limited data exist on effectiveness of cimetidine in BPS.	2b
Amitriptyline is effective for pain and related symptoms of BPS.	1b
Oral pentosane polysulphate is effective for pain and related symptoms of BPS.	1a
Oral pentosane polysulphate plus subcutaneous heparin is effective for pain and related symptoms of BPS, especially in initially low responders to pentosane polysulphate alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosane polysulphate is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical chondroitin sulphate may be effective.	2b
There is insufficient data for the use of bladder distension as a therapeutic intervention.	3
Hydrodistension plus BTX-A is superior to hydrodistension alone.	1b
Intravesical BCG is not effective in BPS.	1b
Transurethral resection (coagulation and laser) may be effective in BPS type 3 C.	3
Sacral neuromodulation may be effective in BPS.	3
Pudendal nerve stimulation is superior to sacral neuromodulation for treatment of BPS.	1b
Avoidance of certain foods and drink may reduce symptoms.	3
Outcome of cystectomy for BPS is variable.	3

Recommendations	Strength rating
Offer subtype and phenotype-oriented therapy for the treatment of Bladder Pain Syndrome (BPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of BPS.	Strong
Offer dietary advice.	Weak
Administer amitriptyline for treatment of BPS.	Strong
Offer oral pentosane polysulphate for the treatment of BPS.	Strong
Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.	Weak
Do not recommend oral corticosteroids for long-term treatment.	Strong
Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures.	Weak
Offer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Offer intravesical heparin before more invasive measures alone or in combination treatment.	Weak
Do not use bladder distension alone as a treatment of BPS.	Weak
Offer submucosal bladder wall and trigonal injection of botulinum toxin type A (BTX-A) plus hydrodistension if intravesical instillation therapies have failed.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Only undertake ablative organ surgery as the last resort and only by experienced and BPS-knowledgeable surgeons.	Strong
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.	Strong
Offer intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies have failed.	Strong
Do not recommend oral corticosteroids for long-term treatment.	Strong
Do not use bladder distension as a treatment of BPS.	Weak

*5.4.3 **Management of scrotal pain syndrome***

Summary of evidence	LE
Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.	2b
Vasovasostomy is effective in post-vasectomy pain.	2b

Recommendations	Strength rating
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	Strong
Do open instead of laparoscopic inguinal hernia repair, to reduce the risk of scrotal pain.	Strong
In patients with testicular pain improving after spermatic block, offer microsurgical denervation of the spermatic cord.	Weak

*5.4.4 **Management of urethral pain syndrome***

Summary of evidence	LE
There is no specific treatment for urethral pain syndrome.	4

*5.4.5 **Management of gynaecological aspects of chronic pelvic pain***

Summary of evidence	LE
Therapeutic options, including pharmacotherapy and surgery, can treat endometriosis effectively.	1b
Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function in vaginal and vulvar pain syndrome.	1b
Most gynaecological pain conditions (including dysmenorrhea, post-mesh insertion and gynaecological malignancy) can be treated effectively using pharmacotherapy.	3
All other gynaecological conditions (including obstetric injury, pelvic organ prolapse) can be treated effectively using surgery.	2

Recommendations	Strength rating
Involve a gynaecologist to provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	Strong
Provide a multi-disciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multidisciplinary service (incorporating pain medicine and surgery).	Strong

5.4.6 Management of anorectal pain syndrome

Summary of evidence	LE
Biofeedback is the preferred treatment for chronic anal pain syndrome.	1a
Electrogalvanic stimulation is less effective than biofeedback.	1b
Botulinum toxin type A is effective.	1b
Percutaneous tibial nerve stimulation is effective in anal pain.	3
Sacral neuromodulation is effective in anal pain.	3
Inhaled salbutamol is effective in intermittent chronic anal pain syndrome.	3

Recommendations	Strength rating
Undertake biofeedback treatment in patients with chronic anal pain.	Strong
Offer botulinum toxin type A in chronic anal pain syndrome.	Weak
Offer percutaneous tibial nerve stimulation in chronic anal pain syndrome.	Weak
Offer sacral neuromodulation in chronic anal pain syndrome.	Weak
Offer inhaled salbutamol in intermittent chronic anal pain syndrome.	Weak

5.4.7 Management of pudendal neuralgia

Summary of evidence	LE
There are multiple treatment options with varying levels of evidence.	3

Recommendation	Strength rating
Neuropathic pain guidelines are well-established. Use standard approaches to management of neuropathic pain.	Strong

5.4.8 Management of sexological aspects in CPP

Summary of evidence	LE
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	Strength rating
Offer behavioural strategies to the patient and his/her partner to reduce sexual dysfunctions.	Weak
Offer pelvic floor muscle therapy as part of the treatment plan to improve quality of life and sexual function.	Weak

5.4.9 Management of psychological aspects in CPP

Recommendation	Strength rating
For CPP with significant psychological distress, refer patient for CPP-focused psychological treatment.	Strong

5.4.10 *Management of pelvic floor dysfunction*

Summary of evidence	LE
Myofascial treatment is effective.	1b
Biofeedback improves the outcome of myofascial therapy.	1a

Recommendations	Strength rating
Apply myofascial treatment as first-line treatment.	Weak
Offer biofeedback as therapy adjuvant to muscle exercises, in patients with anal pain due to an overactive pelvic floor.	Strong

5.4.11 *Management of chronic/non-acute urogenital pain by opioids*

Recommendations	Strength rating
Prescribe opioid treatment, following multi-disciplinary assessment and only after other reasonable treatments have been tried and failed.	Strong
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with the patient and their family doctor.	Strong
Where there is a history or suspicion of drug abuse, involve a psychiatrist or psychologist with an interest in pain management and drug addiction.	Strong

6. EVALUATION OF TREATMENT RESULTS

6.1 Evaluation of treatment

For patients with chronic visceral pain, a visit to the clinician is important because they can ask questions, talk about how the process is going and have some time with the caregiver who understands the nature of their pain. First evaluation should take place after about six weeks to see if the treatment has been successful or not. When necessary adaptations are made and a next evaluation is planned.

6.1.1 *Treatment has not been effective*

6.1.1.1 *Alternative treatment*

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first thing to do is a thorough evaluation of the patients' or care providers' adherence to the treatment that was initiated. Ask the patient if they have taken the medication according to the prescription, if there were any side-effects and if there were any changes in pain and function. Adjustment of medication or dose schemes might help. Another important thing to do is to read the reports of other caregivers, for example, the physiotherapist and the psychologist. Has the therapy been followed until the end, what was the opinion of the therapist about the changes that were observed? In cases where the sessions had been terminated by the patient, ask the patient why they made that decision. Check if the patient has understood the idea behind the therapy that had been prematurely stopped.

6.1.1.2 *Referral to next envelope of care*

If patients and doctors conclude that none of the therapies given showed enough effect, then referral to a next envelope of care is advised. Unfortunately, the terminology used to describe the nature and specialisation level of centres providing specialised care for visceral pain patients is not standardised and is country-based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that is working with a multi-disciplinary team and nationally recognised as specialised in pelvic pain. Such a centre will re-evaluate what has been done and when available, provide specialised care.

6.1.1.3 *Self-management and shared care*

Patients who find themselves confronted with CPP, for which there is no specific treatment option available, will have to live with their pain. They will need to manage their pain, meaning that they will have to find a way to deal with the impact of their pain on daily activities in all domains of life. Self-help programmes may be advised and can be of help. The patient may also benefit from shared care, which means that a caregiver is available for

supporting the self-management strategies. Together with this caregiver, the patient can optimise and use the management strategies.

*6.1.2 **Treatment has been effective***

In cases where treatment has been effective, the caregiver may pay attention to fall-back prevention. If the patient feels the same pain again, it helps to start at an early stage with the self-management strategies that he/she has learned during the former treatment. By doing so they will have the best chance of preventing the re-development of pelvic pain syndromes.

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8. CONFLICT OF INTEREST

All members of the EAU Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website http://www.uroweb. org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN978-94-92671-07-3 .

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Renal Transplantation

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Renal Transplantation Guidelines panel consists of an international multidisciplinary group of urological surgeons, a nephrologist and a pathologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.4 Publication history

The EAU published the first Renal Transplantation Guidelines in 2003 with updates in 2004 and 2009. A comprehensive update of the 2009 document was published in 2017. This document is a full update of the 2017 Renal Transplantation Guidelines. Additional chapters will be added in the coming year to address ethical issues surrounding kidney transplantation as well as the issue of malignancy in kidney transplantation.

2. METHODS

2.1 Introduction

For the 2019 Renal Transplantation Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. Broad and comprehensive literature searches, covering sections 3.1.3, 3.1.9, 3.1.10 and 3.1.11 of the Renal Transplantation Guidelines were performed, covering a time frame between January 1st 2008 and May 31st 2018. A total of 2,833 unique records were identified, retrieved and screened for relevance. In addition, a further broad and comprehensive literature search, covering sections 3.1.1 to 3.1.7 was performed, covering a time frame between June 1st 2016 and May 31st 2018. The shorter time frame reflects the fact these sections were updated prior to publication in 2017. A total of 343 unique records were identified, retrieved and screened for relevance. For all searches databases searched included Medline, EMBASE, and the Cochrane Libraries. All detailed search strategies are available online: http://www.uroweb.org/guideline/renal-transplantation/.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [4]. The strength of each

recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review and future goals

This document was subject to independent peer review prior to publication in 2017. Publications ensuing from systematic reviews have all been peer reviewed.

The results of ongoing systematic reviews will be included in the 2020 update of the Renal Transplantation Guidelines. Ongoing systematic reviews include:

1. What is the best treatment for symptomatic obstructive benign prostatic enlargement in renal transplantation patients?
2. For patients with kidney graft stones, does surgical treatment provide better stone free rates than external shock wave lithotripsy?

3. THE GUIDELINE

3.1 Organ retrieval and transplantation surgery

*3.1.1 **Living-donor nephrectomy***

The endoscopic (laparoscopic) approach is the preferred technique for living-donor nephrectomy in established kidney transplant programmes [5]. Nevertheless, open surgery, preferably by a mini-incision approach, can still be considered a valid option, despite increased pain in the post-operative period [6].

Endoscopic living-donor nephrectomy (ELDN) includes:

- Pure or hand-assisted transperitoneal laparoscopy;
- Pure or hand-assisted retroperitoneal approach;
- Laparo-Endoscopic Single Site Surgery (LESS);
- Natural Orifice Transluminal Endoscopic Surgery-assisted (NOTES);
- Laparo-Endoscopic Single Site Surgery and robotic-assisted transperitoneal or retroperitoneal approach.

There is strong evidence in support of laparoscopic living-donor nephrectomy (LLDN), including several systematic reviews and meta-analysis, which have compared its safety and efficacy to open donor nephrectomy. Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival. However, measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures [7-10].

Standard LLDN is usually done through 5 and 12 mm ports, but has also been done with 3 or 3.5 mm ports [11]. According to a recent meta-analysis, hand-assisted LLDN is associated with shorter operative time and warm ischaemia, but equivalent safety and overall results [12]. Laparoscopic living-donor nephrectomy can also be performed with robotic assistance, with equivalent results according to a recent systematic review [13]. However, the numbers are still low and a recent paper found a higher complication rate for this approach [14].

Laparo-endoscopic single site surgery nephrectomy allows the surgeon to work through a single incision (usually the umbilicus) with a multi-entry port. The same or a separate incision is then used for kidney withdrawal. Several retrospective and at least three prospective randomised trials demonstrated equivalent safety and results, with a trend towards less pain and better cosmetic results [15, 16]. However, LESS is considered a more technically demanding procedure when compared with classic LLDN and its role is yet to be defined.

Natural orifice transluminal endoscopic surgery-assisted transvaginal nephrectomy avoids the abdominal incision needed for kidney extraction, aimed at minimising scaring and pain. Initial reports suggest that this approach is safe, however experience with this technique is still highly limited [17].

Right LLDN has been considered more difficult, yielding inferior results. However, both left and right LLDN can be performed with equivalent safety and efficacy according to large retrospective studies, systematic reviews and meta-analysis [18, 19].

Laparoscopic living-donor nephrectomy has brought attention to potential failures of different devices such as endoscopic staplers and locking and non-locking clips, used to secure the renal hilum [18]. There is no scientific evidence that one device is safer than another for securing the renal artery [20-22]. However, the U.S. Food and Drug Administration (FDA) and the manufacturers of locking clips have issued a contraindication against their use in securing the artery during LLDN.

Summary of evidence	**LE**
Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival to open nephrectomy.	1a
Measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures.	1a

Recommendations	**Strength rating**
Offer pure or hand-assisted laparoscopic/retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	Strong
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	Strong
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly-specialised centres only.	Strong

*3.1.2 **Organ preservation***

In kidneys donated after cardiac death (DCD) evidence suggests that warm ischemia contributes to worse graft outcome. Donor hemodynamic parameters (systolic blood pressure, oxygen saturation and shock index: heart rate divided by systolic blood pressure) may be predictors of delayed graft function (DGF) and graft failure; however, further studies are required to validate this [23]. The duration of asystolic warm ischaemia during procurement in DCD donors is associated with increased risk of graft failure. Overall five year graft failure (including primary graft non-function) was associated with longer asystolic warm ischaemia times [24]. Extraction time (beginning with aortic cross-clamp and ending with placement of the kidneys on ice), is an important factor for DGF. Incidents of DGF were 27.8% and 60% at up to 60 minutes and 120 minutes extraction time, respectively [25].

A retrospective study of 64,024 living donor kidney transplants found that cold ischemic time (CIT), human leukocyte antigen (HLA) mismatch, donor age, panel reactive antibody, recipient diabetes, donor and recipient body mass index (BMI), recipient race and gender, right nephrectomy, open nephrectomy, dialysis status, ABO incompatibility, and previous transplants were independent predictors of DGF in living donor kidney transplants [26]. Five-year graft survival among living donor kidney transplant recipients with DGF was significantly lower than in those without DGF. Delayed graft function increased the risk of graft failure by more than 2-fold [26].

3.1.2.1 Kidney storage solutions and cold storage

There are two main sources for kidney graft injury: ischaemia (warm and cold), and reperfusion injury. The aims of modern kidney storage solutions include: control of cell-swelling during hypothermic ischaemia; maintenance of intra- and extra-cellular electrolyte gradient during ischaemia; buffering of acidosis; provision of energy reserve; and minimisation of oxidative reperfusion injury. There is no agreement on which of the mechanisms is most important for post-ischaemic renal graft function [27]. No storage solution seems to combine all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended.

Presently, University of Wisconsin (UW), and histidine-tryptophan-ketoglutarate (HTK) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures. The characteristics of HTK are its low viscosity, low potassium concentration and low cost. University of Wisconsin solution has been the standard static cold preservation solution for the procurement of liver, kidney, pancreas, and intestine [28]. University of Wisconsin, HTK, and Celsior solutions have provided similar allograft outcomes in most clinical trials, however, some differences have become apparent in recent studies and registry reports [29, 30]. Marshall's hypertonic citrate solution (MHCS) is also suitable for use in the preservation of human kidneys before transplantation [31]. In experimental studies of kidney preservation, HTK and UW retained a greater capacity to preserve endothelial structure and pH buffering function during warm ischaemia in comparison to MHCS and Celsior, especially in DCD donors [32]. In the absence of a cost-utility analysis, the results of the meta-analysis from the randomised controlled trials (RCTs) comparing UW with Celsior and MHSC in standard cadaver donors, indicate that these cold storage solutions are equivalent [33].

For living donors, in whom immediate kidney transplantation is planned, perfusion with crystalloid solution is sufficient. Kidneys coming from DCD donors, especially those uncontrolled are high-risk marginal organs due to prolonged warm ischaemia periods, and require specific measures in order to diminish the rate of non-function or DGF. More than 60% of kidney grafts currently come from Expanded Criteria Donors (ECD) (any donor aged > 65 years and/or donor aged > 55 years with any of the following: acute renal dysfunction, stroke or arterial hypertension) [34].

Summary of evidence	**LE**
University of Wisconsin and HTK solution are equally effective and are standard for multi-organ or single kidney harvesting procedures.	1b
A meta-analysis of RCTs indicated that UW and Celsior solution are equivalent in standard cadaver donors.	1a

Recommendations	**Strength rating**
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	Strong
Use Celsior or Marshall's solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	Strong

3.1.2.2 Duration of organ preservation

Cold ischaemia time should be as short as possible. Kidneys from ECDs after brain death (DBD) and DCD donors are more sensitive to ischaemia than standard criteria donors. Kidneys from DBD donors should ideally be transplanted within a 18 to 21 hour time period; there is no significant influence on graft survival within a 18 hour CIT [33, 35]. Kidneys from DCD donors should ideally be transplanted within 12 hours [36], whilst kidneys from ECDs should ideally be transplanted within 12 to 15 hours [37, 38].

3.1.2.3 Methods of kidney preservation: static and dynamic preservation

Whichever method is used, cold storage is critical. The use of cold preservation as a therapeutic window to deliver pharmacological or gene therapy treatments could, from an investigational point of view, improve both short- and long-term graft outcomes [39]. Cooling reduces the metabolic rate of biological tissue minimising continuous cellular processes that lead to depletion of ATP and accumulation of metabolic products. Reperfusion with oxygenated blood invokes ischaemia-reperfusion injury. Hypothermic perfusion does not enable normal cellular metabolic function or prevent depletion of energy stores [40]; however, it prevents the deleterious effects of simple cooling, especially in the setting of prolonged warm-ischaemic time in uncontrolled DCD donors. Two meta-analyses suggest that hypothermic machine perfusion reduces DGF compared with static cold storage [41, 42]. Outcomes for primary non-function (PNF) are less clear, but one meta-analysis limited to high quality studies suggests a reduction in PNF rates with hypothermic machine perfusion [42].

The increased demand for organs has led to the increased use of "higher risk" kidney grafts. Kidneys from DCD donors or grafts coming from ECDs are more susceptible to preservation injury and have a higher risk of unfavourable outcomes [43, 44].

Dynamic, instead of static, preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve vulnerable grafts. Preclinical findings have driven clinical organ preservation research that investigates dynamic preservation, in various modes (continuous, pre-implantation) and temperatures (hypo-, sub-, or normothermic) [40].

There are several methods of kidney preservation including:

- Initial flushing with cold preservation solution followed by ice storage. However, the limitations of static cold storage (CS) in preserving marginal organs such as ECD kidneys has led to the increased use of dynamic methods.
- Current dynamic preservation strategies entering clinical practice and the different modalities of their use are: hypothermic machine perfusion, hypothermic regional perfusion, normothermic machine perfusion, normothermic regional perfusion, sub-normothermic machine perfusion and sub-normothermic regional perfusion [40].
- Continuous pulsatile hypothermic machine perfusion (HMP) seems to be a good preservation method for marginal organs, either initially or after a period of simple CS (shipping of suboptimal kidneys) [45].
- Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not

flow, using low pressures to avoid pressure-related injury. The perfusion solutions used are specific, and are qualitatively different to CS solution [30].

- Nonoxygenated HMP of the kidney at low perfusion pressures (20-30 mmHg) has been shown to reduce DGF [41]. The largest RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys [46]. Hypothermic machine perfusion of kidneys from type III DCD donors decreased DGF with no impact on graft survival [43].
- Hypothermic machine perfusion reduces the risk of DGF in standard criteria DBD donor kidneys regardless of cold ischaemia time [47].
- Increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF; however, they do not justify discarding the kidney. The flow perfusion value seems to be an indicator of graft viability in uncontrolled DCD donors, particularly donors with a high creatinine level [48]. However, research is required to identify a strong and reliable measure for predicting kidney viability from machine perfusion [33]. Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts [49].
- Oxygenation during HMP appears to be beneficial, improving early kidney graft function [50]. The effect of oxygenated HMP is being investigated in two RCTs initiated by the Consortium on Organ Preservation in Europe (COPE), on type III DCD and ECD kidneys [40].
- A short period of normothermic machine perfusion (NMP) immediately prior to implantation has been shown to improve kidney graft function, replenish ATP and reduce injury in experimental models [51, 52].
- Active research is being developed on preservation of prolonged warm-ischaemically damaged human kidneys (types I and II DCD) by *in situ* normothermic extracorporeal hemoperfusion with oxygenation and leukocyte depletion before procurement [53]. Oxygen carriage is achieved by using blood depleted of leukocytes. Potential advantages of this preservation technique are reduction in ischaemia-reperfusion injury as well as the possibility of assessing organ viability.
- Currently there is one registered ongoing RCT on pre-implantation NMP using an oxygenated, sanguineous normothermic perfusion solution (http://www.isrctn.com/ISRCTN15821205). Kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output [54].
- Continuous subnormothermic machine perfusion and controlled oxygenated rewarming has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP in a research setting [55].

Summary of evidence	**LE**
A meta-analysis of RCTs comparing CS with HMP of deceased donor kidneys showed a reduced risk of DGF for HMP.	1a
Hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury.	2a
Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts.	2b

Recommendations	**Strength rating**
Minimise ischaemia times.	Strong
Use hypothermic machine-perfusion (where available) in deceased donor kidneys to reduce delayed graft function.	Strong
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	Strong
Use low pressure values in hypothermic machine perfusion preservation.	Strong
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	Strong
Do not discard grafts based only on increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine perfusion preservation.	Weak

*3.1.3 **Donor Kidney biopsies***

Donor kidney biopsies can serve different purposes including:

- histological assessment of organ quality prior to transplantation (often referred to as procurement or harvest biopsies);
- histological analysis of focal lesions, especially if there is a suspicion of neoplasia;
- detection of donor derived lesions as reference for subsequent post-transplant biopsies (often referred to as baseline, zero-time or implantation biopsies).

3.1.3.1 Procurement Biopsies

3.1.3.1.1 Background and prognostic value

Procurement biopsies are used for the detection of tissue injury to aid the decision of whether or not a deceased donor kidney is suitable for transplantation. These biopsies are most commonly performed in donors with clinical suspicion of chronic kidney injury (ECDs) [56].

Kidney discard in Europe is rarely based on histology findings, as procurement biopsies are not regularly performed for graft allocation in the Eurotransplant region [56]. However, since biopsy findings are the most frequent cause for discarding donor organs in the United States [57-59], their prognostic value has been analysed in numerous studies. A recently published systematic review of studies on donor kidney biopsies revealed a lack of prospective studies and marked heterogeneity regarding the type of lesions being assessed, their scoring, the definitions of post-transplant outcomes and the statistical methods employed [60]. Therefore, the published evidence suggests that the use of procurement biopsies for deciding on suitability for transplantation of donor kidneys may have some important limitations including the following [56, 60, 61]:

- *There is no consistent association between histological lesions observed in donor kidney biopsies and post-transplant outcomes.*

The concept of procurement biopsies in elderly donors was introduced by a study from Gaber *et al.* in 1995. This study observed significantly worse outcomes in recipients of kidneys with > 20% globally sclerotic glomeruli [62]. However, subsequent studies yielded highly variable results and it cannot be concluded that glomerulosclerosis is independently associated with graft outcomes [60]. A similar variability was also observed for other potentially relevant lesions like arterial injury, interstitial fibrosis and tubular atrophy; each one showing predictive value in some studies but, not in others [60].

- *There is no agreement on prognostically relevant lesions and how they should be scored.*

Specific grading systems for donor kidney biopsies have not yet been developed. Lesion scoring in pre-transplant biopsies is mostly based on the Banff consensus for post-transplant renal allograft pathology, which is supported by the 2007 Banff Conference report [63].

Many attempts have been made to use composite semi-quantitative scoring systems to express the global extent of tissue injury in donor kidney biopsies. These scoring systems are mostly based on simple addition of the Banff scores for individual lesions, most commonly glomerulosclerosis, arteriolar hyalinosis, arterial intimal fibrosis, interstitial fibrosis and tubular atrophy and rarely include clinical parameters like donor age [64], serum creatinine values and donor hypertension [65].

A limited number of histological scoring systems are based on modelling analysis [64-68]. Only the Maryland Aggregate Pathology Index (MAPI) [68] scoring system and the Leuven donor risk score [64], use graft failure as their endpoint and have been independently validated in a second cohort. Other studies used surrogate clinical endpoints like DGF [66] and estimated glomerular filtration rate (eGFR) at three months [67] to calculate histological models. In addition, these models were not validated in independent cohorts. The variation in how the components are weighted to achieve the composite score and the different endpoints used may explain the conflicting conclusions in the literature [56, 60, 61].

- *Due to the time constraints of organ allocation procurement biopsies are mostly read on frozen sections by on-call pathologists, which might affect the diagnostic reliability of reported findings.*

This may have substantial impact on the diagnostic reliability of the procedure since frozen sections are prone to morphological artefacts that can impair the detection and scoring of potentially important lesions such as arteriolar hyalinosis and interstitial fibrosis [69, 70]. There is strong evidence that dedicated renal pathologists should examine formalin-fixed paraffin-embedded core-needle biopsies. Paraffin histology employing special stains is technically superior to frozen sections since morphological details are better preserved on paraffin sections than on frozen sections and potentially confounding artefacts can be avoided. Rapid processing of tissue for paraffin histology is technically feasible, but the respective protocols are not universally implemented and are not available on a 24/7 basis in most departments. Another source of variability is the professional experience of the pathologist in charge. Procurement biopsies are commonly read by the on-call general pathologist who frequently has no specific training in renal pathology. A recent study specifically addressing this issue found that the on-call pathologists tended to overestimate chronic injury in biopsies [71].

3.1.3.2 Type and size of biopsy

Many transplant centres obtain wedge biopsies of donor kidneys rather than needle biopsies due to the presumed higher risk of bleeding complications with the latter. Wedge biopsies sample the cortex superficially whereas needle biopsies reach deeper aspects of the cortex. Needle biopsies also allow sampling from different areas of the kidney. Submit 14 or 16 G needle biopsies as obtaining adequate biopsies with 18 G

needles requires multiple cores [72]. Several studies comparing wedge with needle biopsies concluded that needle biopsies perform much better in the evaluation of vascular lesions because interlobular arteries are rarely sampled in wedge biopsies. Both methods were comparable for glomerular or tubulointerstitial lesions [73-76]. It was also demonstrated that glomerulosclerosis is significantly more pronounced in the subcapsular zone compared with deeper areas of the cortex [77]. The problem of insufficient sampling of arteries and over representation of (subcapsular) glomerular scars in wedge biopsies, can only be avoided if particular attention is paid to the correct performance of the biopsy, with a minimal depth of 5 mm [78]. The predictive value of glomerulosclerosis increases significantly with higher numbers of glomeruli in the wedge biopsy, with ideally at least 25 glomeruli required for evaluation [75]. There is limited evidence regarding complication rates in pre-implantation biopsies.

Use of a skin punch biopsy device might be an attractive alternative. Skin punch biopsies measure 3 mm in diameter. They have a shorter length than needle biopsies therefore avoiding injury to large calibre arteries at the corticomedullary junction whilst still sampling tissue from deeper areas of the cortex [79].

3.1.3.3 Summary of evidence and recommendations

Summary of evidence	**LE**
Individual histologic lesions like glomerulosclerosis, arterial luminal narrowing or tubulointerstitial injury observed in donor kidney biopsies have limited prognostic value for long-term allograft survival.	3
Composite histological scoring systems provide a more comprehensive measure of overall organ damage. However, published scoring systems still lack independent validation and robust thresholds.	3
Size of the biopsy is of critical importance for its diagnostic value. An adequate biopsy reaches beyond the immediate subcapsular area (≥ 5 mm) and contains ≥ 25 glomeruli and ≥ one artery. Needle biopsies, wedge biopsies or specimens obtained with a skin punch biopsy device will result in equally adequate biopsies if sampling is properly performed. Obtaining adequate biopsies with 18 G needles is difficult and requires multiple cores.	3

Recommendations	**Strength rating**
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient including perfusion parameters where available.	Strong
Use paraffin histology for histomorphology as it is superior to frozen sections; however, its diagnostic value has to be balanced against a potential delay of transplantation.	Strong
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	Strong

3.1.3.4 Implantation biopsies

Implantation biopsies are used to provide baseline information on donor kidney injury for comparison with subsequent post-transplant kidney biopsies. Baseline biopsies can be essential for clear distinction between pre-existing damage and acquired lesions. They are particularly valuable in cases of thrombotic microangiopathy, arteriolar hyalinosis or acute tubular injury. In contrast to procurement biopsies that are obtained at the time of organ harvesting, implantation biopsies are usually taken before implantation in order to cover potential effects of cold ischaemia time. Their diagnostic contribution has not been formally quantified in the literature which might be due to the difficulties of measuring the value of implantation biopsies for improving diagnoses. Despite the lack of formal studies investigating their value it seems very reasonable to perform implantation biopsies in deceased donor kidneys.

3.1.4 ***Living and deceased donor implantation surgery***

3.1.4.1 Anaesthetic and peri-operative aspects

Good communication between nephrologists, anaesthetists and surgeons is required for optimal anaesthetic and peri-operative care of the renal transplant patient. Anaesthetic care of the living kidney donor [80] and renal transplant recipient [81] have been reviewed and recent guidelines from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [82] are cross referenced.

3.1.4.2 Immediate pre-op haemodialysis

Routine use of haemodialysis immediately prior to renal transplantation is not indicated [82]. Hyperkalaemia is the most common indication for haemodialysis pre-operatively. The risks of haemodialysis compared with

medical therapy must be considered along with the risks of intra-operative fluid overload, electrolyte and acid-base disturbances, particularly where a deceased donor kidney is transplanted with a significant risk of DGF. Pre-operative haemodialysis may initiate a pro-inflammatory state, delay surgery, increase the CIT and increase the risk of DGF [83].

Summary of evidence	LE
Pre-operative haemodialysis has the potential to delay transplantation, increase CIT and increase the risk of DGF.	2

Recommendation	Strength rating
Use dialysis or conservative measures to manage fluid and electrolyte imbalance prior to transplant surgery taking into consideration the likelihood of immediate graft function.	Weak

3.1.4.3 Operating on patients taking anti-platelet and anti-coagulation agents

Many patients active on the transplant waiting list have vascular disease and/or a pro-thrombotic condition that should be risk-assessed prior to transplantation. Dual anti-platelet therapy is commonly given to patients with coronary artery stents for six to twelve months; peri-operative management plans for these patients should be discussed with a cardiologist so that the risks of withdrawal of the anti-platelet agent can be fully considered. Options for reversal of anti-coagulation and post-operative anti-coagulation should be discussed with a haematologist prior to patient listing.

Some patients will be active on a transplant waiting list whilst continuing to take anti-platelet and/or anti-coagulation agents. The indication for anti-platelet or anti-coagulation agents should be clearly documented for each individual. Potential increased risk of peri-operative bleeding needs to be weighed against potential harm from arterial or venous thrombosis. In accordance with the American College of Chest Physicians and the European Society of Cardiology guidelines [84, 85], the literature suggests that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications [86], however, the number of patients studied was low. If needed, the effect of anti-platelet agents can be reduced with intra-operative platelet infusions.

Summary of evidence	LE
A retrospective single-centre case-control study in patients undergoing kidney transplantation concluded that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications.	3

Recommendations	Strength rating
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	Weak
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/haematologist/nephrologist.	Weak

3.1.4.4 What measures should be taken to prevent venous thrombosis including deep vein thrombosis during and after renal transplant?

Peri-operative administration of short-acting anti-coagulation agents reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins); however, due to associated increased blood loss administration requires knowledge of individual patient risk factors. None of the current major thrombosis prevention guidelines directly address thromboprophylaxis in the renal transplant peri-operative period. A small RCT [87] showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation. Those administered prophylactic anti-coagulation had significantly lower haemoglobin whilst those administered prophylactic unfractionated heparin had prolonged lymph drainage. Based on this study, routine pharmacological prophylaxis is not recommended in low-risk living donor recipients. Mechanical measures to decrease ileo-femoral deep vein thrombosis (DVT) can be used where there is no contraindication due to peripheral vascular disease particularly where there are concerns about bleeding risks with pharmacological prophylaxis.

Summary of evidence	LE
A small RCT (n=75) showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation.	1b

Recommendation	Strength rating
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak

3.1.4.5 Is there a role for peri-operative antibiotics in renal transplantation?

Prophylactic peri-operative antibiotics are generally used in renal transplant surgery but the optimal antibiotic regimen is not known and increasing antibiotic resistance may hamper their effectiveness in this setting. A multicentre, prospective RCT showed no difference at one month in surgical site, bacterial, fungal or viral infection between those receiving a single dose broad spectrum antibiotic at induction of anaesthesia compared to those receiving antibiotic 12 hourly for 3-5 days [88]. A retrospective comparison of peri-operative intravenous cefazolin prophylaxis compared to no antibiotic showed no difference in infectious complications (surgical site, urinary tract, bacteraemia or central catheter-related infection) in the first month after renal transplantation [89].

Summary of evidence	LE
A multicentre, prospective RCT showed that the incidents of surgical site infection and urinary tract infection were similar in those receiving a single dose broad spectrum antibiotic at induction of anaesthesia and those receiving antibiotic 12 hourly for 3-5 days.	1b

Recommendation	Strength rating
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong

3.1.4.6 Is there a role for specific fluid regimes during renal transplantation and central venous pressure measurement in kidney transplant recipients?

Careful peri- and post-operative fluid balance is essential for optimal renal graft function. There is no evidence determining if crystalloids or colloids are better for intravenous fluid management during renal transplant surgery; however, colloids may be immunogenic. If normal saline (0.9%) is used, monitoring for metabolic acidosis is recommended in the peri-operative period. A prospective double-blind RCT compared normal saline to lactated Ringer's solution as intra-operative intravenous fluid therapy. Serum creatinine at day three post-surgery did not differ between the two groups. However, Ringer's lactate caused less hyperkalaemia and metabolic acidosis than normal saline. Balanced solutions may be the optimal and safer option for intra-operative intravenous fluid therapy [90].

Central venous pressure (CVP) measurement helps anaesthetists guide fluid management. A small prospective non-blinded RCT compared two normal (0.9%) saline regimens: constant infusion (10-12 $mL/kg^{-1}/h^{-1}$ from start of surgery until reperfusion) and central venous pressure-based infusion (target CVP appropriate to stage of operation) [91]. Central venous pressure directed infusion produced a more stable haemodynamic profile, better diuresis and early graft function. Directed hydration may decrease DGF rates and CVP measurement may help optimise early graft function.

Summary of evidence	LE
A small (n=51) prospective RCT found that use of Ringer's lactate solution was associated with less hyperkalaemia and acidosis compared with normal saline in patients undergoing kidney transplantation.	1b
A small (n=40) prospective RCT comparing constant infusion vs. CVP found that CVP produced a more stable haemodynamic profile, better diuresis and early graft function.	1b

Recommendations	Strength rating
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	Strong
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	Weak
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	Strong

3.1.4.7 Is there a role for dopaminergic drugs, furosemide or mannitol in renal transplantation?

Low-dose dopamine (LDD) has been used in renal transplantation due to a perceived improvement in urine output and early graft function. Use of LDD in kidney donors is outside of the scope of this section. Conflicting results prevent a consensus statement on routine use of LDD in transplant recipients. A small (n=20) prospective randomised cross-over study in deceased donor renal transplantation suggested significant improvements in urine output and creatinine clearance in the first nine hours post-surgery without adverse events [92]. By contrast, a retrospective comparison of LDD in the first twelve hours post-deceased donor renal transplantation showed no difference in diuresis or kidney function but those administered LDD (n=57) had increased heart rates, longer intensive therapy unit stay and higher six-month mortality than those not treated with LDD (n=48) [93].

Considerable variation exists in the use of diuretics during renal transplant recipient surgery and there is little evidence to suggest any benefit from their use [94]. No evidence on the use of mannitol during renal transplant recipient surgery was found during the panel's literature search. Use of mannitol in kidney donors is outside the scope of this section.

Summary of evidence	**LE**
A retrospective comparative study of LDD treated vs. non-treated renal transplantation patients concluded that LDD administration did not improve kidney function in the first twelve hours post renal transplantation but did result in increased heart rates, longer intensive therapy unit stay and higher six-month mortality in those receiving LDD.	2b

Recommendation	**Strength rating**
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

3.1.5 ***Surgical approaches for first, second, third and further transplants***

Transplant (bench/back-table) preparation is a crucial step in the transplantation process. The kidney must be inspected whilst on a sterile ice slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumours. Biopsy of the kidney on the back-table may be performed to help in the multifactorial decision-making process regarding the quality and usage of the kidney for both single and/or dual transplantation. Suspicious parenchymal lesions also require biopsy. Techniques for intra-operative kidney biopsy are discussed in section 3.1.3.

The number, quality and integrity of renal vessels and ureter(s) should be established and lymphatics at the renal hilum ligated. The quality of the intima of the donor renal artery should be evaluated. Branches of the renal artery not going to the kidney or ureter(s) should be tied.

In deceased donor kidney transplantation the quality of the aortic patch should be determined. If severe atheroma of the patch, ostium or distal renal artery is seen then the aortic patch and/or distal renal artery can be removed to provide a better quality donor renal artery for implantation. Back table reconstruction of multiple donor arteries is discussed in section 3.1.5.1. The length of the renal vein should be evaluated. Renal vein branches should be secured/tied.

For a deceased donor right kidney, lengthening the renal vein on the back table may be performed if needed with donor inferior vena cava [95]. Techniques for lengthening a short living donor right renal vein from donor gonadal vein or recipient saphenous vein require pre-operative planning and specific consent (discussed in section 3.1.5.1).

The length, quality and number of the ureter(s) should be established. The peri-pelvic and proximal peri-ureteral tissue in the 'golden triangle' should be preserved.

Recommendation	**Strength rating**
Assess the utility (including inspection) of the kidney for transplantation before commencement of immunosuppression and induction of anaesthesia for deceased donor kidney transplantation.	Strong

3.1.5.1 Single kidney transplant - living and deceased donors

The standard surgical approach for first or second single kidney transplant (SKT) operations remains open kidney transplant (OKT). Emerging surgical technologies using minimal access surgical approaches have been developed and the different surgical approaches (minimally invasive open, laparoscopic and robot-assisted) were compared in a systematic review [96].

Robot-assisted kidney transplant (RAKT) surgery using living donor kidneys have now been evaluated in multi-centre prospective non-randomised studies (using IDEAL consortium principles) [97]. Single centre prospective non-randomised studies are on-going addressing RAKT with use of deceased donor kidneys. Both trans-peritoneal and extra-peritoneal approaches for RAKT are described. Potential advantages of RAKT may exist (decreased post-operative pain, length of hospital stay, incision length and lymphocele rate). Potential issues with RAKT are the exclusion of recipients with severe atherosclerosis or third (or further) kidney transplants, a higher than expected rate of DGF and a small number of reported early arterial thromboses despite carefully selected cases [98]. Evidence is too premature to recommend RAKT outside of appropriately mentored prospective studies.

An extra-peritoneal approach to either iliac fossa should be used as the operative approach in most first or second single kidney transplant (SKT) operations. There is no evidence to prefer placement of a left or right kidney into either iliac fossa [99]. Peri-iliac vessel lymphatics should be ligated to try and prevent post-operative lymphocele. Appropriate segments of iliac artery and vein should be mobilised to facilitate appropriate tension free vascular anastomoses and the final positioning of the transplanted kidney. There is evidence supporting the benefits of cooling the kidney surface during implantation [100].

Recommendations	Strength rating
Choose either iliac fossa for placement of a first or second single kidney transplant.	Weak
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	Weak

A variety of techniques have been described to help with the anastomosis of a short renal vein. This is most commonly encountered with a right kidney especially from a living donor. To achieve equivalent outcomes with right kidneys appropriate surgical technical manoeuvres may be needed to optimise right kidney implantation.

Data from cohort studies [99, 101] and one registry study [102] suggest equivalent outcomes with either left or right deceased donor kidneys. By contrast, another registry study of 2,450 paired kidneys, donated after cardiac death, observed with right kidneys: more early surgical complications; an increased risk in DGF (Odds Ratio [OD] 1.46); and inferior one year graft survival (OD 1.62) but not at subsequent time points [103]. However, surgical techniques used to compensate for a right kidney, anastomosis time and surgeon experience were not recorded.

Data from at least two large registry studies demonstrate a slightly higher risk of early graft failure using right compared to left kidneys from living donors [102, 104, 105]. However, meta-analysis of data from one RCT and fourteen cohort studies suggested equivalent graft outcomes [106].

Techniques to manage a short renal vein can be addressed in the donor and/or recipient. Ligation of internal iliac vein(s) may be necessary to elevate the iliac vein and avoid tension on the renal vein anastomosis [99]. Transposition of the iliac artery and vein may enhance the position for the venous anastomosis [107]. The right renal vein may be lengthened. With deceased donor kidneys this is usually done with donor inferior vena cava (IVC) [101]. In living donors, lengthening of the renal vein may be achieved with donor gonadal vein retrieved at donor nephrectomy [108] or with recipient saphenous vein [109], although both require specific consent and in general the other aforementioned techniques are preferred.

Summary of evidence	LE
Prospective cohort studies demonstrated that: • transposition of the recipient iliac vein is an appropriate technical solution to compensate for the short length of the renal vein in right kidney LDN (n=43); • the living donor right kidney renal vein can be successfully lengthened using donor gonadal vein (n=17) or recipient saphenous vein (n=19).	3

Recommendation	Strength rating
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	Weak

A history suggesting previous iliac or femoral vein thrombosis should initiate pre-operative imaging to establish patency of one iliac vein and the IVC. An intra-operative finding of an unexpected iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

The external or common iliac arteries are equally good for arterial anastomosis. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended in general over an end-to-end anastomosis to the internal iliac artery. The only RCT comparing these techniques suggests no difference [110]. However, the study was limited by small numbers and a high (8%) overall renal artery thrombosis rate.

The sites of the vascular anastomosis should be chosen carefully according to the length of the renal artery and vein to avoid kinking of the vessels when the kidney is placed into its final location, usually in the iliac fossa. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery to decrease the risk of iliac artery dissection. The intima of the donor and recipient arteries should be checked prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to, or as part of, the arterial anastomosis.

A Carrel patch is usually maintained on a deceased donor renal artery although it can be removed if there is either severe ostial atheroma/stenosis (with good quality proximal renal artery) or if the length of the renal artery is too long for the appropriate implantation site on the iliac artery (which is more common with the right renal artery).

Multiple renal arteries supplying a deceased donor kidney can be maintained on a Carrel patch (of appropriate length) and implanted as a single anastomosis. In living donor transplantation, multiple renal arteries require a variety of strategies to achieve optimum re-perfusion [94]. Two arteries can be implanted separately or to achieve a single anastomosis: a very small second artery (especially if supplying the upper pole) may be sacrificed; the two arteries may be joined together (as a trouser graft); or the smaller artery can be anastomosed onto the side of the main artery (end-to-side anastomoses). A lower polar artery may be re-vascularised via anastomosis to the inferior epigastric artery [111]. In living donor transplantation where three or more donor arteries exist consideration should be given to alternate kidney donors. In circumstances using a living donor kidney with three or more donor arteries, strategies include a combination of the above techniques or, after appropriate consent, use an explanted (recipient's own) internal iliac artery graft [112] or saphenous vein graft [113].

In cases where an iliac artery prosthetic replacement has previously been carried out because of severe symptomatic iliac atheroma, the renal artery should be implanted into the prosthesis. Administration of systemic heparin should be considered prior to clamping of a vascular prosthesis [114].

A variety of sutures and suturing techniques for the vascular anastomosis are described, but in general practice, a 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis. Despite this, there is no evidence to recommend one suturing technique over another to prevent, for example, transplant artery stenosis. Use of an expanded polytetrafluroethylene suture compared to standard polypropylene suture may reduce blood loss due to a better needle/thread ratio [115].

In third or further transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney [116, 117]. Nephrectomy of an old transplant kidney may be required prior to transplantation or at the time of transplantation [116]. Mobilisation of the common or internal iliac artery, internal iliac vein or IVC may be required. An intra-peritoneal approach (via the iliac fossa or midline) may be required [118]. Rarely orthotopic transplantation is needed [116, 119].

Evidence suggests that minimising the anastomosis time and/or rewarming time results in reduced DGF [120]. The effect on long term graft function is uncertain, but may also be impacted by short anastomosis time [121].

Summary of evidence	**LE**
A small RCT (n=38) comparing end-to-end anastomosis to the internal iliac artery vs. end-to-side anastomosis to the external iliac artery found that both techniques showed similar results in the post-operative period and at three-years follow-up.	1b
Cohort studies have demonstrated third or further transplants are a valid therapeutic option with reasonable short- and long-term patient and graft survival.	3

Recommendations	Strength rating
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	Weak
Use an end-to-end anastomosis to the internal iliac artery as an alternative to external or common iliac arteries.	Weak
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	Strong
Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	Strong

3.1.5.2 Dual kidney transplants

Dual kidney transplant (DKT) is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant the pair of donor kidneys [122]. These include unilateral extra-peritoneal (UEP) or intra-peritoneal (UIP) and bilateral extra-peritoneal (BEP) or intra-peritoneal (BIP) that can be via a midline [123] or two lateral incisions.

The aim of a unilateral approach is to leave the contralateral iliac fossa intact for future transplantation in the event of graft loss and to reduce CIT for the second kidney transplant [124]. The unilateral approach may require mobilisation and division of the internal iliac vein to facilitate the two renal veins to iliac vein anastomoses. Modifications of the unilateral technique include single renal artery and vein anastomoses (with bench reconstruction) to further reduce CIT for the second kidney [125-127]. Dual kidney transplant takes longer and has higher blood loss than SKT regardless of the technique used. Data suggest shorter operative time and hospital stay with UEP compared to BEP [128] but other data suggest similar outcomes from all DKT techniques. No RCT exists to recommend one technique for all patients or situations.

En-bloc retrieval is performed when kidneys are retrieved from children weighing < 15 kg. Depending on the size of the donor kidney and size and weight of the adult recipient(s), *en-bloc* transplantation of the two kidneys may be performed or, if appropriate, the aorta and IVC patch may be divided for SKT [129].

3.1.5.3 Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Leadbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter. A meta-analysis [130] of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique to an intravesical approach leading to reduced overall complications (specifically urine leak, stricture and post-operative haematuria). Fewer urinary tract infections (UTIs) were observed with the extravesical approach when compared with the intra-vesical technique in one RCT [131]. Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters [132]. A meta-analysis suggested ureteric stricture, obstruction, and stone formation were more common after uretero-ureterostomy whereas vesicoureteral reflux and UTIs were more common after uretero-neo-cystostomy [133].

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply. The location on the bladder to position an extra-vesical anastomosis was shown in one small RCT to be advantageous at the posterior bladder rather than anterior position to facilitate future endoscopic manipulation if needed, and reported less hydronephrosis post stent removal [134]. In cases where donor ureter has been damaged at retrieval then pyelo-native-ureterostomy or pyelo-neo-cystotomy can be performed. Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material [135].

Summary of evidence	LE
A meta-analysis of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications.	1a
A multi-centre prospective comparison study found the incidence of overall complications was similar for pyelo- and uretero-ureteral anastomosis and that for both procedures no graft was lost due to urological complications.	2b

Recommendations	Strength rating
Perform Lich-Gregoir-like extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	Strong
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	Strong

Transplant ureteric anastomosis can be performed with or without a ureteric stent. If a stent is placed a second procedure is generally required for removal. A Cochrane review [136] concluded that stents are recommended to reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined but if left over 30 days is associated with more UTIs [137].

Most commonly, stents are removed with local anaesthetic flexible cystoscopy unless there is a need to combine with another procedure warranting general anaesthetic. Various techniques to reduce the morbidity of a second procedure involve tying the stent to the catheter or use of percutaneous stents [138].

Recommendation	Strength rating
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong

Duplex ureters are not infrequently identified at organ retrieval/kidney benching or during work-up for LDN [139, 140]. Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. This also applies to the two single ureters in DKT in adults or with *en-bloc* transplantation from paediatric donors. The arguments for two separate ureteric anastomoses to the bladder are that an already tenuous blood supply may be further compromised with added suturing and handling, and if there is an issue with one ureter the other should remain unaffected. The advantages to forming one single (two ureter) anastomosis to the bladder are that only one cystotomy is needed; it may be faster and complications may be reduced. There is a lack of high quality evidence relating to duplex ureters.

Recommendation	Strength rating
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

3.1.5.4 Transplantation/ureteric implantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter [141].
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extra-vesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intra-peritoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

*3.1.6 **Donor complications***

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Potential complications should be included in the process of informed consent.

Reported surgical mortality is 0.01% to 0.03% with no apparent alteration due to changes in surgical techniques or donor selection in recent years [142, 143]. According to a recent systematic review (190 studies) and meta-analysis (41 studies) on complications in minimally invasive LDN, reporting on a total of 32,308 LDNs, intra-operative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%) [142]. Conversion to open surgery was reported in 1.1%, half due to bleeding and half due to injury to other organs. Surgical re-interventions occurred in 0.6%; the majority due to bleeding or

to evacuate a haematoma [142]. A low trigger for conversion or re-operation should be observed in order to minimise the risk of serious complications.

A recent review looked for complications in 14,964 LDNs performed in the U.S. from 2008-2012 and found an overall peri-operative complication rate of 16.8%, gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), surgical/anaesthesia-related injuries (2.4%), and "other" complications (6.6%). Among the sample, 2.4% required intensive care and in-hospital mortality was 0.007% [14].

Major Clavien Classification of Surgical Complications grade IV or higher affected 2.5% of donors. Risk factors for Clavien grade IV or higher events included obesity (adjusted odds ratio [aOR] 1.55, $p = 0.0005$), pre-donation haematologic (aOR 2.78, $p = 0.0002$), psychiatric conditions (aOR 1.45, $p = 0.04$) and robotic nephrectomy (aOR 2.07, $p = 0.002$). An annual centre volume > 50 (aOR 0.55, $p < 0.0001$) was associated with lower risk [14].

3.1.6.1 Long-term complications

Long-term complications are mostly related to the single-kidney condition. Renal function in living donors decreases after donation before improving for many years; however, in the long run it shows signs of slight deterioration [144-146]. There is a steady increase in the incidence of proteinuria; hypertension post-transplant having been shown as the main cause of increased albumin excretion [147].

The overall incidence of end-stage renal disease (ESRD) (0.4-1.1%) does not differ from the general population [144, 145, 148, 149]. According to a recent large retrospective study, the majority of ESRD developing after living kidney donation is due to new-onset disease that would have affected both kidneys [150]. However, there are some identified risk factors for deterioration of renal function after donation. According to a recent study that evaluated 119,769 live kidney donors in the United States, obese (BMI > 30) living kidney donors have a 1.9-fold higher risk for ESRD compared to their non-obese counterparts [151]. Long-term risk of death is no higher than for an age- and co-morbidity-matched population [143, 148].

Health related quality of life (HRQoL), including mental condition, remains on average better than the general population after donation [148, 149, 152]. However, some donors experience significant deterioration in their perceived QoL [152]. While global HRQoL is comparable or superior to population normative data, some factors identifiable around time of donation including longer recovery, financial stressors, younger age, higher BMI, lower education, smoking and higher expectations prior to donation, may identify donors more likely to develop poor HRQoL, providing an opportunity for intervention [148, 149, 152]. It is paramount that a careful risk–benefit assessment is done and that proper information is given to the prospective donor, this should also include recommendations on health-promoting behaviour post-donation [153].

Summary of evidence	**LE**
A systematic review and meta-analysis on complications in minimally invasive LDN concluded that the techniques used for minimally invasive LDN are safe and associated with low complication rates.	1a
Survival rates and risk of end-stage renal disease are similar to those in the general population whilst donors HRQoL remains on average better than the general population.	2b

Recommendations	**Strength rating**
Restrict living-donor nephrectomy to specialised centres.	Strong
Offer long-term follow-up to all living kidney donors.	Strong

*3.1.7 **Recipient complications***

3.1.7.1 General complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such complications is therefore of primary importance [130, 137, 154-166]. We herein describe in detail the most common surgical complications in renal transplantation.

3.1.7.2 Haemorrhage

Haematomas are usually a minor complication in renal transplantation. Their incidence is reported to be between 0.2-25% [167, 168]. Small and asymptomatic haematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessel complications can be present. These cases may be treated by percutaneous drainage under computed tomography (CT) or ultrasound (US) guidance or may require surgical treatment [167].

3.1.7.3 Arterial thrombosis

Transplant renal artery thrombosis is a rare complication with a prevalence ranging from 0.5-3.5% [169]. Usually, it is a consequence of a technical error during the anastomosis although other causes may be related to both the donor and recipient's artery condition (i.e. atherosclerosis), intimal rupture during kidney harvesting, acute rejection episodes, external compression by haematoma or lymphocele, hypercoagulative state, severe hypotension, and toxicity of immunosuppressive agents (cyclosporine or sirolimus) [170]. The clinical manifestations are acute reduction of urine output and the elevation of renal function tests, often resulting in graft loss [167]. The diagnosis is obtained with eco-colour-Doppler [167]. Surgical exploration is usually recommended to evaluate the status of the graft. In the rare event the graft appears salvageable, a thrombectomy must be performed. In this situation, the iliac artery is clamped and an arteriotomy vs. a dissection of the vascular anastomosis must be performed in order to remove the clot. The graft can be flushed *in-situ* and re-vascularised [167]. Unfortunately, in the majority of the situations, the graft is not perfused and therefore an allograft nephrectomy must be performed [167, 171]. Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery can be an efficient treatment, after the first ten to fourteen post-transplantation days [167].

Summary of evidence	**LE**
The diagnosis of renal artery thrombosis depends on eco-colour-Doppler followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal artery thrombosis.	2b

Recommendations	**Strength rating**
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Strong
Perform a surgical thrombectomy in case of a salvageable graft if arterial thrombosis is confirmed intra-operatively.	Weak
Perform an allograft nephrectomy in case of a non-viable graft.	Strong

3.1.7.4 Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month [172]. The aetiology includes technical errors and/or difficulties during surgery [167] and the hypercoagulative state of the recipient [173, 174]. Colour-Doppler-flow-ultrasonography shows absence of venous flow with an abnormal arterial signal (usually a plateau-like reversed diastolic flow). Furthermore, it is common to see an enlargement of the graft due to venous congestion [175]. Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. In those cases where the venous thrombosis has not resulted in kidney loss at surgical exploration, a venotomy with surgical thrombectomy after clamping the iliac vein can be performed. Alternatively, an explantation and subsequent re-implantation can be considered [167]. Thrombolytic agents can also be used; however, their results have not been satisfactory [167, 176, 177].

Summary of evidence	**LE**
The diagnosis of renal vein thrombosis depends on colour-Doppler-flow-ultrasonography followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal vein thrombosis.	2b

Recommendations	**Strength rating**
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Weak
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	Weak
Do not routinely use pharmacologic prophylaxis to prevent transplant renal vein thrombosis.	Strong

3.1.7.5 Transplant renal artery stenosis.

The incidence of transplant renal artery stenosis is 1-25% [178, 179]. Risk factors include small calibre and

atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted vs. continuous), and damage to the iliac artery during transplantation [180, 181]. It is more common at the site of the anastomosis [180, 181]. It can be suspected in case of arterial hypertension refractory to medical treatment and/or an increase in serum creatinine without hydronephrosis or urinary infection (30). The diagnosis is performed by US-colour-Doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery [180]. In cases of doubt a magnetic resonance angiogram or a CT angiogram can be performed [182]. It is important to determine whether the stenosis is haemodynamically significant or not. Usually, a stenosis of over 50% is considered a risk for kidney impairment [183]. In case of mild stenosis (< 50%) and absence of symptoms with no deterioration of the allograft, the management is normally conservative; although, a strict follow-up with US-colour-Doppler and clinical parameters has to be adopted due to the possible risk of graft failure [180]. In cases of clinically significant stenosis and/or > 50% on US-colour-Doppler, a confirmatory angiogram should be performed. If confirmed and a decision to treat is taken, treatments include percutaneous transluminal angioplasty/stent or surgical intervention. Interventional radiology is typically the first choice although patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment [180, 181].

Summary of evidence	**LE**
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/or increasing serum creatinine without hydronephrosis/infections.	3
The diagnosis for transplant renal artery stenosis is by US-colour-Doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery.	2a
Interventional radiology is the first-line treatment option for transplant renal artery stenosis; however, in patients considered unsuitable for radiological angioplasty surgical treatment may be considered.	3

Recommendations	**Strength rating**
Perform ultrasound-colour-Doppler to diagnose an arterial stenosis, in case of undetermined results on ultrasound consider a magnetic resonance or computed tomography angiogram.	Strong
Perform percutaneous transluminal angioplasty/stent, if feasible, as first-line treatment for an arterial stenosis.	Strong
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	Strong

3.1.7.6 Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous (AV) fistulae and/or intra-renal pseudo-aneurysms in 1-18% of cases [184]. The aetiology of the AV fistula is related to the simultaneous injury of adjacent arterial and venous branches. A pseudo-aneurysm occurs when only the arterial branch is damaged. Both conditions are diagnosed with US-colour-Doppler [167]. The majority of AV fistulae are asymptomatic, resolving in one to two years spontaneously, whilst approximately 30% of them persist and become symptomatic. Typically, the symptoms are hypertension, haematuria, and graft dysfunction due to shunting between arterial and venous vessels. There is an increased risk of spontaneous rupture in case of enlarging pseudo-aneurysms. For both AV fistulae and pseudo-aneurysm, angiographic selective or super selective embolisation represents the treatment of choice [185]. Partial or radical allograft nephrectomy is currently considered the last option [167].

Recommendations	**Strength rating**
Perform a ultrasound-colour-Doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	Strong
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	Strong

3.1.7.7 Lymphocele

Lymphocele is a relatively common (1-26%) complication [186]. There is a significant aetiological association with diabetes, mammalian target of rapamycin (mTOR) inhibitors (i.e sirolimus) therapy, and acute rejection [187]. For large and symptomatic lymphocele, laparoscopic fenestration is associated with the lowest overall recurrence (8%) and complication (14%) rate compared to open surgery and aspiration therapy [188]. Placement of a percutaneous drain (i.e. Pig-Tail) is an option with a success rate as high as 50% [163].

Percutaneous aspiration can be performed although the recurrence rate can be as high as 95% [188], with an increased risk of local infection (6-17%) [188]. Furthermore, sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration [188, 189].

Recommendations	Strength rating
Perform percutaneous drainage placement as the first treatment for large and symptomatic lymphocele.	Strong
Perform fenestration when percutaneous treatments fail.	Strong

3.1.7.8 Urinary leak

Urinary leakage occurs in 0-9.3% of cases [190]. Anastomotic urine leaks can be ureteral or vesical [191]. Ureteral necrosis and/or suture failure are the most important causes [192, 193]. Non-technical risk factors include recipient age, number of renal arteries, site of arterial anastomosis, occurrence of acute rejection episodes, bladder problems, and immunosuppressive regimen [194]. Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid [192]. In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter [192]. Furthermore, the routine use a JJ-stent is recommended [193, 195]. The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak. For early and low volume urine leaks the treatment may be conservative (i.e. urethral catheter, percutaneous nephrostomy and JJ-stent) [196]. In case of failure of the conservative management, or massive leak, surgical repair must be undertaken. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results [133, 196].

Summary of evidence	LE
Suspect urinary leakage based on the urine output and the creatinine level in the drain fluid.	3
For early and low volume urine leaks conservative management may be considered.	3
Surgical repair should be undertaken when conservative management fails or massive urine leak occurs.	2b

Recommendations	Strength rating
Manage urine leak by JJ-stent and bladder catheter and/or percutaneous nephrostomy tube.	Strong
Perform surgical repair in cases of failure of conservative management.	Strong

3.1.7.9 Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5% [197]. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after > six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection [192, 198]. Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function. The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram [197]. The following treatment options depend mainly on the timing, recoverable kidney function, anatomy of the stricture, patient body habitus/comorbidities, and surgeon preference. Strictures < 3 cm in length may be treated endoscopically either with percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision. In this scenario the success rate approaches 50%; although, maximum success is obtained for strictures < 1 cm [199-201]. In case of a recurrence after a primary endourological approach and/or stricture > 3 cm in length, surgical reconstruction should be performed [198] including direct ureteral re-implantation, pyelo-vesical re-implantation (with or without psoas hitch and/or Boari Flap) or in cases with a normal native ureter, uretero-ureterostomy [202, 203]. Long-term graft and patient survival are not significantly affected [204].

Summary of evidence	LE
Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function.	3
The first approach in the management of a stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram.	2b
Strictures < 3 cm in length may be treated endoscopically.	3
For strictures > 3 cm in length or those which have reoccurred following a primary endourological approach surgical reconstruction should be performed.	2b

Recommendations	Strength rating
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	Strong
Manage strictures < 3 cm in length either with surgical reconstruction or endoscopically (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision).	Strong
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	Strong

3.1.7.10 Haematuria

The incidence of haematuria ranges from 1-34% [190]. According to the literature, the Lich-Gregoir technique provides the lowest incidence of haematuria. Furthermore, meticulous haemostasis during re-implantation results in minimal bleeding [130, 190, 191]. Bladder irrigation is the first-line treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites [190].

3.1.7.11 Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86% [190, 205]. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus (CMV) infection present a higher risk of acute graft pyelonephritis [206]. Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis, with a success rate ranging from 57.9% after the first injection to 78.9% after the second injection [207]. Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option [202].

Recommendation	Strength rating
Use an endoscopic approach as first-line treatment for symptomatic reflux.	Weak

3.1.7.12 Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients [208, 209]. The most frequent causes are hyper filtration, renal tubular acidosis, recurrent UTIs, hypocitraturia, hyperoxaluria, hyperuricaemia, excessive alkaline urine, persistent tertiary hyperparathyroidism and ureteral strictures [210, 211]. Another risk factor can be urinary anastomosis, with the lowest stone rate using Lich-Gregoir technique [209]. The most frequent clinical signs are fever, increased serum creatinine level, decreased urine output, and haematuria. Pain is usually not referred to due to impaired innervation. A US examination usually provides the diagnosis although a CT of the kidneys, ureters and bladder may be needed to confirm the location and size of the stone [210]. The management depends on the location and size of the stone, and the presence of obstruction. In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a JJ-stent [212]. Extracorporeal shock wave lithotripsy (ESWL) is usually considered the first approach for stones < 15 mm with stone-free rates varying between 40 and 80% depending on the location of the stone [212]. Ureteroscopy, including antegrade and retrograde approaches, can be considered for stones < 20 mm, with a success rate of up to 67% [132, 209, 213]. For larger stones (> 20 mm), percutaneous nephrolithotomy (PNL) can be offered with high overall effective stone-free rates. In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis, or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction [209].

Summary of evidence	LE
Extracorporeal shockwave lithotripsy should be considered as the first-line treatment option for stones < 15 mm.	2b
Antegrade/retrograde ureteroscopy and PNL may be considered as treatment options as they provide high stone-free rates.	2b
For larger stones (> 20 mm), PNL can be offered with a high overall effective stone-free rate.	2b

Recommendations	Strength rating
Evaluate the causes of urolithiasis in the recipient.	Strong
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	Strong
Perform shockwave lithotripsy or antegrade/retrograde ureteroscopy for stones < 15 mm.	Strong
Perform percutaneous nephrolithotomy for stones > 20 mm.	Weak

3.1.7.13 Wound infection

Wound infections occur in about 4% of cases. Risk factors include recipients > 60 years, high BMI, anaemia, hypo-albuminaemia, long surgical times (> 200 min) [214]. Bacteria commonly involved are Enterobacteriaceae, *Staphylococcus aureus* and *Pseudomonas* [202]. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load, and avoiding sirolimus/everolimus therapy can decrease wound complication rates [214].

3.1.7.14 Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Risk factors include age, obesity, diabetes, haematoma, rejection, re-operation through the same transplant incision and use of m-TOR inhibitors. Mesh infection is a risk factor for incisional hernia recurrence [215]. Open and laparoscopic repair approaches are safe and effective [215].

*3.1.8 **Urological malignancy and renal transplantation***

The following section is limited to a synopsis of three systematic reviews conducted by the EAU Renal Transplantation Panel. The scope of this section will be expanded in the 2020 edition of the EAU Guidelines to address the rates of urological cancers prior to and following renal transplantation and the role of immunosuppression in recurrence of urological cancers after transplantation. In addition, more detailed recommendations on waiting time from cancer treatment to listing for renal transplantation will be given.

3.1.8.1 Malignancy prior to renal transplantation

3.1.8.1.1 In the recipient

Standard procedure for transplant candidates includes systematic screening for the presence of any active/latent cancer or a past history of cancer. In candidates with a previous history of urological cancer, it can be challenging to decide if patients are suitable for transplantation and if so how long the waiting period prior to transplantation should be. To date, the waiting period has been primarily based on the Cincinnati Registry, which takes into account the type of tumour and the time between its treatment and kidney transplantation. However, the Cincinnati Registry has potential drawbacks as it does not consider the epidemiology of tumours or that diagnostic and therapeutic procedures/tests have changed over time and that prognostic tools have improved. Additionally, treatment and the staging of the disease are not defined.

According to a recent systematic review the risk of tumour recurrence was similar between transplantation (n=786) and dialysis (n=1,733) populations for renal cell carcinoma (RCC) and prostate cancer (PCa). This was especially true for low grade/stage PCa, for which the risk of recurrence was low and consistent with nomograms [216]. For low stage/grade RCC the recurrence rate was significant for both dialysis and renal transplantation; however, recurrences were actually contralateral RCC with no impact on patient or graft survival [216].

Testicular cancer had a low risk of recurrence but case reports highlighted the possibility of late recurrence even for stage I tumours [216].

For urothelial carcinoma, studies were mainly related to upper urinary tract carcinomas in the context of aristolochic acid nephropathy for which the rate of synchronous bilateral tumour was 10-16% and the rate of contralateral recurrence was 31-39% [216].

These findings imply that a kidney transplant candidate with a history of appropriately treated low stage/grade PCa (PSA ≤ 10, Gleason score ≤ 6 and T1/T2a) or low grade T1 RCC could be listed for renal transplantation without any additional delay compared to a cancer-free patient. However, as the level of evidence was low, more studies are needed to standardise waiting periods before renal transplantation.

Summary of evidence	LE
Renal Cell Carcinoma	
The recurrence rates for transplanted vs. dialysed patients at <1, 1–5, and > 5 years were 0–8% vs. 0%, 0–27% vs. 0–9% and 0–41% vs. 0–48%, respectively.	2b
Overall five year survival rates for transplantation vs dialysed patients were 80–100% vs. 76–100%, respectively.	
Prostate Cancer	
The recurrence rates for transplantation patients at <1 and > 5 years were 0–9% and 4–20%, respectively.	2b
Overall, 1–5 year survival rates for transplantation patients ranged from 62% to 100%.	

Recommendation	Strength rating
List for renal transplantation patients with a history of appropriately treated low stage/grade renal cell carcinoma or prostate cancer without additional delay.	Weak

3.1.8.1.2 In the potential donor kidney

In the general population, RCC constitutes 3% of all malignancies, with the incidence being highest in patients aged > 60 years. The current increasing age of donors may lead to a higher number of incidental RCCs found in donor kidneys and could theoretically decrease the number of kidneys suitable for transplantation. The main surgical approach to these kidneys is *ex vivo* tumour excision on the back-table with an oncological margin, frozen section biopsy, bench surgery renorraphy, and finally transplantation in the conventional fashion [217].

A recent systematic review assessed the effectiveness and harms of using kidneys with small renal tumours, from deceased or living donors, as a source for renal transplantation and it reported that five year overall and graft survival rates were 92% and 95.6%, respectively [217]. Tumour excision was performed *ex-vivo* in all cases except for two (107/109 patients), and the vast majority of excised tumours were RCCs (88/109 patients), with clear-cell subtype the most common [217]. This systematic review, although with low-level evidence, suggested that kidneys with small renal masses are an acceptable source for renal transplantation and do not compromise oncological outcomes with similar functional outcomes to other donor kidneys.

Summary of evidence	LE
Tumour excision was performed *ex-vivo* in all cases except for two (107/109 patients).	2b
Overall survival rates at one, three and five years were 97.7%, 95.4%, and 92%, respectively.	
Mean graft survival rates at one, three and five years were 99.2%, 95%, and 95.6%, respectively.	

Recommendation	Strength rating
Do not discard a kidney for potential transplantation on the basis of a small renal mass alone.	Weak

3.1.8.2 Malignancy after renal transplantation

Cancer development after kidney transplant has become a major problem as it is one of the main causes of death in this population. Urological cancers, have an increased incidence after kidney transplantation partly due to the increasing age of recipients and their prolonged survival after transplantation.

Treatment of localised PCa following kidney transplantation is challenging due the presence of the kidney graft in the pelvic cavity close to the prostate. Two systematic reviews reported that oncological outcomes following PCa treatment in kidney transplant recipients are comparable to the non-transplanted population [218, 219] and surgery (radical prostatectomy) carried out in tertiary high-volume referral centres, was the treatment choice in 75 to 85% of patients [218, 219]. Marra *et al.* reported cancer-specific survival rates of 96.8% for surgery, 88.2% for radiotherapy with androgen deprivation therapy and 100% for brachytherapy at mean follow-up of 24 months [219]. Hevia *et al.* reported five year cancer-specific survival of 97.5% for surgery, 87.5% for external beam radiation and 94.4% for brachytherapy [218].

Summary of evidence	LE
Surgery (radical prostatectomy) was the most frequently performed treatment for localised PCa after kidney transplant.	2b
Overall oncological outcomes following PCa treatment in kidney transplant recipients were comparable to the non-transplanted population.	2b

Recommendations	Strength rating
Be aware of the presence of a kidney transplant in the pelvis and the possibility of subsequent transplants when planning treatment for prostate cancer.	Strong
Refer kidney transplant patients with prostate cancer to an integrated transplant urology centre.	Strong

3.1.9 Matching of donors and recipients

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches [220-223]. Human leukocyte antigen incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This may lead to cellular and humoral graft rejection. Matching should concentrate on HLA antigens, which impact outcome. Human leukocyte antigens A, B, C as well as DR must be determined in all potential recipients and donors according to current guidelines and national allocation rules [220-225]. Additionally, it is recommended to determine HLA-DQ antigens of donor and recipient. Furthermore, HLA-DP antigen characterisation may be performed, especially for sensitised recipients [220-225].

All patients registered for renal transplantation must have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions [220-225]. Thorough pre-transplant testing for HLA antibodies must be performed according to current recommendations [220-225]. Sera from potential organ recipients should be screened for HLA-specific antibodies every three months or as stipulated by the national and/or international organ exchange organisations [220-225]. In addition, screening for HLA-specific antibodies should be carried out at two and four weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation [220-225]. Highly sensitised patients should have prioritised access to special allocation programmes [222, 223, 225], such as the acceptable mismatch (AM) programme of Eurotransplant [226]. A careful analysis of HLA antibody specificities must be carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. The definition of unacceptable HLA antigens should be implemented according to local allocation rules and international recommendations [220-224, 227]. The information on unacceptable HLA antigens should be highlighted with the patient's details in the database of the national kidney-sharing programme, preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity.

To avoid hyper-acute rejection (HAR), adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation in accordance with national and international recommendations [220-223, 225].

Laboratories which provide HLA-testing, HLA antibody testing and cross-matching for transplant centres must have valid accreditation to ensure accuracy and reliability [214, 215, 220-222]. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics [225].

Previously, compatibility for ABO blood group antigens and HLA antigens was of critical importance in kidney transplantation. This may change in the future, e.g. in the new U.S. allocation system A2 and A2B donors are transplanted into B recipients [223]. To avoid an increasing imbalance between demand and supply in deceased donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys [223, 224]. With the introduction of antibody elimination methods, potent immunosuppression and novel agents (e.g. anti B-cell drugs), successful ABO-incompatible living donor transplantations, with good long-term outcomes are possible [228, 229]. However, higher costs and infection rates have been described.

Even the barrier of a positive cross-match due to preformed HLA antibodies is under discussion with newer "desensitisation" techniques available in cases with available living donors [230, 231]. Success rates are lower, antibody-mediated rejections are frequent, but survival may be better compared to waiting list survival on dialysis. While this is a rapidly evolving field, further research is needed to define

standard protocols. Until then such “desensitisation” protocols are experimental and patients undergoing “desensitisation” should be treated in specialised centres, where outcomes are documented. Patients should be informed adequately of the risks and limitations and alternative strategies (e.g. acceptable mismatch programmes, cross-over transplantation and donor chains) should be discussed.

Summary of evidence	LE
Human leukocyte antigen matching is very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches. Matching should concentrate on HLA antigens, which impact outcome.	3
In accordance with national and international recommendations adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation to avoid hyper-acute rejection.	3

Recommendations	Strength rating
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	Strong
Test both the donor and recipient for human leukocyte antigen DQ. Human leukocyte antigen DP testing may be performed for sensitised patients.	Strong
Perform thorough testing for HLA antibodies before transplantation.	Strong
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	Strong

*3.1.10 **Immunosuppression after kidney transplantation***

The principle underlying successful immunosuppression is ‘the balance of survival’. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient’s health. Increased understanding of immune rejection has led to the development of safe modern immune suppression agents [232, 233], which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, ‘graft adaptation‘ occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) [232-234].

Non-specific side effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections [232-234]. All immunosuppressants also have dose-dependent specific side effects. Current immunosuppressive protocols aim to reduce drug-specific side effects using a synergistic regimen. A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs; therefore, reducing side effects whilst still maintaining efficacy due to the synergistic effects of the immunosuppressants.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability [232-235]. It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium [EC-MPS]);
- steroids (prednisolone or methylprednisolone);
- induction therapy (preferably basiliximab in low- and standard-risk patients and anti-thymocyte globulin (ATG) in high-risk patients).

This multidrug regimen reflects the current standard of care for the majority of transplant recipients worldwide [232-234] and may be modified according to local needs and immunological risk. This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed [232-234]. In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side effects, lack of efficacy or protocol-driven requirements.

Recommendation	Strength rating
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	Strong

3.1.10.1 Calcineurin inhibitors

Both cyclosporine and tacrolimus have significant side effects that are hazardous to the graft and patient [232-238]. Most importantly, both are nephrotoxic [239, 240], and long-term use is an important cause of chronic allograft dysfunction [241], eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs. Both CNIs are considered to be 'critical-dose' drugs, so that any deviations from exposure can lead to severe toxicity or failure of efficacy. Because of the narrow therapeutic window and the potential for drug-to-drug interaction, CNIs should be monitored using trough levels, which provide a reasonable estimate for exposure.

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival [232-238, 242, 243]. Tacrolimus provided better rejection prophylaxis and was associated with better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus treated patients, in a number of trials [243-247]. Therefore, both CNIs can be used for the effective prevention of acute rejection, but due to higher efficacy tacrolimus is recommended by current guidelines as first-line CNI [233].

For both CNIs several different formulations are available [248-255]. Tacrolimus once-daily dosing seems to be preferred by patients and is associated with better adherence and lower pharmacokinetic variability [256]. Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one formulation to another [257-261]. In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to another CNI can be a successful strategy to reduce side effects [232-234, 262]. Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than twenty years as they have resulted in an exemplary improvement in kidney graft survival [232, 233]. Future protocols aim to minimise or even eliminate CNIs [234, 237, 263-266]. However, until such strategies provide superior outcomes, CNIs remain the standard of care [232, 233, 267]. For severe CNI-related side effects, CNI withdrawal, replacement, or profound reduction may be needed [232, 234, 237, 263, 264]. Special attention should be paid to maintenance patients, who may need less CNIs than previously thought [232, 234, 264, 265, 268].

Summary of evidence	**LE**
Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival however, tacrolimus provided better rejection prophylaxis.	1a
Due to differences in the efficacy and safety profile, the choice of CNI should take into account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1

Recommendations	**Strength rating**
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	Strong
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	Strong
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	Strong

3.1.10.2 Mycophenolates

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid, which inhibits inosine monophosphate dehydrogenase (IMPDH) [269-273]. This is the rate-limiting step for the synthesis of guanosine monophosphate in the *de novo* purine pathway. As the function and proliferation of lymphocytes is more dependent on *de novo* purine nucleotide synthesis compared to other cell types, IMPDH inhibitors may provide more specific lymphocyte-targeted immunosuppression. The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections [232, 235, 269-273]. Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause CMV infections and gastrointestinal side effects, particularly diarrhoea [232, 235, 269-273]. There is also a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus [274].

Both MPA formulations are equally effective with an almost identical safety profile [230, 264, 267, 269-272],

though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking [269-273, 275].

Mycophenolic acid is recommended by guidelines [233]. Standard doses in combination with cyclosporine are MMF 1 g or EC-MPS 720 mg twice daily, although higher initial doses have been suggested [232, 233, 269-273]. Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination [232, 269, 271, 272, 276]. Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine. Most transplant centres use the same starting dose as in cyclosporine-treated patients, however dose reductions are frequent, especially because of gastrointestinal side effects. Weak evidence suggests that MPA dose reductions are associated with inferior outcomes, especially in cyclosporine treated patients [270-272, 277, 278]. Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients [269, 271]. Regular monitoring for polyoma (BK virus) is recommended in patients given MPA combined with tacrolimus [232, 274].

Due to a higher incidence of CMV disease with MPA [273], either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted [232, 279]. Cytomegalovirus prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV-positive recipients and in CMV-negative recipients of CMV-positive organ transplants, because prophylaxis has recently been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients, and leads to better long-term graft survival in kidney allograft recipients.

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients [269, 271, 272, 280].

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients [281] or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function [232-235, 237, 264, 282]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first three years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies [232, 234, 264]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond five years post-transplant and resulted in improved renal function [232, 234, 237, 264, 282, 283].

Summary of evidence	**LE**
The co-administration of MPA with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections.	1
Both MPA formulations, MMF and EC-MPS, are equally effective with an almost identical safety profile.	1
Due to a higher incidence of CMV disease with MPA either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted	1

Recommendation	**Strength rating**
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong

3.1.10.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, mycophenolate reduced rejection rates significantly in prospective randomised trials [232, 233, 235, 269-273]. Although a large, prospective study found that azathioprine may give acceptable results in a low-risk population [284], azathioprine is usually reserved for patients who cannot tolerate MPA [232, 233, 269, 270, 272]. When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters [285].

Recommendation	**Strength rating**
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak

3.1.10.4 Steroids

Steroids have a large number of side effects [232-234, 281], especially with long-term use. Most practitioners still consider steroids (either prednisolone or methylprednisolone) to be a fundamental adjunct to primary immunosuppression, even though successful steroid withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials [232, 234, 235, 281, 286, 287]. The risk of steroid withdrawal depends on the use of concomitant immuno-suppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period [232-235, 281]. A recent study suggests similar efficacy but less diabetes after early steroid withdrawal in low risk patients treated with tacrolimus, mycophenolate and induction (either basiliximab or ATG) [288].

Recommendations	Strength rating
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	Strong
Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	Weak

3.1.10.5 Inhibitors of the mammalian target of rapamycin

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin and suppress lymphocyte proliferation and differentiation [232, 263, 289-291]. They inhibit multiple intracellular pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells. Inhibitors of m-TOR are as effective as MPA when combined with CNIs in preventing rejection [232, 235, 263, 289-291]. However, m-TOR inhibitors exhibit dose-dependent bone marrow toxicity [232, 263, 289-291]. Other potential side effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility. The extensive side effect profile is responsible for inferior tolerability compared to MPA and potential differences in outcome in early years, when higher doses were used [292-297].

To date, no prospective comparative studies have been carried out on the m-TOR inhibitors sirolimus and everolimus. Both m-TOR inhibitors have an almost identical side effect profile and mainly differ in their pharmacokinetic properties [232, 263, 289-291, 298]. Sirolimus has a half-life of about 60 hours, is given once a day and is licensed for prophylaxis in kidney recipients only. Everolimus has a half-life of about 24 hours, is licensed for kidney, liver and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine and can be given simultaneously with cyclosporine, while sirolimus should be given four hours after cyclosporine. The pharmacological drug-drug interaction with cyclosporine is far less relevant for tacrolimus, resulting in the need for a higher starting dose of m-TOR inhibitors in combination with tacrolimus [247, 299, 300]. Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine.

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions [232, 263, 289-291, 298].

When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation, e.g. low-dose cotrimoxazole [232, 289-291]. Most importantly, combination therapy with CNIs aggravates CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic [232]. Several studies suggest less favourable outcomes and increased drug discontinuations due to adverse events for this combination, especially if CNIs are maintained at standard dosages [232, 235, 237, 247, 293, 294, 301-303]. Calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy [263, 289-291, 296, 298].

Several studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side effect profile, particularly wound healing problems and lymphoceles [230, 232, 233, 260, 284, 285, 289, 291]. Other trials suggest that m-TOR inhibitors may replace CNI at later stages, e.g. three months after transplantation, with improvements in renal function, predominately in cyclosporine treated patients [232, 234, 235, 237, 245, 263, 289-291, 293, 294, 296, 304-306]. It is unclear if there is a real benefit in comparison to patients on tacrolimus and MPA [245, 305]. However, there is an increased risk of rejection and development of HLA antibodies [232, 234, 245, 263, 307], which may be offset by the benefit of the non-nephrotoxic immunosuppression. Patients treated with m-TOR inhibitors develop less

leucopenia and opportunistic viral infections, especially less CMV infections compared to MPA [247, 293, 296, 304].

Proteinuria and poor renal function at conversion are associated with inferior outcomes [232, 234, 263, 289-291]. Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.

Due to an anti-proliferative effect and a lower incidence of malignancy in m-TOR inhibitor treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy or skin cancer [232, 234, 263, 289-291, 295-297, 308-311]. Several studies and case reports have suggested that patients with Kaposi sarcoma under CNI therapy benefit from conversion to an m-TOR inhibitor [309].

In summary, m-TOR inhibitors are not recommended as initial immunosuppressive therapy due to their side effect profile and higher discontinuation rates [233]. However, m-TOR inhibitors are a well-studied alternative treatment option.

Summary of evidence	**LE**
Combination therapy with CNI-induced nephrotoxicity. Therefore, CNI dosage should be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy.	1
Take into consideration impaired wound healing and prophylactic surgical measures when m-TOR inhibitors are used as part of the initial immunosuppressive regimen or when patients treated with m-TOR inhibitors undergo major surgery.	1
When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation.	1
Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.	1

Recommendations	**Strength rating**
The m-TOR inhibitors may be used to prevent rejection in patients who are intolerant to standard therapy.	Weak
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	Strong
Do not convert patients with proteinuria and poor renal function to m-TOR inhibitors.	Strong
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	Strong

3.1.10.6 Induction with Interleukin-2 receptor antibodies

Basiliximab, a high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibody is approved for rejection prophylaxis following organ transplantation [232, 233, 235, 312-316]. Basiliximab is given before transplantation and on day four post-transplant. The drug is safe, and IL-2 receptor antibodies have been shown in RCTs to reduce the prevalence of acute cellular rejection by approximately 40% [232, 233, 235, 312-314]. Meta-analyses [235, 312-314] have confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated, large retrospective cohort studies and recent large prospective studies suggest such a benefit [232, 233, 317]. Several large controlled trials support the efficacy and safety of quadruple therapy with tacrolimus, mycophenolate and steroids. Interleukin-2 receptor antibodies may allow early steroid withdrawal [281], although higher rejection rates were described. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs or steroids, while maintaining excellent efficacy and renal function [232-235, 288, 312-314]. Therefore, this regimen is proposed as first-line immunosuppression in patients with low to normal immunological risk [233].

Recommendation	**Strength rating**
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak

3.1.10.7 T-cell depleting induction therapy

Prophylactic immunosuppression regimens in many countries, particularly the U.S., use potent T-cell depleting 'induction' treatments [232, 233, 235, 312, 317-321]. Most frequently, ATG is used for prevention of rejection in immunological high-risk patients, as recommended by guidelines [233, 322]. In addition, these potent biological agents are used for the treatment of severe, steroid resistant rejection episodes [318, 321].

Use of T-cell depleting antibodies in immunological low-risk patients has not been associated with improved long-term outcomes but with an increased risk of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease [232, 233, 235, 312, 318, 319]. Some centres use these agents to provide effective rejection prophylaxis in order to facilitate steroid withdrawal [288, 317, 320].

Recommendation	Strength rating
T-cell depleting antibodies may be used for induction therapy in immunologically high-risk patients.	Weak

3.1.10.8 Belatacept

Belatacept is a fusion protein, which effectively blocks the CD28 co-stimulatory pathway and thereby prevents T-cell activation [263, 323, 324]. Belatacept is intravenously administered and indicated for use as part of a CNI-free regimen together with basiliximab induction, mycophenolate, and corticosteroids. Long-term data from three randomised studies of *de novo* kidney transplant recipients demonstrated better renal function vs. cyclosporine-based immunosuppression, although rates and grades of acute rejection were higher for belatacept in the first year post-transplant [232, 235, 246, 263, 323-329]. In patients receiving a standard deceased or living donor kidney, better graft survival was observed, while similar graft survival rates were found with ECDs. Interestingly, belatacept-treated patients had better preserved histology and developed less donor specific antibodies (DSA) compared to cyclosporine [330]. The long-term safety profile of belatacept treated patients was similar to cyclosporine controls, less belatacept treated patients developed metabolic complications or discontinued treatment due to adverse events [328, 329, 331, 332]. In addition, the option of converting patients (either stable patients or due to CNI or m-TOR associated toxicity) was explored with promising initial results [326, 333-335]. Specific safety signals include a higher rate of post-transplant lymphoproliferative disorder (especially in Epstein-Barr virus (EBV) negative patients), more herpes infections, and tuberculosis in patients from endemic areas [263, 323, 324]. Belatacept was approved in the U.S. and in Europe for EBV positive patients, but is not yet available in many countries. Additional studies are ongoing to fully explore the value of this compound.

Recommendation	Strength rating
Belatacept may be used for immunosuppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

*3.1.11 **Immunological complications***

Immunological rejection is a common cause of early and late transplant dysfunction [233, 336-339]. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Today two main types of immunological reactions are distinguished, T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR) [233, 336-338]. Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection (HAR), acute rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

The ultimate standard for the diagnosis of rejection is transplant biopsy [233], because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy and biopsies should be classified according to the most recent Banff criteria [340], which are the basis for prognosis and treatment [231, 336, 339]. Renal transplant biopsy should be conducted preferably under US control, using an automated needle biopsy system (e.g. Tru-Cut biopsy gun) [233, 336] with a 16 G needle to assure specimen adequacy. The biopsy procedure is considered safe but complications such as bleeding and AV fistulas may occur [233, 341, 342]. The reported risk of major complications (including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss) is approximately 1%. Most important contraindications are anti-coagulant therapy including anti-platelet agents and uncontrolled hypertension.

Summary of evidence	LE
There must be routine access to US-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a rapid and clear-cut diagnosis of rejection or other type of allograft dysfunction.	2
Steroid treatment for rejection may start before the renal biopsy is performed.	2

Recommendations	Strength rating
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	Strong
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	Strong
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	Strong
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	Strong
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	Strong
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	Strong
Reassess the immunosuppressive therapy of all patients with rejection, including patient adherence to the medication, which is of particular importance in late rejections.	Strong

3.1.11.1 Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft [220, 233, 336, 337]. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation. It occurs in ABO-incompatible grafts due to the presence of high titres of pre-existing iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies. With the development of the cross-match test before transplantation, HAR has become an extremely uncommon complication [220]. Imaging and histology reveals generalised infarction of the graft, which has to be treated by graft nephrectomy. Therefore, prevention is crucial, either by avoidance of high iso-antibodies against incompatible blood group antigens in case of an ABO-incompatible renal transplant and/or by performing a regular cross-match before transplantation (see section 3.1.8).

Recommendation	Strength rating
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	Strong

3.1.11.2 Treatment of T-cell mediated acute rejection

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience rather than on clinical evidence [233, 321, 336]. Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for three days. Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another three day course of pulsed methylprednisolone therapy [233, 336]. In addition, baseline immunosuppression should be optimised to ensure adequate drug exposure [233, 336]. In severe rejection, a conversion from cyclosporine to tacrolimus and/or from azathioprine to mycophenolate is recommended [233, 336].

T-cell depleting biological agents, such as ATG may be given in severe steroid-refractory cases [233, 318, 321, 336]. If biological agents are used, other immunological suppression should be adapted and daily T-cell monitoring should be considered to minimise the dose of the biological agent [318]. Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately.

Recommendations	Strength rating
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	Strong
In severe or steroid-resistant rejection, use intensified immunosuppression, high-dose steroid treatment, and eventually T-cell depleting agents.	Strong

3.1.11.3 Treatment of antibody mediated rejection

Antibody mediated rejection is treated in a similar way as T-cell mediated rejection [233, 318, 336, 343-346]. Treatment relies on retrospective studies and empirical treatment guidelines. Treatment with a steroid bolus (at least three days of 500 mg/day) and adequate maintenance therapy with mycophenolate and tacrolimus and sufficient tacrolimus trough levels are common in acute ABMR [233, 336, 343-346]. Although T-cell depleting agents such as ATG appear to have limited value they are frequently used during mixed acute rejection [241]. There are controversial data on the utility of the anti-CD20 antibody, rituximab [233, 321, 336, 343-348]. A retrospective series suggests aggravated toxicity, when rituximab is combined with ATG [349], or steroids [321].

Some centres advocate intravenous immunoglobulin (IVIG) [233, 336, 343-348], which may modulate and/or suppress antibody production. Intravenous immunoglobulin alone seems insufficient for effective treatment and IVIG is used today in a multimodal regimen. Dosages vary widely from 0.2-2.0 g/kg bodyweight, and no comparative studies (e.g. on the dose or optimal concomitant immunosuppression) have been published.

In addition, to drug therapy most centres also try to remove antibodies using plasmapheresis or immune-adsorption columns. Retrospective and prospective case series clearly suggest efficacy [233, 336, 343-348], although details of the procedures vary widely.

Treatment recommendations for chronic ABMR lack firm evidence, and treatment appears to be less successful [336, 343, 345]. Treatment relies on the same principles as for acute ABMR [233, 318, 336, 343-346, 348]. Most centres have similar treatment algorithms and perform antibody elimination together with IVIG and eventually add anti-CD20 and/or bortezomib. Unfortunately, prospective trials on efficacy and side effects are lacking.

In summary, several regimens have proven some efficacy in ABMR. However, except for a beneficial effect of early antibody removal, the lack of firm evidence does not permit evidence-based recommendations for treatment. As a consequence, prevention of ABMR by adequate pre-transplant screening, regular DSA monitoring, avoidance of suboptimal immunosuppression and reinforcement of adherence are crucial [220, 336, 348, 350].

Recommendation	Strength rating
Treatment of antibody mediated rejection should include antibody elimination.	Strong

3.1.12 ***Follow-up after transplantation***

Long-term graft function is of critical importance for the success of a transplant [233, 234]. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen. Complications of immunosuppression occur frequently including specific complications of the different drugs as well as over immunosuppression (namely opportunistic infections and malignancy) [233, 234]. The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population [233, 351, 352]. Cardiovascular disease is the most frequent cause of death in renal allograft recipients [233, 353, 354]. Other important long-term problems are non-adherence, the development of anti-HLA antibodies, recurrence of the original disease and CNI-associated nephrotoxicity [233, 234].

3.1.12.1 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy

Many patients lose their grafts due to chronic allograft dysfunction [233, 234, 355]. Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA) [356]. Some patients will have immunological chronic ABMR [357], as discussed in section 3.1.11.3. Interstitial fibrosis and tubular atrophy takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months [233, 355, 356]. It is likely that IF/TA is more common in patients who have had early attacks of acute rejection or infection. The main differential diagnosis is chronic nephrotoxicity [358], which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney [233, 355, 356].

Diagnosis is by renal biopsy [233, 355]. In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen [201-203, 263, 264]. Conversion to m-TOR inhibitors is an option for patients without significant proteinuria (< 800 mg/day), but moderate renal function [232-234]. Alternatively, successful conversion to a mycophenolate based regimen has been described, especially in patients beyond the first three years post-transplant [232, 234, 264]. If there is intolerance to m-TOR inhibitors or MPA, conversion to belatacept or an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance [333]. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA [234, 264].

In patients with proteinuria, intervention with an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker [233, 355] together with tight blood pressure control may slow down renal progression. Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease [233]. However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Summary of evidence	**LE**
Regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen.	4
Annual screening should include a dermatological examination, cardiovascular history and exam, tumour screening (including a nodal examination, faecal occult screening, chest x-ray, gynaecological and urological examination), and an abdominal US, including US of the native and transplanted kidney. If appropriate, further diagnostic tests should be prompted to treat or slow down the progression of any identified complication.	4
In patients diagnosed early with IF/TA, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA.	1
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4

Recommendations	**Strength rating**
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	Strong
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	Strong
Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immunosuppression and complications after renal transplantation. Changes in these parameters over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	Strong
Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	Strong
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor (CNI) therapy and/or with histological signs suggestive of CNI toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider CNI reduction or withdrawal.	Strong
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	Strong

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5. CONFLICT OF INTEREST

All members of the EAU Renal Transplantation Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Thromboprophylaxis in Urological Surgery

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and objectives

Due to the hypercoagulable state induced by surgery, serious complications of urological surgery include deep vein thrombosis (DVT) and pulmonary embolism (PE) - together referred to as venous thromboembolism (VTE) - and major bleeding [1-4]. Decisions regarding pharmacologic thromboprophylaxis in urologic surgery involve a trade-off between decreased risk of (VTE) and increased risk of bleeding [1-3]. Currently, there exists substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries [5-7]. This variation is unsurprising when one considers that recommendations from national and international guidelines often conflict [2].

To date, existing recommendations for thromboprophylaxis have been limited by a lack of urology-specific evidence [2]. Decisions regarding thromboprophylaxis require both estimates of relative effects on VTE and bleeding, and absolute risks of VTE and bleeding in the absence of prophylaxis (the latter is refered to as baseline risk). Substantial evidence from randomised control trials (RCTs) across a range of surgical procedures is available, and it is reasonable to assume that relative effects of prophylaxis are similar across surgical procedures. Evidence regarding baseline risk across urological procedures is, however, more limited, and systematic summaries of the available evidence have thus far been unavailable [1, 3].

To develop these guidelines, the Panel conducted systematic reviews of the baseline risk of VTE and bleeding in a wide variety of urological procedures [1, 8, 9]. These reviews provide a stronger evidence base for urological thromboprophylaxis guidelines than has been previously available.

Utilising this newly summarised evidence [8, 9], these Guidelines from the European Association of Urology (EAU) Working Panel on Thromboprophylaxis in Urological Surgery provide practical evidence-based guidance regarding post-surgery thromboprophylaxis and peri-operative management of antithrombotic agents in urology.

Clinicians who wish to implement our recommendations should bear in mind that guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to guide decisions that must also take into account patients' values and preferences as well as their individual circumstances. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel consists of physicians/methodologists with expertise from urology, internal medicine, haematology, gynaecology and clinical epidemiology. Although the Guidelines are written primarily for urologists, they can also be used by other physicians, patients or other interested parties.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Thromboprophylaxis in Urological Surgery Guidelines. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guidelines/.

1.4 Publication history

These EAU Guidelines on Thromboprophylaxis in Urological Surgery are the first of their kind.

2. METHODS

2.1 Guideline methodology

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations [10-12].

GRADE offers four levels of evidence quality, reflecting the degree of certainty or confidence in the evidence: high, moderate, low, and very low [11]. For relative treatment effect, RCTs are high-quality evidence

and observational studies are low-quality evidence. For baseline risk (such as risk of VTE post-surgery), observational studies are high-quality evidence. Quality may be rated down as a result of limitations in study design or implementation (risk of bias), imprecision of estimates (wide confidence intervals), inconsistency (variability in results), indirectness of evidence, or publication bias. Quality may be rated up on the basis of a very large magnitude of effect, a dose-response gradient, and if consideration of all plausible biases would reduce an apparent treatment effect, or create an effect when none is apparent. The lowest quality of any critical outcome represents the overall quality of evidence.

The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak [12]. Strong recommendations mean that all or virtually all informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Weak recommendations mean that patients' choices will vary according to their values and preferences, and that clinicians must ensure that patients' care is in keeping with their values and preferences through shared decision-making. Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence (certainty in estimates), and nature and variability of values and preferences.

Post-operative thromboprophylaxis and peri-operative management of antithrombotic agents in urology are discussed seperately. Specific methods are presented in the context of the relevant recommendations.

3. GUIDELINE

3.1 Thromboprophylaxis post-surgery

*3.1.1 **Introduction***

This guideline provides procedure and patient risk-specific guidance weighing the benefit of reduced VTE with the harm of increased bleeding. The Panel provides recommendations for numerous urologic procedures with a simple and practical patient risk stratification scheme.

*3.1.2 **Outcomes and definitions***

The Panel defined non-fatal and fatal symptomatic VTE and non-fatal and fatal major bleeding as key outcomes. Venous thromboembolism was defined as symptomatic DVT or PE and major bleeding was defined as bleeding requiring re-operation or intervention (such as angioembolisation). Transfusion, indwelling catheter, or change in hemoglobin levels were not considered as part of "major bleeding".

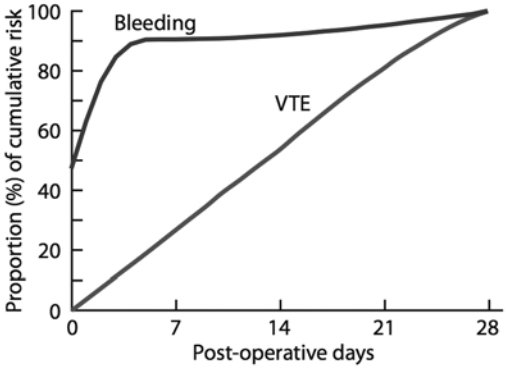
*3.1.3 **Timing and duration of thromboprophylaxis***

High-quality evidence suggests that, of the cumulative risk during the first four weeks post-surgery, approximately 50% of major bleeds occur between surgery and the next morning and approximately 90% during the first four post-surgical days. In contrast, the risk of VTE is almost constant during these first four post-surgical weeks (Figure 1) [1, 13-15].

There are no direct comparisons of the same agent administered before versus after surgery. Recent studies with direct-acting oral anticoagulants (DOACs) in orthopedic surgery have, however, suggested that, relative to starting low molecular weight heparin (LMWH) before surgery, prophylaxis can begin 24 hours after surgery without an increase in VTE but with a decrease in bleeding complications [16, 17]. Given these findings, in addition to the compelling rationale regarding the relative timing of bleeds versus thrombosis (Figure 1), we recommend administration of thromboprophylaxis beginning the day after surgery.

One could argue that prophylaxis be started even later than this, especially in procedures with high bleeding risk. The extent to which an even later start would decrease the effectiveness of thromboprophylaxis is, however, open to question. Given that the further the patient is from surgery the greater the net benefit of prophylaxis (as bleeding risks decreases), while the risk of VTE is just as great in the fourth week after surgery as in the first, the optimal duration of pharmacological prophylaxis is approximately four weeks post-surgery [1, 13-15].

Figure 1: Proportion of cumulative risk (%) of VTE and major bleeding by week since surgery during the first four post-operative weeks



	Proportion of 28-day cumulative bleeding risk
Operation day	47.4%
Post-operative day 1	63.3%
Post-operative day 2	76.6%
Post-operative day 3	84.9%
Post-operative day 4	89.2%
Post-operative day 28	100.0%

Figure modified from: Tikkinen KA, *et al.* Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. *Syst Rev* 2014;3:150. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

*3.1.4 **Basic principles for recommending (or not recommending) post-surgery thromboprophylaxis***

Considerations in the administration of thromboprophylaxis include the relative effect of prophylaxis on key outcomes, baseline risk of key outcomes, as well as patient-related risk (and protective) factors. Finally, one must consider the quality of evidence (certainty in estimates) as well as the relative importance of the relevant outcomes.

3.1.4.1 Effect of prophylaxis on key outcomes

The Panel performed several meta-analyses of RCTs in urology, general surgery, gynecology, and gastrointestinal surgery to inform relative risk estimates of thromboprophylaxis [1, 8, 9]. These meta-analyses demonstrated that anticoagulants (such as LMWH) reduce the relative risk of VTE by approximately 50% and increase the relative risk of major bleeding by approximately 50% [1, 8, 9]. These meta-analyses also demonstrated 50% VTE risk reduction for mechanical prophylaxis [1, 8, 9]. An earlier meta-analysis informing the risk estimates for direct-acting oral anticoagulants yielded similar estimates: a decrease in the relative risk of VTE by approximately 50% and an increase of major bleeding by approximately 50% [18]. The evidence regarding pharmacological prophylaxis was judged as high-quality but low-certainty for mechanical prophylaxis because studies used surrogate outcomes, had very few events, unblinded patients and assessors, and provided almost no information on intermittent pneumatic compression (low-quality evidence) [1, 8, 9].

3.1.4.2 Baseline risk of key outcomes

The Panel performed a series of systematic reviews to provide estimates of absolute risk of symptomatic VTE and bleeding requiring re-operation in urologic surgery [1, 8, 9]. The cited publications, with minor modifications, provide the evidence summary used to develop these recommendations.

3.1.4.3 Patient-related risk (and protective) factors

The Panel conducted a comprehensive literature search addressing VTE and bleeding risk factors in the context of urology, general surgery, gynecology, and gastro intestinal surgery [1]. A model was developed for VTE risk based on the studies reporting the most relevant and high-quality evidence [19-27] (Table 1). However, this model has not been validated and clinicians may consider other factors, including the length of the surgical procedure, oral contraception, immobility, spinal cord injury, and inheritable blood disorders such as

antiphospholipid antibody syndromes, factor V Leiden, antithrombin, protein C or S deficiencies, when making decisions. The Panel's search did not reveal studies demonstrating convincing and replicable risk factors for bleeding [1]; therefore, bleeding risk was not stratified by patient specific factors.

Table 1: Venous thromboembolism (VTE) according to patient risk factors

	Risk	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child).	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

3.1.4.4 From evidence to recommendations

When creating recommendations, the Panel first calculated the net benefit (absolute reduction in VTE risk – absolute increase in bleeding risk) and thereafter considered quality of evidence, separately for both pharmacological and mechanical prophylaxis. The Panel made strong recommendations only if the quality of evidence was moderate or high and net benefit fulfilled threshold criteria (see below); otherwise, the Panel made weak recommendations.

When calculating the net benefit, twice the weight was assigned for major bleeding as for 'any symptomatic VTE'. The most comprehensive guideline published in the field, the American College of Chest Physicians (ACCP) guideline on "Prevention of VTE in Nonorthopedic Surgical Patients" considered symptomatic VTE and major bleeding as having the same weight. However, they included transfusions in their definition of major bleeding [28] which the Panel considered less relevant because: 1) studies often did not report transfusions, 2) criteria for transfusion vary widely between studies, and use of transfusion may have limited relation to underlying bleeding, and 3) transfusions are less important to patients than are reoperations. Given this guideline's focus on only the more severe bleeds – those that require re-operation – the greater weight on preventing bleeding is appropriate.

For each procedure (and separately for each patient risk factor stratum), the net benefit of using pharmacological thromboprophylaxis (benefit from VTE reduction – harm from bleeding) was calculated. After considering the net benefit and quality of evidence, the thresholds presented in Table 2 were indentified.

Table 2: Thresholds of net benefit and quality of evidence used when creating recommendations

Net benefit*	Recommendation	Note
Pharmacological prophylaxis		
≥ 10 per 1000	STRONG in FAVOUR	If based on moderate or high-quality evidence
≥ 10 per 1000	WEAK in FAVOUR	If based on low or very low-quality evidence
≥ 5-10 per 1000	WEAK in FAVOUR	In borderline situations prophylaxis was always favoured as case fatality is higher for VTE than for bleeding [8, 9]
≥ 1-5 per 1000	WEAK AGAINST	
< 1 per 1000	WEAK AGAINST	If based on low or very low-quality evidence
< 1 per 1000	STRONG AGAINST	If based on moderate or high-quality evidence
Mechanical prophylaxis		
≥ 2.5 per 1000	WEAK in FAVOUR	
< 2.5 per 1000	WEAK AGAINST	

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). The net benefit is positive when the value of reduced VTE is greater than increased bleeding.

These thresholds reflect value and preference considerations for which there is limited evidence available [29]. A recent multinational study found that the median threshold net benefit at which women with a history of VTE were willing to accept use of heparin to prevent VTE during pregnancy or the post-partum period is 30 in 1,000 [30]. In that study, the use of prophylaxis spanned the entire duration of pregnancy and continued during the

post-partum period. As post-surgery prophylaxis has a much shorter duration, and is thus less burdensome, our threshold of strong recommendation when net benefit is 10 in 1,000 or more is consistent with this evidence. As mechanical prophylaxis is typically used for a shorter duration than the Panel recommend for pharmacological prophylaxis [31], a lower threshold for mechanical prophylaxis was used.

Making a recommendation regarding thromboprophylaxis requires trading off VTE reduction against bleeding increase, and thus placing a relative value on the two events. A serious bleed (defined as bleeding requiring re-operation or intervention) was considered twice as important as a VTE (defined as symptomatic DVT or PE) event. For patients who feel very differently about this relative value judgment, the Panel's recommendations may not be optimal.

3.1.5 General statements for all procedure-specific recommendations

Consistent with GRADE guidance [32], a single good practice statement was made in which the supporting evidence is compelling, though indirect, and which was not summarised systematically. This association between early ambulation and decreased post-operative complications, in particular decrease in VTE, and early discharge from hospital is convincing. Further, early ambulation has no important adverse consequences. Therefore, the Panel believes that early ambulation for all patients after surgery represents good clinical practice.

The following apply to all recommendations for pharmacologic prophylaxis:

- All recommendations are based on a starting time of the morning after surgery.
- The optimal duration of prophylaxis for all recommendations is approximately four weeks post-surgery.
- There are number of acceptable alternatives for pharmacologic prophylaxis (Table 3).

Table 3: Alternative regimens for pharmacological prophylaxis

Pharmacological agent	Dosage*
Low molecular weight heparins:	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux†	2.5 mg injection once a day
Direct acting oral anticoagulants†:	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

** Dosages may not apply in renal impairment.*

† Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

3.1.6 Recommendations

Ambulatory day surgery

R1. In all patients undergoing minor ambulatory day surgery (for example, circumcision, hydrocelectomy and vasectomy), the Panel recommends against use of pharmacological prophylaxis (***strong, moderate-quality evidence***), and against use of mechanical prophylaxis (***strong, moderate-quality evidence***).

Note: The Panel is of the opinion that these patients have risk of VTE close to the general population with an increased risk of bleeding.

Open radical cystectomy

R2. In all patients undergoing open radical cystectomy, the Panel recommends use of pharmacological prophylaxis (***strong, moderate or high-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Robotic radical cystectomy

R3. In all patients undergoing robotic radical cystectomy, the Panel suggests use of pharmacological prophylaxis (***weak, low-quality evidence***), and suggest use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Table 4: Procedure-specific evidence summaries with recommendations for radical cystectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Cystectomy, Open	Venous thromboembolism	Low-risk	29	13	Moderate	Strong, for	Weak, for
		Medium-risk	58	27	High	Strong, for	Weak, for
		High risk	116	56	High	Strong, for	Weak, for
	Bleeding requiring reoperation		3.0		Moderate/ High		
Cystectomy, Robotic	Venous thromboembolism	Low-risk	26	11	Low	Weak, for	Weak, for
		Medium-risk	52	24	Low	Weak, for	Weak, for
		High risk	103	50	Low	Weak, for	Weak, for
	Bleeding requiring reoperation		3.0		Low		

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). For instance, in medium-risk patients undergoing open radical cystectomy, use of pharmacological prophylaxis, such as LMWH, beginning first post-surgery day for four weeks decreases absolute risk of VTE by 29 per 1,000 and increases absolute risk of bleeding by 0.8 per 1,000 (Figure 1). As twice the weight for major bleeding was assigned as for VTE, the net benefit is 27 per 1,000.

Laparoscopic radical prostatectomy

R4. For patients undergoing laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***) and suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); for those at moderate and high risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate or high quality evidence***) and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R5. For patients undergoing laparoscopic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R6. For patients undergoing laparoscopic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, high-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Open radical prostatectomy

R7. For patients undergoing open radical prostatectomy without PLND or with standard PLND, for those at low risk of VTE, the use of pharmacologic prophylaxis is suggested (***weak, moderate-quality evidence***); for those at medium and high risk, the use of pharmacologic prophylaxis is recommended (***strong, moderate or high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R8. For all patients undergoing open radical prostatectomy with extended PLND, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate or high-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Robotic radical prostatectomy

R9. For patients undergoing robotic radical prostatectomy without PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***) and suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); for those at medium and high risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***) and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R10. For patients undergoing robotic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R11. For patients undergoing robotic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Table 5: Procedure-specific evidence summaries with recommendations for radical prostatectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Prostatectomy, Laparoscopic without pelvic lymph node dissection (PLND)	Venous thromboembolism	Low-risk	4.0	-1.7	Moderate	Strong - against	Weak – against
		Medium-risk	8.0	0.30	Moderate	Weak - against	Weak - for
		High-risk	15	4.0	High	Weak - against	Weak - for
	Bleeding requiring reoperation		7.0		Moderate		
Prostatectomy, Laparoscopic with standard PLND	Venous thromboembolism	Low-risk	8.0	-1.3	Moderate	Strong - against	Weak - for
		Medium-risk	15	2.2	Moderate	Weak - against	Weak - for
		High-risk	30	10	High	Strong - for	Weak - for
	Bleeding requiring reoperation		10		Moderate		
Prostatectomy, Laparoscopic with extended PLND	Venous thromboembolism	Low-risk	15	0.10	Moderate	Weak - against	Weak - for
		Medium-risk	30	7.6	High	Weak - for	Weak - for
		High-risk	60	23	High	Strong - for	Weak - for
	Bleeding requiring reoperation		14		Moderate		
Prostatectomy, Open without PLND	Venous thromboembolism	Low-risk	10	4.5	Moderate	Weak - for	Weak - for
		Medium-risk	20	9.5	Moderate	Strong - for	Weak – for
		High-risk	39	19	High	Strong - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		

Prostatectomy, Open with standard PLND	Venous thrombo-embolism	Low-risk	20	8.9	Moderate	Weak – for	Weak - for
		Medium-risk	39	18	High	Strong - for	Weak - for
		High-risk	79	38	High	Strong -for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Open with extended PLND	Venous thrombo-embolism	Low-risk	39	18	Moderate	Strong - for	Weak - for
		Medium-risk	79	38	High	Strong - for	Weak - for
		High-risk	157	77	High	Strong - for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Robotic without PLND	Venous thrombo-embolism	Low-risk	2.0	-1.1	Moderate	Strong - against	Weak - against
		Medium-risk	5.0	0.40	Moderate	Weak - against	Weak - for
		High-risk	9.0	2.4	Moderate	Weak - against	Weak - for
	Bleeding requiring reoperation		4.0		Moderate		
Prostatectomy, Robotic with standard PLND	Venous thrombo-embolism	Low-risk	5.0	-0.7	Moderate	Strong - against	Weak - for
		Medium-risk	9.0	1.3	Moderate	Weak - against	Weak - for
		High-risk	19	6.3	Moderate	Weak - for	Weak - for
	Bleeding requiring reoperation		6.0		Moderate		
Prostatectomy, Robotic with extended PLND	Venous thrombo-embolism	Low-risk	9.0	0.3	Moderate	Weak - against	Weak - for
		Medium-risk	19	5.3	Moderate	Weak - for	Weak - for
		High-risk	37	14	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		8.0		Moderate		

Nephrectomy

R12. For patients undergoing laparoscopic partial nephrectomy, for those at low and medium-risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, low-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R13. For all patients undergoing open partial nephrectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R14. For patients undergoing robotic partial nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R15. For patients undergoing laparoscopic radical nephrectomy, for those at low or medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R16. For patients undergoing open radical nephrectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R17. For all patients undergoing radical nephrectomy with thrombectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R18. For all patients undergoing open nephroureterectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 6: Procedure-specific evidence summaries with recommendations for kidney procedures for cancer

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Nephrectomy, Laparoscopic partial	Venous thromboembolism	Low-risk	11	-3.4	Low	Weak - against	Weak – for
		Medium-risk	21	1.6	Low	Weak - against	Weak – for
		High-risk	42	12	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		17		Low/ Moderate		
Nephrectomy, Open partial	Venous thromboembolism	Low-risk	10	4.5	Very low	Weak - for	Weak – for
		Medium-risk	20	9.5	Very low	Weak - for	Weak – for
		High-risk	39	19	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		
Nephrectomy-Robotic partial	Venous thromboembolism	Low-risk	10	2.4	Moderate	Weak - against	Weak – for
		Medium-risk	19	6.9	Moderate	Weak - for	Weak – for
		High-risk	39	17	high-quality	Strong - for	Weak - for
	Bleeding requiring reoperation		5.0		Moderate		
Nephrectomy, Laparoscopic radical	Venous thromboembolism	Low-risk	7.0	0.9	Very low	Weak - against	Weak – for
		Medium-risk	13	3.9	Very low	Weak - against	Weak – for
		High-risk	26	10	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		5.0		Very low		
Nephrectomy, Open radical	Venous thromboembolism	Low-risk	11	5.2	Low	Weak - for	Weak – for
		Medium-risk	22	11	Low	Weak - for	Weak – for
		High-risk	44	22	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		
Radical nephrectomy with thrombectomy	Venous thromboembolism	Low-risk	29	4.0	Very low	Weak - for	Weak - for
		Medium-risk	58	19	Very low	Weak - for	Weak - for
		High-risk	116	48	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		20		Very low		
Open nephroureterectomy	Venous thromboembolism	Low-risk	16	7.7	Very low	Weak - for	Weak - for
		Medium-risk	31	15	Very low	Weak - for	Weak - for
		High-risk	62	31	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		

R19. For all patients undergoing primary nerve sparing RPLND, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 7: Procedure-specific evidence summaries with recommendations for primary nerve sparing retroperitoneal lymph node dissection

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharma-cological prophylaxis*	Certainty in estimate	Recommendations for pharma-cological prophylaxis	Recommendations for mechanical prophylaxis
Primary nerve sparing retroperitoneal lymph node dissection	Venous thrombo-embolism	Low-risk	23	10	Very low	Weak - for	Weak – for
		Medium-risk	45	21	Very low	Weak - for	Weak – for
		High-risk	91	44	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		2.0		Very low		

Non-cancer urological procedures

R20. For all patients undergoing transurethral resection of the prostate (TURP) or equivalent procedures, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); and for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R21. For patients undergoing laparoscopic donor nephrectomy or open donor nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests against use of mechanical prophylaxis (***weak, very low or low-quality evidence***); for medium risk patients, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***); and for high risk patients, the Panel suggests use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***).

R22. For all patients undergoing open prolapse surgery or reconstructive pelvic surgery, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, very low or low-quality evidence***); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***).

R23. For all patients undergoing percutaneous nephrolithotomy, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, very low-quality evidence***); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 8: Procedure-specific evidence summaries (with recommendations) for non-cancer procedures

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharma-cological prophylaxis*	Certainty in estimate	Recommendations for pharma-cological prophylaxis	Recommendations for mechanical prophylaxis
Transurethral resection of the prostate (TURP) or equivalent	Venous thrombo-embolism	Low-risk	2.0	-0.1	Low	Weak - against	Weak - against
		Medium-risk	4.0	0.9	Low	Weak - against	Weak - against
		High-risk	8.0	2.9	Low	Weak - against	Weak - for
	Bleeding requiring reoperation		2.0		Very low		
Donor nephrectomy, laparoscopic	Venous thrombo-embolism	Low-risk	4.0	1.5	Low	Weak - against	Weak – against
		Medium-risk	7.0	3.0	Low	Weak - against	Weak – for
		High-risk	14	6.5	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Low		
Donor nephrectomy, open	Venous thrombo-embolism	Low-risk	3.0	1.0	Very low	Weak - against	Weak – against
		Medium-risk	7.0	3.0	Very low	Weak - against	Weak – for
		High-risk	13	6.0	Very low	Weak - for	Weak – for
	Bleeding requiring reoperation		1.0		Very low		
Recipient nephrectomy, open	Venous thrombo-embolism	Low-risk	13	-5.6	Very low	Weak - against*	Weak - for
		Medium-risk	27	1.4	Very low	Weak - against*	Weak – for
		High-risk	53	14	Very low	Weak – for*	Weak - for
	Bleeding requiring reoperation		23		Very low		
Prolapse surgery, open	Venous thrombo-embolism	Low-risk	2.0	-1.1	Low	Weak - against	Weak – against
		Medium-risk	3.0	-0.6	Low	Weak - against	Weak – against
		High-risk	7.0	1.4	Low	Weak - against	Weak – for
	Bleeding requiring reoperation		4.0		Very low		
Reconstructive pelvic surgery (including sling surgery for stress urinary incontinence and vaginal prolapse surgery)	Venous thrombo-embolism	Low-risk	1.0	-1.1	Very low	Weak - against	Weak – against
		Medium-risk	3.0	-0.1	Very low	Weak - against	Weak – against
		High-risk	5.0	0.9	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		3.0		Very low		
Percutaneous nephrolitho-tomy	Venous thrombo-embolism	Low-risk	2.0	-3.7	Very low	Weak - against	Weak – against
		Medium-risk	4.0	-2.7	Very low	Weak - against	Weak – against
		High-risk	7.0	-1.2	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		9.0		Low		

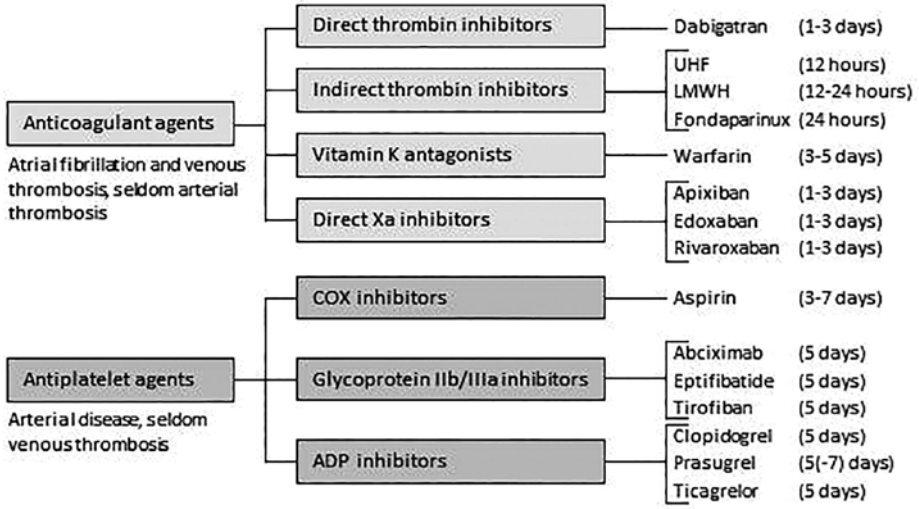
* The Panel understands that patients will receive anticoagulation in the peri-operative period. The recommendations against refer to extended prophylaxis.

3.2 Peri-operative management of antithrombotic agents in urology

*3.2.1 **Introduction***

In principle, there are four options to manage use of antithrombotic agents (Figure 2) during the peri-operative period: 1) to defer surgery until antithrombotic agents are not needed, 2) stop antithrombotic agents prior to surgery and restart some time after surgery, 3) continue through the surgical procedure, or 4) administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding than agents patients are currently using ("bridging").

Figure 2: The most widely used antithrombotic agents in patients undergoing urologic surgery
Required period of stopping drug before surgery (if desired) provided in parentheses.



*3.2.2 **Evidence summary***

Earlier major guidelines addressing perioperative management of antithrombotic agents in surgery [2, 33-35] preceded recent major studies, including large, rigorous randomised trials [15, 36-38]. With respect to anti-platelet agents, a recent large, rigorous randomised trial comparing aspirin to placebo has demonstrated that aspirin increases post-operative bleeding without reducing arterial thrombotic events [15]. These results provide indirect evidence for antiplatelet agents other than aspirin. Although the absence of large, rigorous placebo-controlled trials to inform recommendations for other antiplatelet agents constitutes a limitation, given similar antithrombotic and bleeding profiles, the indirect evidence provides useful information to inform our recommendations.

Recommendations that preceded the recent much higher-quality evidence often recommended, in the peri-operative context, substitution of alternative agents for the antithrombotic agents patients were using on a regular basis [39]. The recent evidence has demonstrated that bridging increases bleeding without preventing thrombosis. The Panel therefore essentially have two recommendations for patients receiving antithrombotic agents regularly and contemplating surgery: 1) discontinue antithrombotic therapy for the period around surgery, or 2) in those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay, continuing antithrombotic therapy or bridging through surgery may be advisable.

*3.2.3 **Recommendations***

Five days is an appropriate time to stop antiplatelet agents before surgery while the optimal time to stop varies across anticoagulants (for details, see Figure 2).

R24. In all patients receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor), except those with very high risk of thrombosis (see recommendations 26 and 27), the Panel recommends stopping antiplatelet agents before surgery and not initiating any alternative antithrombotic therapy (***strong, high-quality evidence***).

R25. In patients in whom antiplatelet agents have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (***strong, moderate-quality evidence***).

R26. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; transient ischemic attack (TIA) or

stroke within 30 days) in whom surgery can be delayed, the Panel recommends delaying surgery (***strong, high-quality evidence***).

R27. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; TIA or stroke within 30 days) in whom surgery cannot be delayed, the Panel suggests continuing the drugs through surgery (***weak, low-quality evidence***).

R28. In all patients receiving anticoagulant agents (unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis (see recommendation 26), the Panel recommends stopping drugs before surgery (see Figure 2) and not initiating any alternative antithrombotic therapy (***strong, high-quality evidence***).

Note: Patients with creatinine clearance < 30 ml/min should not receive dabigatran, apixaban, rivaroxaban or edoxaban.

R29. In patients in whom anticoagulants have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (***strong, moderate-quality evidence***).

R30. In patients with a new VTE, it is recommended that surgery is delayed for at least one month, and if possible three months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis (***strong, high-quality evidence***).

R31. In patients receiving any anticoagulant with a severe thrombophilia, such as antithrombin deficiency and antiphospholipid antibody syndrome, the Panel suggests anticoagulation with either heparin or low molecular weight heparin through surgery, rather than stopping anticoagulation before and after surgery (***weak, low-quality evidence***).

R32. In patients with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, the Panel recommends bridging with LMWH prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively (***strong, high-quality evidence***).

Anticoagulation in these patients involves stopping the warfarin five days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.

4. RESEARCH RECOMMENDATIONS

The evidence base for this guideline is limited. Much of the evidence regarding baseline risk is low, or very low quality [8, 9]. Prospective observational studies to establish baseline risk of VTE and bleeding in a wide variety of urologic procedures, as well as addressing patient risk factors for both thrombosis and bleeding, will be necessary to create more definite guidelines. Examples of procedures in which the evidence base is particularly limited include robotic cystectomy, laparoscopic radical nephrectomy, open nephroureterectomy, TURP and prolapse surgery. To confidently establish the baseline risk of VTE and bleeding for specific surgery will require studies that meet certain methodologic standards, such as comprehensive characterisation of the patient populations and follow-up times, documentation of the prophylaxis used, and explicit criteria with demonstration of reproducibility of judgments for documentation of DVT, PE, and bleeding assessments. Furthermore, the optimal timing and duration of thromboprophylaxis remains unclear. Timing and duration questions will be best addressed by large-scale randomised trials.

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6. CONFLICT OF INTEREST

All members of the Thromboprophylaxis working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a nonprofit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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8. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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