EAU GUIDELINES ON UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT (UTUCs)

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Epidemiology

Upper urinary tract urothelial carcinomas (UTUCs) are uncommon and account for only 5-10% of urothelial carcinomas (UCs). They have a similar morphology to bladder carcinomas and nearly all UTUCs are urothelial in origin.

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

Staging and grading systems

The UICC 2017 TNM (Tumour, Node, Metastasis Classification) for renal pelvis and ureter is used for staging (Table 1).

Tumour grade

The 2004/2016 WHO classification distinguishes between non-invasive tumours:

- papillary urothelial neoplasia of low malignant potential;
- low-grade papillary urothelial carcinomas;
- high-grade papillary urothelial carcinomas.

As well as define flat lesions (carcinoma *in situ*) and invasive carcinoma.

Upper urinary tract tumours with low malignant potential are very rare.

Table 1: TNM Classification 2017

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
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 greatest dimension

N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Diagnosis

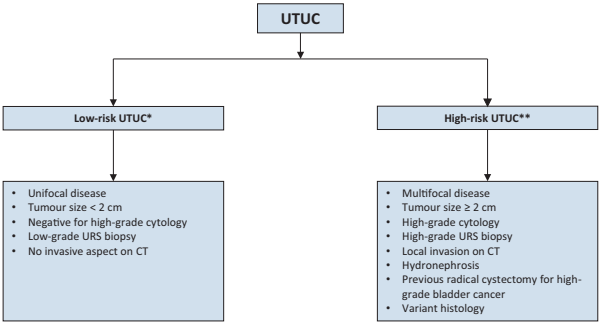
UTUCs are diagnosed using imaging, cystoscopy, urinary cytology and diagnostic ureteroscopy. Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques. In case conservative management is considered, a pre-operative ureteroscopic assessment is needed.

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform a computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk stratification of the tumour.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/computed tomography may be used when CT is contra-indicated.	Weak

Prognosis

Invasive UTUC usually have a very poor prognosis. The main factors to consider for risk stratification are listed in Figure 1.

Figure 1: Risk stratification of non-metastatic UTUC

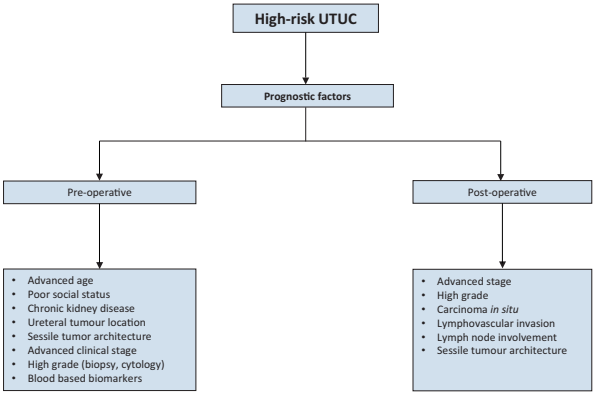


CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
**All these factors need to be present.*
***Any of these factors need to be present.*

Risk stratification

As tumour stage is difficult to assess clinically in UTUC, it is useful to "risk stratify" UTUC between low- and high-risk tumours to identify those patients who are more likely to benefit from kidney-sparing treatment. Those factors can be used to counsel patients regarding follow-up and administration of peri-operative chemotherapy (see Figures 1 and 2). Currently, no prognostic biomarkers are validated for clinical use.

Figure 2: UTUC prognostic factors included in prognostic models



UTUC = upper urinary tract urothelial carcinoma.

Recommendation	Strength rating
Use prognostic factors to risk-stratify patients for therapeutic guidance.	Weak

Disease management *(see also Figures 3 & 4)*

Localised disease

Kidney-sparing surgery

Kidney-sparing surgery for low-risk UTUC consists of surgery preserving the upper urinary renal unit and should be discussed in all low-risk cases, irrespective of the status of the contralateral kidney.

Kidney-sparing surgery potentially allows avoiding the morbidity associated with open radical surgery without compromising oncological outcomes and kidney function.

Kidney-sparing surgery can also be considered in select patients with serious renal insufficiency or solitary kidney (i.e., imperative indications).

Recommendations	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Offer kidney-sparing management (distal ureterectomy) to patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to patients with solitary kidney and/or impaired renal function, providing that it will not compromise survival. This decision will have to be made on a case-by-case basis in consultation with the patient.	Strong

The instillation of bacillus Calmette-Guérin or mitomycin C in the urinary tract by percutaneous nephrostomy, or via a ureteric stent is technically feasible after kidney-sparing management, or for treatment of carcinoma *in situ*. However, the benefits have not been confirmed.

High-risk non-metastatic disease

Radical nephroureterectomy

Open nephroureterectomy (RNU) with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location.

- In high-risk patients, neoadjuvant chemotherapy has been associated with significant downstaging at surgery and ultimately survival benefit as compared to RNU alone.

- Adjuvant chemotherapy was only associated with an OS benefit in patients with pure urothelial carcinoma and the main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver full dose cisplatin-based regimen after RNU, given that this surgical procedure is likely to impact renal function.
- In patients with regional lymph node invasion who are cisplatin-unfit after RNU, induction chemotherapy with radiological evaluation and consolidating surgery is a treatment option.
- A single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2-10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU.

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with muscle-invasive UTUC.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Metastatic disease

Radical nephroureterectomy has no benefit in metastatic (M+) disease but may be used in palliative care. As UTUCs are urothelial tumours, platinum-based chemotherapy should provide similar results to those in bladder cancer. Currently, insufficient data are available to provide any recommendations. Radiotherapy is no longer relevant nowadays, neither as a sole treatment option, nor as an adjunct to chemotherapy.

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
Do not offer carboplatin or non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemo-therapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong

Offer checkpoint inhibitor (atezolizumab or nivolumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong

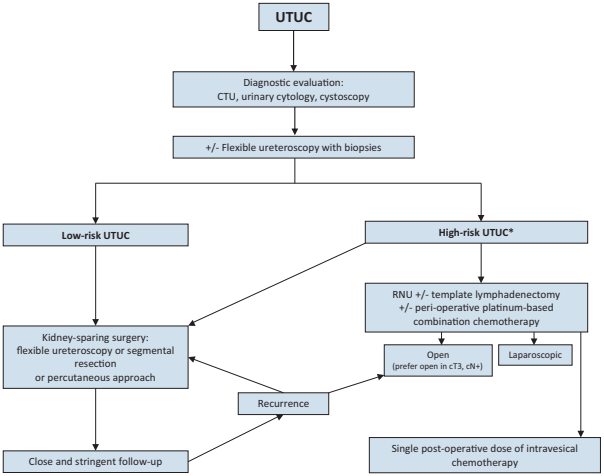
GC = gemcitabine plus cisplatin; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

Follow-up after initial treatment

In all cases, there should be strict follow-up after radical management to detect metachronous bladder tumours, as well as invasive tumours, local recurrence and distant metastases. When kidney-sparing surgery is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence.

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every six months for two years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy (URS) at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at three and six months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at three and six months.	Weak

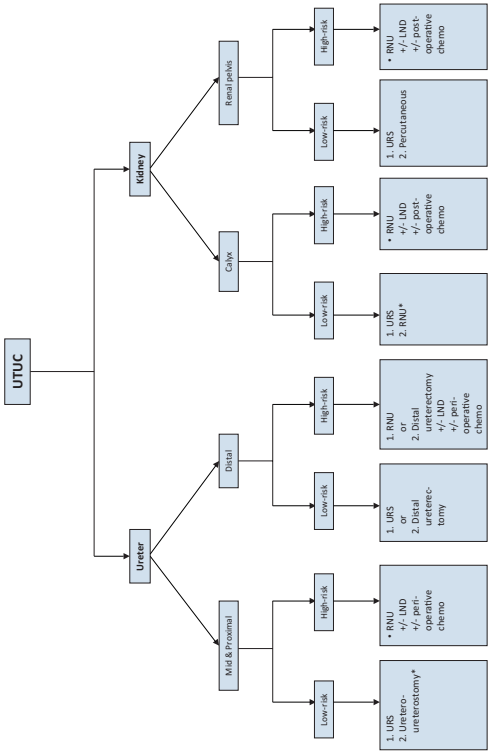
Figure 3: Proposed flowchart for the management of UTUC



** In patients with a solitary kidney, consider a more conservative approach.*

CTU = computed tomography urography; RNU = nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

Figure 4: Surgical treatment according to location and risk status



1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy;
UTUC = upper urinary tract urothelial carcinoma.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.