

# 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 7.3 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, a radiotherapist 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. In the course of 2021 two patient representatives have formally joined the MIBC Guidelines Panel. 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 Available publications

A quick reference document (Pocket guidelines) is available in print, presenting the main findings of the Primary Urethral Carcinoma Guidelines. This is an abridged version which may require consultation together with the full text version. The most recent scientific summary was published in 2020 [3].

## 1.4 Publication history & summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013. This is the tenth update of this document.

### 1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, where relevant, resulting in a changed recommendation in Section 4.4 Guideline for staging and classification systems.

Recommendation	Strength rating
Use the 2017 TNM classification and 2022 WHO grading systems for pathological staging and grading of primary urethral carcinoma.	Strong

# 2. METHODS

## 2.1 Data identification

For the 2023 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 July 14<sup>th</sup> 2021 and August 8<sup>th</sup> 2022. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 122 unique records were identified, retrieved, and screened for relevance. Five new references were included in this 2023 publication. A detailed search strategy is available online: <https://uroweb.org/guidelines/primary-urethral-carcinoma/publications-appendices>.

For each recommendation within the guidelines there is an accompanying online strength rating form which includes the assessment of the benefit to harms ratio and patients' preferences for each recommendation.

The strength rating forms draw on the guiding principles of the GRADE methodology but do not purport to be GRADE [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 2021.

# **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 updated analysis of the Surveillance, Epidemiology and End Results (SEER) database (2004–2016), 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]. After matching for tumour and patient characteristics, women present with higher disease stage and exhibited higher cancer-specific mortality (CSM) [12].

## **3.2 Aetiology**

For male primary urethral carcinoma, various predisposing factors have been reported, including urethral strictures [13, 14], chronic irritation after intermittent catheterisation/urethroplasty [15–17], external beam irradiation therapy (EBRT) [18], radioactive seed implantation [19], chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e., condylomata associated with human papilloma virus 16) [20, 21] and lichen sclerosis [14]. In female urethral carcinoma, urethral diverticula [22–24] and recurrent urinary tract infections [25] have been associated with primary urethral carcinoma. Mid-urethral sling meshes have not been associated with an increased risk of primary urethral carcinoma [26]. Clear-cell adenocarcinoma (AC) may also have a congenital origin [27, 28].

## **3.3 Histopathology and genomic profiling**

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, 29].

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 [30]. 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%) [31, 32]. Primary UC with unconventional histological subtypes are very rare and exhibit a dismal prognosis [33].

## 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 8<sup>th</sup> 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 [34].

**Table 4.1: TNM classification (8<sup>th</sup> edition) for urethral carcinoma [9]**

<b>T - Primary Tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
<b>Urethra (male and female)</b>	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma <i>in situ</i>
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)
<b>Urothelial (transitional cell) carcinoma of the prostate</b>	
Tis pu	Carcinoma <i>in situ</i> , involvement of prostatic urethra
Tis pd	Carcinoma <i>in situ</i> , 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 spongiosum, 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)
<b>N - Regional Lymph Nodes</b>	
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
<b>M - Distant Metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis

### 4.2 Tumour grade

Non-urothelial urethral carcinoma is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). In primary urothelial carcinoma histological subtypes are extremely rare. Table 4.2 lists the different grading systems according to the WHO 2022 system [35].

**Table 4.2: Histopathological grading of urothelial and non-urothelial primary urethral carcinoma [35]**

<b>Urothelial urethral carcinoma</b>	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated
<b>Non-urothelial urethral carcinoma</b>	
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 [36].

**Table 4.3: Required and recommended elements for pathology reporting of carcinoma of the urethra in urethrectomy specimens [9, 36]**

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	Strength rating
Use the 2017 TNM classification and 2022 WHO grading system for pathological staging and grading of primary urethral carcinoma.	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) [37]. 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%), urethrocuteaneous fistula (10%), abscess formation (5%) or dyspareunia [37].

### 5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [38]. In women, further pelvic examination and palpation of the urethra should be performed. In addition, bimanual examination, when necessary under general anaesthesia, should be

performed for local clinical staging and to assess whether colorectal or gynaecological malignancies are present.

Bilateral inguinal palpation should be done to assess the presence of enlarged LNs, describing location, size, and mobility [39].

### 5.3 Urinary cytology

Urinary cytology is part of the standard work-up of a patient with suspected primary urethral carcinoma. Reporting of urinary cytology findings should follow the Paris system [40]. However, the role of urinary cytology in primary urethral carcinoma is limited since its sensitivity ranges between 55% and 59% [41]. 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 [41].

### 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 [38]. Cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [42].

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 [43]. 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 [44].

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) [36].

### 5.5 Imaging for diagnosis and staging

Radiological imaging of urethral carcinoma aims to assess local staging and to detect lymphatic and distant metastatic spread. In a recent multicentre study, the accuracy of cross-sectional imaging for clinical tumour and nodal staging predicting final pathological staging was found to be 72.9% and 70.6%, respectively [45]. Imaging work-up should include computed tomography (CT) of the chest, abdomen and pelvis for staging, including CT urography for urothelial evaluation. Magnetic resonance imaging (MRI) can be used to evaluate tumour location and size, as well as local tumour extent and presence of regional LN metastases, focusing in particular on inguinal and pelvic LNs [46-50].

For local staging, there is 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 [51].

<sup>18</sup>F-Fluorodeoxyglucose positron emission tomography/MRI has shown to improve the diagnostic evaluation in patients with metastatic disease [52].

### 5.6 Regional lymph nodes

In urethral carcinoma enlarged LNs often represent metastatic disease (~84% of patients) [53-55], which is in contrast to penile cancer where this is the case in ~41% of patients [56]. 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 [57, 58].

### 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	Strength rating
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	Strong



Assess the presence of distant metastases by computed tomography of the thorax and abdomen/pelvis.	Strong
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour and regional lymph node enlargement.	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]. Based on longer follow-up, an analysis of the SEER database, comparing prognostic factors in rare pathological types of primary urethral carcinoma (n = 257) and common pathological groups (n = 2,651), reported 10-year OS rates of 42.4% and 31.9%, respectively [59]. Cancer-specific survival (CSS) rates at five and ten years were 68% and 60%, respectively [60]. 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 [59].

### 6.2 Predictors of survival in primary urethral carcinoma

Previous series reported no substantial difference in 5-year OS rates between the sexes [10, 32, 61], whereas in a recent SEER analysis female patients showed higher stage disease and 5-year CSM despite higher use of multimodal therapy [12, 62]. Prognostic factors of worse survival in patients with primary urethral carcinoma are:

- advanced age (> 65 years) and black race [10, 32, 62, 63];
- higher stage, grade, nodal involvement [54, 64] and metastasis [30];
- increased tumour size and proximal tumour location [30];
- underlying (non-urothelial or unconventional) histology [10, 30, 33, 63–66];
- presence of concomitant bladder cancer [42];
- extent of surgical treatment and treatment modality [30, 63, 64];
- treatment in academic centres [67];
- location of recurrence (urethral vs. non-urethral) [68].

Some limitations have to be considered when interpreting these results as the number of patients included in most studies were low [65].

### 6.3 Summary of evidence for prognosis

Summary of evidence	LE
Prognostic factors for survival in primary urethral carcinoma are: age, gender, 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
In locally-advanced urothelial- and SCC of the urethra, treatment in academic centres improves OS.	3

## 7. DISEASE MANAGEMENT

### 7.1 Treatment of primary urethral carcinoma in males

Previously, treatment of male distal urethral carcinoma followed the procedure for penile cancer, with surgical excision of the primary lesion with a wide safety margin [38]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [69]. Therefore, in the treatment of distal urethral carcinoma the focus of clinicians has shifted towards improving functional outcomes and quality of life (QoL), 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 penile-preserving surgery and additional iliac/inguinal lymphadenectomy (LND) for clinically suspected LN disease [70]. Similar results for the feasibility of penile-preserving surgery have also been reported in recent series [71, 72]. However, a series on patients treated with penile-preserving surgery

for distal urethral carcinoma reported a higher risk of progression in patients with positive proximal margins, which was also more frequently observed in cases with lymphovascular and peri-neural invasion of the primary tumour [73].

### 7.1.1 **Summary of evidence and guidelines for the treatment of 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	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penile preserving surgery is intended.	Strong

## 7.2 **Treatment of localised primary 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 include removal of 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 [39].

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 [74, 75]. In longer-term series with a median follow-up of 153–175 months, local recurrence rates in women undergoing partial urethrectomy with intra-operative 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 [74, 75].

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 [74].

### 7.2.2 **Radiotherapy**

In women, RT was investigated in several older series with a medium follow up of 91–105 months [76]. 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% [76]. Most local failures (95%) occurred within the first two years after primary treatment [76]. 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 [76]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [77]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [76].

### 7.2.3 **Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in females**

Summary of evidence	LE
In females with distal urethral 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	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to females with distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to females with localised urethral tumours but discuss local toxicity.	Weak

## **7.3 Multimodal treatment in locally-advanced urethral carcinoma in both males and females**

### **7.3.1 Introduction**

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with additional RT [78]. Multimodal therapy was often underutilised as shown by Cahn and colleagues in locally-advanced disease (only 16%) notwithstanding promising results [78-81]. In a recent study monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex, and year of treatment ( $p = 0.017$ ). Its use has decreased over time [82]. Treatment in academic centres was reported to result in higher utilisation of neoadjuvant- and multimodal treatment and improved OS in patients with locally-advanced urothelial- and SCC primary urethral carcinoma [67].

### **7.3.2 Preoperative cisplatin-based chemotherapy**

Retrospective studies 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 emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally-advanced urethral carcinoma. In a study using the National Cancer Database in men with primary urothelial carcinoma, NAC was reported to decrease the risk of all-cause mortality, while AC was not associated with an OS benefit, as compared to no chemotherapy in men, with primary urothelial carcinoma neoadjuvant chemotherapy (NAC) was reported to exhibit improved OS compared with adjuvant chemotherapy [83].

In a series of 124 patients, 39 (31%) were treated with peri-operative platinum-based chemotherapy for advanced primary urethral carcinoma (twelve patients received NAC, six received neoadjuvant chemoradiotherapy and 21 adjuvant chemotherapy). Patients who received NAC or chemoradiotherapy for locally-advanced primary urethral carcinoma ( $\geq cT3$  and/or  $cN+$ ) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [84]. 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 [53].

### **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 [85-89]. 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 clinical response was observed in ~80% of patients. 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 [85].

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 [90].

### **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 as 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 [68].

### **7.3.5 Treatment of regional lymph nodes**

Nodal control in urethral carcinoma can be achieved either by regional lymph node (LN) dissection [38], RT [76] or chemotherapy [53]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic LND in all patients with urethral carcinoma [55]. However, in patients with clinically enlarged inguinal/pelvic LNs or invasive tumours, regional LND should be considered as initial treatment since cure might still be achievable with limited disease [38]. It was recently shown that in patients with invasive urethral SCC and  $cN1-2$  disease, inguinal LND conferred an OS benefit [55].

### 7.3.6 **Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both males and females**

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
In locally-advanced urothelial- and SCC of the urethra, treatment in academic centres improves OS.	3

Recommendations	Strength rating
Refer patients with advanced urethral carcinoma to academic centres.	Strong
Discuss treatment of patients with locally-advanced urethral carcinoma within a multidisciplinary team of urologists, radiation-oncologists, and oncologists.	Strong
In locally-advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	Weak
In locally-advanced squamous cell carcinoma (SCC) of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with limited LN-positive urethral SCC.	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 [91]. A systematic review reported patients treated with TURP before BCG show a better local response in the prostatic urethra with a higher disease-free survival (80–100% vs. 63–89%) and progression free survival (PFS) (90–100% vs. 75–94%) than patients in studies in which no TURP was performed [91]. Risk of understaging local extension of prostatic urethral cancer at TUR is high in patients with ductal or stromal involvement [92]. 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 [93, 94]. 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 [95].

### 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

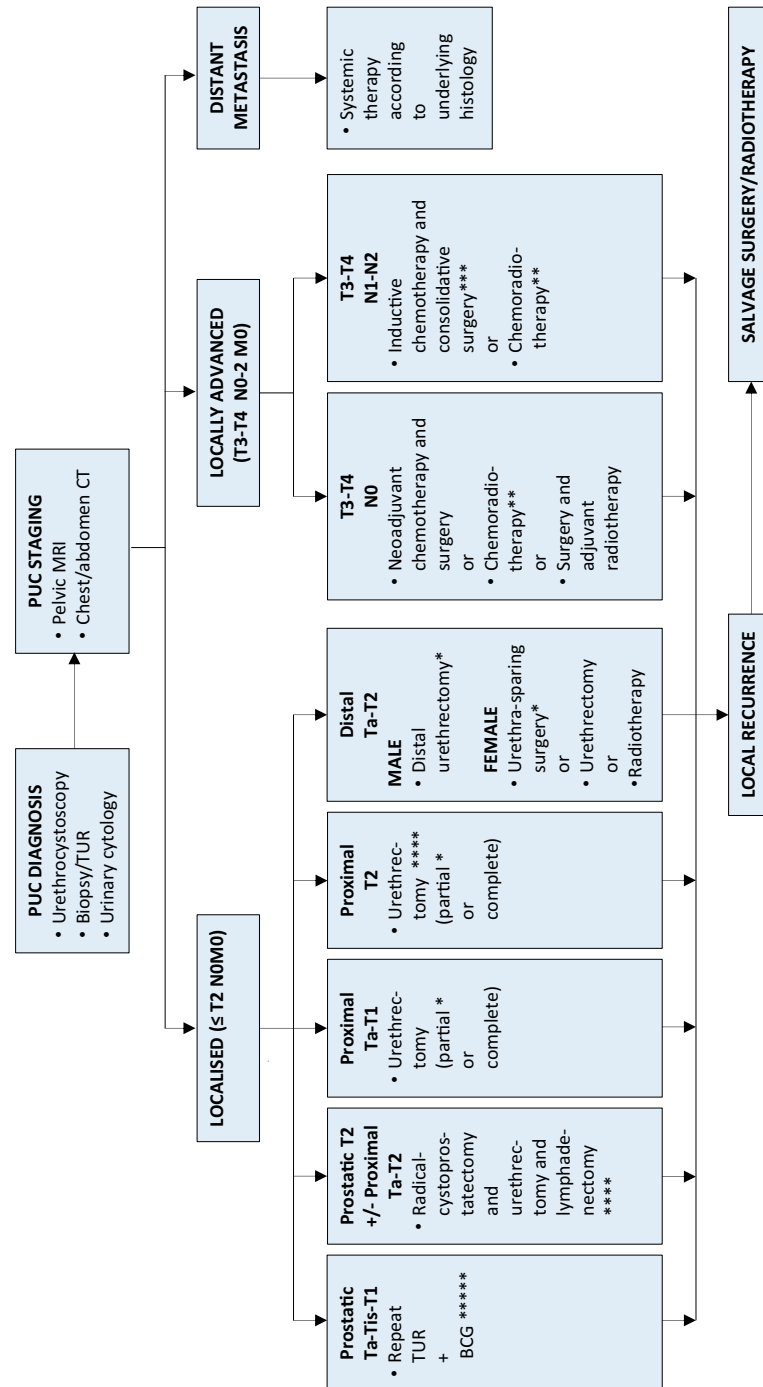
Recommendations	Strength rating
Offer a urethra-sparing approach with transurethral resection (TUR) and bacillus-Calmette Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma <i>in situ</i> of the prostatic urethra and prostatic ducts.	Strong
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	Weak

## 7.5 **Metastatic disease**

A recent analysis of the SEER database reported that patients with M1 disease who underwent primary site surgery did not exhibit any survival benefit [61]. Systemic therapy in metastatic disease should be selected based on the histology of the tumour. The EAU Guidelines on Muscle-invasive and 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 [96].

In addition, there is an urgent clinical need to better address the role of local palliative treatment strategies in primary urethral carcinoma including surgery, which has shown to impact positively on QoL aspects in selected patients with advanced genital cancers [97].

**Figure 7.1: Management of primary urethral carcinoma**



\* Ensure complete circumferential assessment if penile-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 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.

### 8.1 Research priorities

There are clear gaps in the clinical literature related to the diagnosis, management and follow-up of patients with primary urethral carcinoma. As this is a rare disease, data will likely become available through quality registries and datasets, similar to those currently being set up by the eUrogen initiative.

The Panel identified the following topics as of interest:

- 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 therapeutic benefit and clinical safety of programmed cell death (ligand)-1 inhibitors for the treatment of advanced primary urethral carcinoma;
- The role of MRI in the local assessment of response to therapy.

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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 open access available on the European Association of Urology website:  
<http://www.uroweb.org/guidelines/primary-urethral-carcinoma/>.

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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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