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: www.uroweb.org/guidelines/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 sixth update of this document.

1.3.1 Summary of changes

The literature for the complete document has been assessed and updated, where relevant.

2. METHODS

2.1 Data identification

For the 2019 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 November 9th 2017 and June 30th 2018. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 110 unique records were identified, retrieved and screened for relevance. A total of 9 new references were included in this 2019 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 radiochemotherapy 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 malignancies [8] (ICD-O3 topography code: C68.0) [9]. In early 2008, the prevalence of urethral carcinoma in the 28 European Union countries was 4,292 cases with an estimated annual incidence of 655 new cases [10]. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; with a male to female ratio of 2.9:1) [10]. There were differences between European regions; potentially caused by registration or classification [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], and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [19-21]. 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

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, 11]. 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 peri-urethral 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 sponsiosumspongiosum, 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 of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high 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). 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 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) [32, 33, 35]. 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 [35].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [36]. 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 [37].

5.3 Urinary cytology

Cytological assessment of urine specimens in suspect cases of primary urethral carcinoma should be conducted according to the Paris system [38]. The role of urinary cytology in primary urethral carcinoma is limited since its sensitivity ranges between 55% and 59% [39]. 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 [38].

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 [36]. 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.

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [3, 40]. 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. 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 [41].

5.5 Radiological imaging

Radiological imaging of urethral carcinoma aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. Either MRI or CT can be used to evaluate presence of regional LN metastases, focussing in particular on inguinal and pelvic LNs [42]. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (> cT1N0M0) [43-46]. If imaging of the remainder of the urothelium is required, CT urography should be performed [47].

5.6 Regional lymph nodes

In contrast to penile cancer (41%) [48] enlarged LNs in urethral carcinoma often represent metastatic disease (84%) [49-51]. 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 [52, 53].

5.7 Summary of evidence and guidelines for diagnostic evaluation and staging

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node 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.	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 five-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 1,615 cases reported five- and ten-year OS rates of 46% and 29%, respectively. Cancer-specific survival (CSS) rates at five and ten years were 68% and 60%, respectively [11].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, five-year OS rate does not substantially differ between the sexes [10, 31]. Predictors of decreased survival in patients with primary urethral carcinoma are:

- advanced age (> 65 years) and black race [10, 31, 54];
- stage, grade, nodal involvement [50] and metastasis [29];
- tumour size and proximal tumour location [29];
- extent of surgical treatment and treatment modality [29, 54];
- underlying histology [10, 54, 55];
- presence of concomitant bladder cancer [40];
- location of recurrence (urethral vs. non-urethral) [56].

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) [55]. In the large SEER database (n = 2,046), therapy is not well specified in relation to survival [29]. Finally, in contrast to the RARECARE project [10], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [29].

6.3 Summary of evidence for prognosis

Summary of evidence	LE
Risk 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 has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [36]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [57]. 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 [58]. 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 [59, 60]. 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 [61].

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 [36].

Recent series have reported outcomes in women with mainly distal urethral carcinoma undergoing primary treatment with urethra-sparing surgery or radiotherapy (RT) compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [62-64]. In long-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 required additional reconstructive surgery [63].

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 [62].

7.2.2 Radiotherapy

In women RT was investigated in several older long-term series with a medium follow up of 91-105 months [58, 65]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the five-year local control rate was 64% and seven-year CSS was 49% [65]. Most local failures (95%) occurred within the first two years after primary treatment [65]. 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 [65]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [66]. 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 [65].

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 localised 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. Multimodal therapy is often underutilised (16%) in locally advanced disease. It confers an OS benefit in primary urethral carcinoma of urothelial origin [67-69]. 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 [70].

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 [71].

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 [72]. 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 [49].

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 [72-77]. 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 five-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 [73].

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 [78].

7.3.5 *Treatment of regional lymph nodes*

Nodal control in urethral carcinoma can be achieved either by regional LN dissection [36], RT [65] or chemotherapy [49]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral carcinoma. 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 [36].

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.	4	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 [79, 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% [79, 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
In patients with non-invasive urethral carcinoma or carcinoma *in situ*, 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].

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/.

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