Guidelines on Primary Urethral Carcinoma

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1. INTRODUCTION

The European Association of Urology (EAU) Guidelines Group on Muscle-invasive and Metastatic Bladder Cancer has prepared these guidelines to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary UC, in contrast to secondary UC, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary UC is reported after radical cystectomy for bladder cancer (1) (see Chapter 14 of the EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer [2]).

2. METHODOLOGY

A systematic literature search was performed to identify studies reporting urethral malignancies. Medline was searched using the controlled vocabulary of the Medical Subject Headings (MeSH) database, along with a free-text protocol, using one or several combinations of the following terms: *adenocarcinoma, adjuvant treatment, anterior, chemotherapy, distal urethral carcinoma, lower, neoadjuvant, partial, penectomy, penile-preserving surgery, posterior, primary, proximal urethral carcinoma, radiotherapy, recurrence, risk factors, squamous cell carcinoma, survival, transitional cell carcinoma, urethra, urethrectomy, urethral cancer, urinary tract, and urothelial carcinoma*. No randomised controlled trials (RCTs) were identified and articles were selected based on study design, treatment modality and long-term outcomes. Older studies (> 10 years) were considered if they contained historically relevant data or in the absence of newer data.

3. LEVEL OF EVIDENCE AND GRADE OF RECOMMENDATION

References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded according to the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given (3). Due to the fact that primary UC belongs to the family of rare cancers, most studies are retrospective, and recommendations given in these guidelines are mainly based on level 3 evidence.

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 randomisation.
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 Sackett et al. (3).*

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation when there are methodological limitations or disparity in published results.

Alternatively, the absence of a high level of evidence does not preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed - perhaps for ethical or other reasons - and in this case, unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very

important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever these data are available, the Expert Panel will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

**Modified from Sackett et al. (3).*

Publication history

This 2013 guidelines document on Primary Urethral Carcinoma is the first publication on this topic by the EAU. This is the current authorised edition of this guideline.

This document was subjected to blinded peer review prior to publication.

Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements that can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

4. EPIDEMIOLOGY

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies (7) (ICD-O3 topography code: C68.0 [8]).

The RARECARE project, which has been set up to describe the epidemiology of rare urogenital cancers in 64 European population-based cancer registries (covering 32% of the population of the 27 Member States of the European Union (EU), has reported recently on 1,059 new cases of epithelial urethral tumours detected between 1995 and 2002 (9). In early 2008, the prevalence of UC in the 27 EU countries was 4,292 cases with an estimated annual incidence of 655 new cases. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; a male to female ratio of 2.9) (9). There were differences between European regions; potentially caused by registration or classification (9). Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the ≥ 75 years age group (7.6/1,000,000). 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) (10).

5. AETIOLOGY AND RISK FACTORS

For male primary UC, various predisposing factors have been reported, including urethral strictures (11,12), chronic irritation after intermittent catheterisation/urethroplasty (13-15), external beam irradiation therapy (16), radioactive seed implantation (17), and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) (18,19). In female UC, urethral diverticula (20-22) and recurrent urinary tract infections (23) have been associated with primary carcinoma. Clear cell adenocarcinoma may also have a congenital origin (24).

6. HISTOPATHOLOGY

Both the RARECARE project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC; 16-22%) and adenocarcinoma (AC; 10-16%) (9,10). A recent SEER analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma (78%) was most common, and SCC (12%) and AC (5%) were significantly less frequent (25). In women, a recent report of the National Cancer Registry of the Netherlands on primary urethral cancer reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% (26). Several other rare histological types of urethral malignancies have been also described in these studies.

7. CLASSIFICATION

7.1 TNM staging system

In men and women, UC is classified according to the 7th edition of the TNM classification (8) (Table 3). It should be noted that there is a separate TNM staging system for prostatic UC (8). Of note, for cancers occurring in urethral diverticulum stage T2 is not applicable as urethral diverticula are lacking periurethral muscle (27).

Table 3: TNM classification (7th edition) for UC (8). Primary tumour stage is separated into UC and UC of the prostate

T - Primary tumour (men and women)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumour invades other adjacent organs
Primary tumour in prostatic urethra	
Tx	Primary tumour cannot be assessed
Tis pu	Carcinoma *in situ* in the prostatic urethra
Tis pd	Carcinoma *in situ* in the prostatic ducts
T0	No evidence of primary tumour
T1	Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumour invades other adjacent organs
N - Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node ≤ 2 cm in greatest dimension
N2	Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes
M - Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

7.2 Tumour grade

The former 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 PUNLMP, low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately differentiated (G2), and poorly differentiated tumours (G3). Table 4 lists the different grading systems according to the WHO 1973 and 2004 systems (28).

Table 4: Histopathological grading of urothelial and non-urothelial primary UC (28)

PUNLMP	**Papillary urothelial neoplasm of low malignant potential**
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial UC	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Recommendation	**LE**	**GR**
Pathological staging and grading of primary UC should follow the 2009 TNM classification und WHO 2004 grading system.	3	B

8. SURVIVAL

8.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-year overall survival in patients with UC in Europe is 71% and 54%, respectively (9). With longer follow-up, a SEER analysis of 1,615 cases reported median 5- and 10-year overall survival rates of 46% and 29%, respectively. Cancer-specific survival at 5 and 10 years was 68% and 60%, respectively (10).

8.2 Predictors of survival in primary urethral carcinoma

In Europe, mean 5-year overall survival does not substantially differ between the sexes (9). Predictors of decreased survival in patients with primary UC are:

- Advanced age and race (≥ 65 years) (9,29)
- Stage, grade, nodal involvement and metastasis (25)
- Tumour size and proximal tumour location (25)
- Extent of surgical treatment and treatment modality (25, 29)
- Underlying histology (9,26,29)

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) (26). In the large SEER database (n = 2,046), therapy is not well specified in relation to survival (25). Finally, in contrast to the RARECARE project (9), the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients (29).

Conclusion	**LE**
Risk factors for survival in primary UC are: age, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, and type and modality of treatment.	3

9. DIAGNOSIS AND STAGING

9.1 History

When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) (26,30). 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 extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia (30).

9.2 Clinical examination

In men, physical examination should comprise palpation of the extern genitalia for suspicious indurations or masses and digital rectal examination (31). 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 lymph nodes, describing location, size and mobility (32).

9.3 Urinary cytology

The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55 and 59% (33). Detection rate depends on the underlying histological entity. In male patients, the sensitivity for urothelial carcinoma 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 urothelial carcinoma.

9.4 Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology (31). 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 (2). 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 urothelial carcinoma of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate (34).

9.5 Radiological imaging

Radiological imaging of urethral cancer aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is superior to computed tomography (CT) in terms of staging accuracy. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (≥ cT1N0M0 (35-39). If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase (40).

9.6 Regional lymph nodes

In contrast to penile cancer, in which clinically enlarged lymph nodes at initial diagnosis are not uncommon due to inflammatory conditions (41), enlarged lymph nodes in urethral cancer often represent metastatic disease (42). In men, lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drains into the superficial and deep inguinal nodes (43,44).

Nodal control in urethral cancer can be achieved either by regional lymph node dissection (31), radiotherapy (45) or chemotherapy (42). Currently, there is no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral cancer. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease (31).

Conclusion	LE
Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node metastasis.	3

Recommendations	LE	GR
Diagnosis includes urethrocystoscopy with biopsy and urinary cytology.	3	B
CT of the thorax and abdomen should be used to assess distant metastases.	3	B
Pelvic MRI is the preferred method to assess local extent of urethral tumour.	3	B

10. TREATMENT OF LOCALISED PRIMARY URETHRAL CARCINOMA

10.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior urethral cancer has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin (31). Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours (46). Therefore, optimising treatment of distal urethral cancer 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 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease (47). This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have been reported in other retrospective series (30,48).

Recommendation	LE	GR
In localised anterior urethral tumours, penile-preserving surgery is an alternative to primary urethrectomy, if negative surgical margins can be achieved.	3	B

10.2 Treatment of localised urethral carcinoma in females

*10.2.1 **Urethrectomy and urethra-sparing surgery***

In women with localised urethral cancer, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral 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 proximal diversion through appendico-vesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women (31).

Many recent series have reported outcomes in women with mainly anterior urethral cancer undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract (49,50). In long-term series with 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 required additional reconstructive surgery (49,50). Ablative surgical techniques, that is, transurethral resection (TUR) or laser, used for small distal urethral cancer, have also resulted in a considerable local failure rate of 16%, with a cancer-specific survival rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral cancer to prevent local and systemic progression (49).

*10.2.2 **Radiotherapy***

In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months (45,47). With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year cancer-specific survival was 49% (45). Most local failures (95%) occurred within the first 2 years after primary treatment (47). The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam vs. interstitial brachytherapy) was not (45). In one study, the addition of brachytherapy to external beam radiotherapy reduced the risk of local recurrence by a factor of 4.2 (51). Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and haemorrhagic cystitis, with 30% of the reported complications graded as severe (45).

Recommendations	LE	GR
In women with anterior urethral tumours, urethra-sparing surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved intraoperatively.	3	B
In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours.	3	C

11. MULTIMODAL TREATMENT IN ADVANCED URETHRAL CARCINOMA

11.1 Preoperative cisplatinum-based chemotherapy

Recent retrospective studies have reported that modern cisplatinum-based polychemotherapeutic regimens are effective in advanced primary urethral cancer, providing prolonged survival even in lymph-node-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy for achieving long-term survival in patients with locally advanced urethral cancer. The largest retrospective series reported outcomes in 44 patients with advanced primary urethral cancer. Patients were subjected to specific cisplatinum-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72%. The median overall survival of the entire cohort was 32 months. Of note, patients who underwent surgery after chemotherapy had significantly improved overall survival compared with those who were managed with chemotherapy alone (42).

11.2 Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy prior to surgery in locally advanced SCC has been reported in several case series (52-57). The largest and most recent series reported outcomes in 18 patients with primary locally advanced urethral cancer. A complete response to primary chemoradiotherapy was observed in 83% of the patients. The 5-year overall and disease-specific survival was 60% and 83%, respectively. Patients undergoing salvage surgery after chemoradiotherapy experienced a higher 5-year disease-free survival than those without salvage surgery (72% vs. 54%) (57).

Conclusions	LE
In locally advanced UC, cisplatinum-based chemotherapy with curative intent prior to surgery improves survival compared to surgery alone.	4
In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy with curative intent prior to surgery improves survival compared to surgery alone.	4

Recommendations	LE	GR
Patients with locally advanced UC should be discussed within a multidisciplinary team of urologists, radio-oncologists and oncologists.	4	A
Chemotherapeutic regimens with curative intent should be cisplatinum based.	4	C
In locally advanced SCC of the urethra, chemoradiotherapy with curative intent prior to surgery is an option.	4	C

12. TREATMENT OF UROTHELIAL CARCIMONA OF THE PROSTATE

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC (58,59). Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) (60). Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement (61). In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% (58,62). Some former series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement (63,64). In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation (65).

Recommendations	LE	GR
Patients with non-invasive UC or carcinoma *in situ* of the prostatic urethra and prostatic ducts can be treated with a urethra-sparing approach with TUR and BCG.	3	C
In patients with non-invasive UC or carcinoma *in situ*, prior TUR of the prostate should be performed to improve response to BCG.	3	C
Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or as primary treatment option in patients with extensive ductal or stromal involvement.	3	C

13. FOLLOW-UP

COMMENTARY: Given the low incidence of primary urethral cancer, defined follow-up has not been investigated systematically so far. Therefore, it seems reasonable to tailor surveillance regimens according to the patients' individual risk factors (Chapter 8.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocytoscopy and cross-sectional imaging despite the lack of specific data.

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15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AC	Adenocarcinoma
AJCC	American Joint Committee on Cancer
BCG	Bacille-Calmette-Guérin
BT	Brachytherapy
CT	Computed tomography
MRI	Magnetic resonance imaging
MVAC	Methotrexate, Vinblastin, Doxorubicin, Cisplatin
PUNLMP	Papillary urothelial neoplasm of low malignant potential
RC	Radical cystectomy
RCT	Randomized Controlled Trial
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
TNM	Tumour-Node-Metastasis
TUR	Transurethral Resection
UC	Urothelial carcinoma
WHO	World Health Organization

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 publically accessible through the European Association of Urology website. 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.