

GUIDELINES ON UPPER URINARY TRACT UROTHELIAL CELL CARCINOMAS

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Introduction

The EAU Working Group for upper urinary tract urothelial cell carcinomas (UUT-UCCs) has recently updated guidelines for this tumour type. This document provides a brief overview of the updated EAU guidelines.

UUT-UCCs are uncommon and account for only 5-10% of UCCs. The estimated annual incidence of UUT-UCCs in Western countries is about 1-2 new cases per 100,000 population. Pyelocaliceal tumours are about twice as common as ureteral tumours.

The principal environmental factors which contribute to the development of UUT-UCCs are similar to those associated with bladder cancer, namely tobacco and occupational exposure. Other environmental factors that are specifically associated with UUT-UCCs include phenacetin, aristolochic acid nephropathy, and blackfoot disease.

The morphology of UUT-UCCs is similar to those of bladder carcinomas. Over 95% of UCCs are derived from the urothelium, comprising of either UUT-UCCs or bladder carcinomas.

Classification

The classification of UUT-UCCs is given in the TNM classification of Malignant Tumours 7th edition, 2009.

Table 1: TNM classification 2009 for renal pelvis and ureter*

T - Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i>
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat

N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

**All EAU guidelines advocate the TNM system of tumour classification.*

Tumour grade

Until 2004, the most common classification used for UUT-UCCs was the WHO classification of 1973, which distinguishes among three grades (G1, G2 and G3). Since 2004, the new WHO classification distinguishes among three groups of non-invasive tumours: papillary urothelial neoplasia of low malignant potential, low-grade carcinomas, and high-grade carcinomas. Both classifications are in use currently for UUT-UCCs. There are almost no tumours of low malignant potential in the UUT.

Diagnosis

The diagnosis of a UUT-UCC depends on imaging, cystoscopy, urinary cytology, and diagnostic ureteroscopy.

Recommendations for diagnosis of UUT-UCC	GR
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
MDCT urography	A

MDCT = multidetector computed tomography.

In addition, the possible advantages of ureteroscopy should be discussed in the preoperative assessment of any UUT-UCC patient.

Prognostic factors

UUT-UCCs that invade the muscle wall usually have a very poor prognosis. The recognised prognostic factors in decreasing order of importance include:

- tumour stage and grade;
- concomitant carcinoma *in situ* (CIS);
- age;
- lymphovascular invasion;
- tumour architecture;
- extensive tumour necrosis;
- molecular markers;
- tumour location;
- gender.

Treatment

Localised disease

The radical management of UUT-UCC consists of radical nephroureterectomy (RNU) by open surgery with excision of the bladder cuff. This is the gold standard treatment for UUT-UCC, regardless of the location of the tumour in the UUT. Resection of the distal ureter and its orifice is per-

formed because this part of the urinary tract carries a considerable risk of recurrence. Lymph node dissection associated with RNU is of therapeutic interest and allows for optimal staging of the disease.

Recommendations for radical management of UUT-UCC: RNU

Indications for radical management of UUT-UCC	GR
Suspicion of infiltrating UUT-UCC (imaging)	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Techniques for RNU in UUT-UCC	
Open and laparoscopic access are equally effective	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable, except stripping	C
Lymphadenectomy is recommended in the case of invasive UUT-UCC	C

RNU = radical nephroureterectomy.

The conservative management of low-risk UUT-UCC consists of conservative surgery, which allows for preservation of the upper urinary renal unit. Conservative management of UUT-UCC can be considered in imperative cases (renal insufficiency, solitary functional kidney) or in selected elective cases (functional contralateral kidney) for low-grade, low-stage tumours. The choice of technique (ureteroscopy, segmental resection, percutaneous access) depends on technical constraints, the anatomical location of the tumour, and the experience of the surgeon.

Recommendations for conservative management of UUT-UCC	
Indications for conservative management of UUT-UCC	GR
Unifocal tumour	B
Small tumour (size < 1cm)	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on MDCT urography	B
Understanding of close follow-up	B
Techniques used for conservative management of UUT-UCC	
Laser should be used in the case of endoscopic treatment	C
Flexible ureteroscopy is preferable to rigid ureteroscopy	C
Open partial resection is an option for pelvic ureteral tumours	C
A percutaneous approach is an option for small, low-grade, caliceal tumours unsuitable for ureteroscopic treatment	C

MDCT = multidetector computed tomography.

The instillation of Bacillus Calmette-Guérin (BCG) or mitomycin C in the urinary tract by percutaneous nephrostomy or via a ureteric stent is technically feasible after conservative treatment of UUT-UCCs. However, benefits have not been confirmed.

Advanced disease

There are no benefits of RNU in metastatic (M+) disease, although it can be considered as a palliative option.

As UUT-UCCs are urothelial tumours, platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer. Currently, insufficient data are available to provide any recommendations.

Radiation therapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as tumour adjuvant.

Follow-up

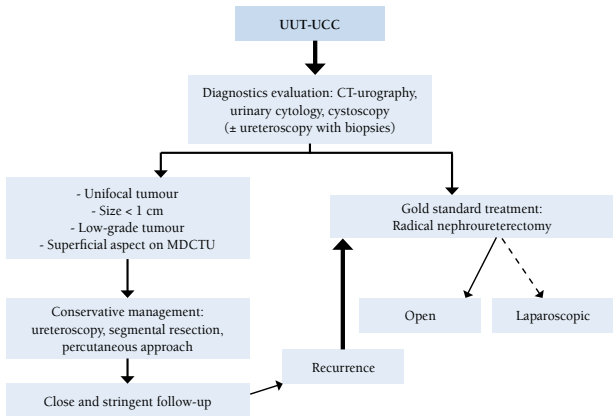
Strict follow-up of UUT-UCC patients after radical management is necessary in order to detect metachronous bladder tumours (in all cases), local recurrence and distant metastases (in the case of invasive tumours). With conservative management, the ipsilateral UUT requires careful follow-up due to the high risk of recurrence.

Recommendations for follow-up of UUT-UCC patients after initial treatment	
After radical management, over at least 5 years	GR
<i>Non-invasive tumour</i>	
Cystoscopy/urinary cytology at 3 months and then yearly	C
MDCT urography yearly	C
<i>Invasive tumour</i>	
Cystoscopy/urinary cytology at 3 months and then yearly	C

MDCT urography every 6 months for 2 years and then yearly	C
After conservative management, over at least 5 years	
Urinary cytology and MDCT urography at 3 months, 6 months and then yearly	C
Cystoscopy, ureteroscopy and cytology <i>in situ</i> at 3 months, 6 months, every 6 months for 2 years and then yearly	C

MDCT = multidetector computed tomography; RNU = radical nephroureterectomy.

Figure 1: Proposed flowchart for the management of UUT-UCC



MDCT = multidetector computed tomography.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN: 978-90-79754-96-0), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.