EAU GUIDELINES ON PRIMARY URETHRAL CARCINOMA

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Epidemiology

Primary Urethral Carcinoma is a rare cancer, accounting for < 1% of all malignancies. The age-standardised ratio is 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).

Aetiology

Predisposing factors include urethral strictures, chronic irritation after intermittent catheterisation/urethroplasty, external beam irradiation therapy, radioactive seed implantation, and chronic urethral inflammation following sexually transmitted diseases (especially human papilloma virus).

Staging and Grading systems

The 2017 TNM classification (8th edition) is used for the staging of urethral carcinoma. Of note, a separate staging system exists for urothelial carcinoma (UC) of the prostatic urethra.

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma *in situ*, involvement of prostatic urethra
Tis pd	Carcinoma *in situ*, involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus sponsiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes

M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Histopathology

Urothelial carcinoma of the urethra is the predominant histological type in men with primary urethral carcinoma followed by squamous cell carcinoma and adenocarcinoma. In women, recent studies report higher rates of adenocarcinoma rather than UC.

Recommendation for staging and grading	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

Diagnosis

Diagnosis of primary urethral carcinoma is based on clinical examination, urine cytology, urethroscopy with biopsy and cross-sectional imaging for the assessment of the primary tumour, lymph nodes (LNs) and distant organs. Patients with clinically enlarged inguinal or pelvic LNs often exhibit pathological LN metastasis.

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

Prognosis

The majority of patients are diagnosed late, with local symptoms due to advanced disease and the prognosis is poor. Risk factors for survival include age, race, tumour stage, grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and the type and modality of treatment.

Disease management

Localised disease in males

Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours. 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. Penis-preserving surgery for tumours confined to the corpus spongiosum (stage ≤ T2) using various reconstructive techniques has been investigated. In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence when complete circumferential assessment of the margins shows no evidence of disease.

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

Localised disease in females

In women with distal tumours, urethra-sparing surgery and local radiotherapy (RT) present alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.

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 intra-operatively.	3	Weak
Offer local radiotherapy as an alternative to urethral surgery to women with localised urethral tumours, but discuss local toxicity.	3	Weak

Multimodal therapy in advanced disease in both genders

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with the option of additional RT. Multimodal therapy is often underutilised in locally advanced disease. It confers an overall survival benefit in primary urethral carcinoma of urothelial origin.

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 chemo-therapy for definitive treatment and genital preservation.	3	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	3	Weak

Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive transurethral resection (TUR) and subsequent Bacillus-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic urethral carcinoma. Patients undergoing TUR of the prostate for prostatic urethral carcinoma prior to BCG treatment show superior complete response rates compared to those who do not.

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 prior TUR of the prostate 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

Follow-up

Given the low incidence of primary urethral cancer, follow-up has not been systematically investigated. Therefore, it seems reasonable to tailor surveillance regimens according to patients' individual risk factors. 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.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-04-2), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.