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

(Limited text update March 2023)

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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 the renal pelvis and ureter is used for staging (Table 1).

Tumour grade

The 2022 WHO classification distinguishes between non-invasive tumours:

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

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

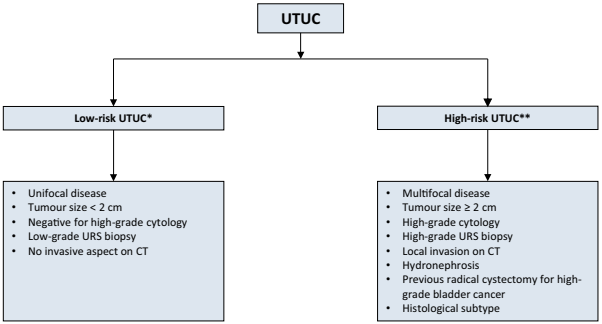
UTUCs are diagnosed using imaging, cystoscopy, urinary cytology and diagnostic ureteroscopy. Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques. In case conservative management is considered, a pre-operative ureteroscopic assessment is needed.

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 (preferably without biopsy) if imaging and/or voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected of having UTUC.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/CT (to assess [nodal] metastasis) may be used when CT is contra-indicated.	Weak

Prognosis

Invasive UTUCs 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. These factors can be used to counsel patients regarding follow-up and administration of peri-operative chemotherapy (see Figure 1).

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

Disease management *(see also Figures 2 & 3)*

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 tumours, 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

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. Minimally-invasive approaches (i.e., pure laparoscopic and/or robot-assisted RNU) have shown oncologic equivalence in experienced hands.

- 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 overall survival benefit in patients with pure UC 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.
- Preliminary data have shown improved disease-free survival rates for adjuvant immunotherapy (nivolumab).

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic UTUC.	Strong
Perform open RNU in non-organ-confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Weak
Offer adjuvant platinum-based chemotherapy after RNU to patients with pT2–T4 and/or pN+ disease.	Strong

Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong
Discuss adjuvant nivolumab with patients ineligible for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ disease after RNU alone or ≥ypT2 and/or ypN+ disease after neo-adjuvant chemotherapy, followed by RNU.	Weak
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to high-risk patients with imperative indication on a case-by-case basis, in consultation with the patient.	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.

Data are emerging for systemic treatments; both in first-line and subsequent-line settings. Encouraging results allow providing recommendations for a number of drugs.

Recommendations	**Strength rating**
First-line treatment in cisplatin-eligible patients	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong

Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin/ carboplatin.	Strong
First-line treatment in patients ineligible for cisplatin or carboplatin	
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy.	Strong
Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong
Only offer vinflunine to patients with metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong

Offer erdafitinib as subsequent-line therapy to platinum-refractory patients with *FGFR* DNA genomic alterations (*FGFR2/3* mutations, or *FGFR3* fusions).	Weak
Offer nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak

FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L(1) = programmed death ligand (1).

Follow-up after initial treatment

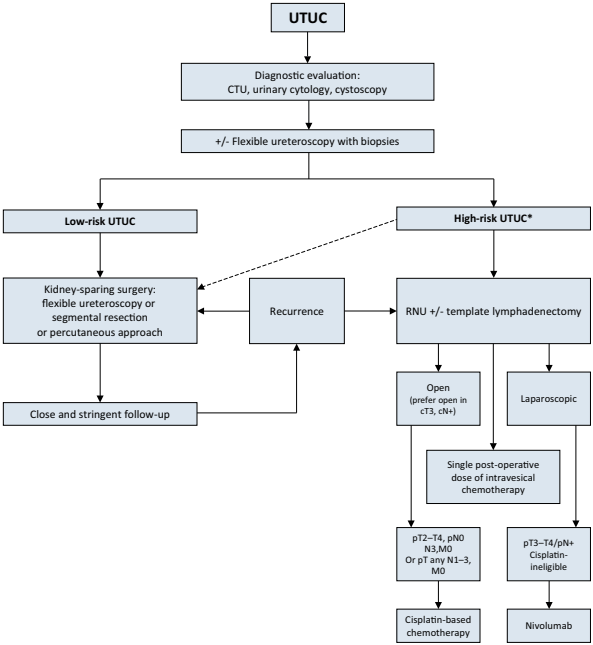
In all cases, there should be strict follow-up after radical management to detect metachronous bladder tumours, as well as invasive tumours, local recurrence and distant metastases. When kidney-sparing surgery is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high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

Recommendations	**Strength rating**
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at 3 months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak

After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months if no second-look ureteroscopy was performed.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at 3 and 6 months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at 3 and 6 months.	Weak

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-19-6) available on the EAU website, http://www.uroweb.org/guidelines/.

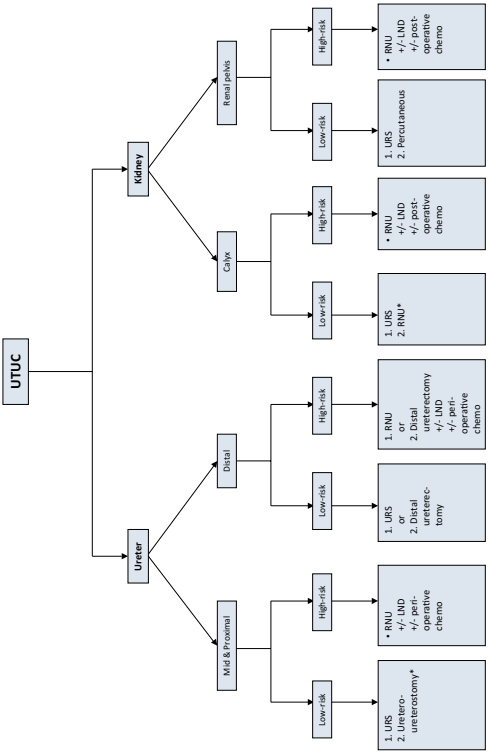
Figure 2: Proposed flowchart for the management of UTUC



** 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



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