EAU GUIDELINES ON UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT

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Introduction

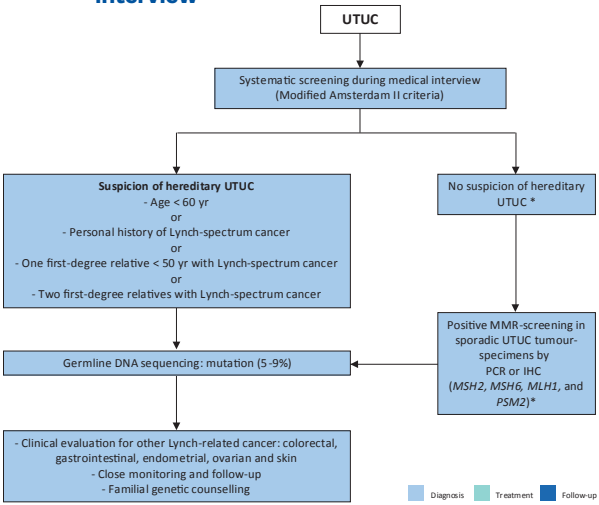
Epidemiology, aetiology and pathology

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. A number of environmental risk factors have been implicated in the development of UTUC including exposure to smoking and aristolochic acid. In addition, patients with Lynch syndrome are at risk for UTUC.

Recommendations for epidemiology, aetiology and pathology	Strength rating
Evaluate patient and family history to screen patients for Lynch syndrome using modified Amsterdam II criteria.	Strong

Perform germline deoxyribonucleic acid sequencing in patients with clinical suspicion of hereditary upper urinary tract urothelial carcinomas (UTUC).	Strong
Offer testing for mismatch repair proteins or microsatellite instability in patients without clinical suspicion of hereditary UTUC.	Weak

Figure 1: Selection of patients with UTUC for Lynch syndrome screening during the first medical interview



**These patients may benefit from MMR deficiency screening using PCR or IHC. A positive result should prompt subsequent testing for germline DNA sequencing mutations.*

DNA = deoxyribonucleic acid; IHC = immunohistochemistry; MMR = mismatch repair; mismatch repair genes = MSH2, MSH6, MLH1 and PMS2; PCR = polymerase chain reaction; UTUC = upper urinary tract urothelial carcinoma.

Histology

Upper urinary tract tumours are almost always UCs with pure non-urothelial histology being rare; however, histological subtypes are present in approximately 25% of UTUCs.

Staging and classification systems

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

Tumour grade

In 2004 and 2022, the World Health Organization (WHO) published a new histological classification of UCs which provides a different patient stratification between individual categories compared to the older 1973 WHO classification. The UTUC Guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification.

Table 1: TNM Classification 2025

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

Diagnostic evaluation

The diagnosis of UTUC is by 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 for diagnosis	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform voided urinary cytology in any case of suspicion of upper tract tumour.	Weak

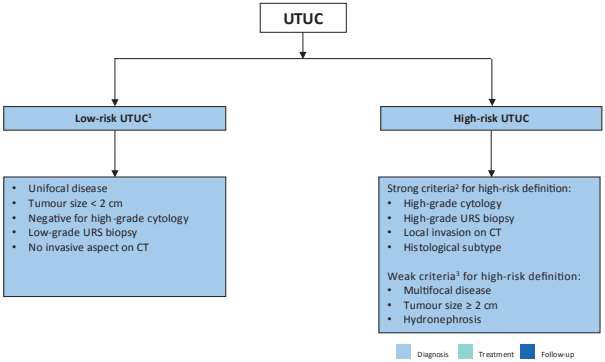
Perform computed tomography (CT), or magnetic resonance imaging if CT is contraindicated, with urography for diagnosis and staging of all upper tract tumours.	Strong
Perform a chest CT in high-risk tumours (see Figure 2).	Strong
^{18}F-Fluorodeoxglucose positron emission tomography/CT may be used to rule out metastases in high-risk disease.	Weak
Use diagnostic ureteroscopy if imaging and voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have upper urinary tract urothelial carcinomas.	Strong
Test for fibroblast growth factor receptor 2/3 alterations at initial diagnosis in the metastatic setting.	Strong

Risk stratification

The main prognostic factor in UTUC is pathological tumour stage. Upper urinary tract UCs that invade the muscle have a poor prognosis. 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 2).

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

Figure 2: Risk stratification of non-metastatic UTUC according to the risk of progression to a > pT2/ non-organ-confined disease



CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
[1] All these factors need to be present.
[2] Any of these factors need to be present.
[3] In the presence of low-grade tumour these factors are not strong predictors of invasive disease.

Disease management

Low-risk disease

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 avoids the morbidity associated with radical nephroureterectomy without compromising oncological outcomes and kidney function.

Endoscopic laser ablation must be considered in patients with low-risk cancer. Second-look ureteroscopy after initial endoscopic treatment is recommended to ensure complete tumour resection and evaluate residual disease.

Recommendations for kidney-sparing management of localised low-risk upper urinary tract urothelial carcinoma	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Discuss both endoscopic management and distal ureterectomy in low-risk tumours of the distal ureter based on tumour characteristics and shared decision-making with the patients.	Strong
Perform second-look ureteroscopy within eight weeks following initial endoscopic management.	Weak

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.

Localised high-risk disease

Radical 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.

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

Chemotherapy and immunotherapy

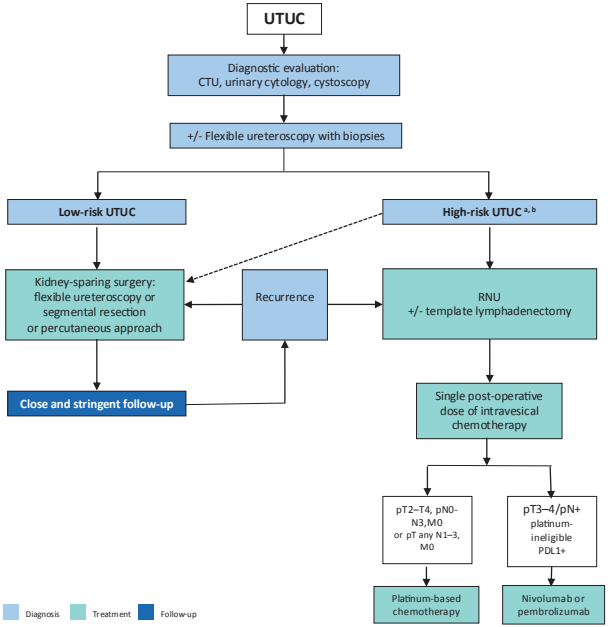
- Neoadjuvant chemotherapy has been associated with significant downstaging at surgery and potential survival benefit as compared to RNU alone.
- Adjuvant chemotherapy is associated with a disease-free survival (DFS) benefit in patients with advanced UTUC (pT2-T4 and/or pN+ disease) after RNU.
- A single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) two to ten days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU.
- Adjuvant nivolumab and pembrolizumab improved DFS compared to placebo in patients with high-risk muscle-invasive UC who had undergone radical surgery (pT3, pT4a or pN+) and cannot undergo platinum-based chemotherapy.
- In patients with clinical locoregional lymph node metastasis, first-line treatment relies on systemic therapy. Induction platinum-based chemotherapy or enfortumab vedotin plus pembrolizumab (EV + P) combination could be considered for these patients.

Recommendations for the management of high-risk non-metastatic upper urinary tract urothelial carcinoma (UTUC)	**Strength rating**
Discuss all patients with suspicion of UTUC on imaging in a multidisciplinary team meeting.	Strong

Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic UTUC.	Strong
Use open, laparoscopic or robotic approach to perform RNU in patients with high-risk non-metastatic UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Weak
Offer adjuvant platinum-based chemotherapy after RNU to eligible patients with pT2-T4 and/or pN+ disease.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate in patients without a history of bladder cancer.	Strong
Discuss adjuvant nivolumab with programmed death-ligand 1 (PD-L1) positive patients unfit for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ disease after previous RNU alone or ≥ ypT2 and/or ypN+ disease after previous neoadjuvant chemotherapy followed by RNU.	Weak
Discuss adjuvant pembrolizumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ and/or positive margin disease after previous RNU alone or ≥ ypT2 and/or ypN+ and/or positive margin disease after previous neoadjuvant chemotherapy, followed by RNU.	Weak

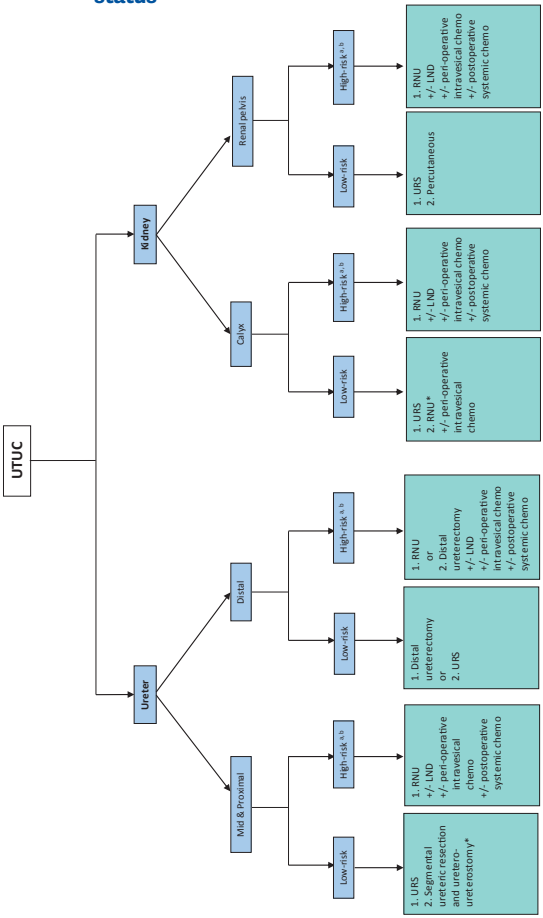
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Discuss kidney-sparing management of high-risk patients with imperative indication on a case-by-case basis in a shared decision-making process with the patient, despite the higher risk of disease progression.	Strong

Figure 3: Proposed flowchart for the management of UTUC



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
CTU = computed tomography urography; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

Figure 4: Surgical treatment according to location and risk status



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
Chemo = chemotherapy; LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

Metastatic disease

Radical nephroureterectomy has no benefit in metastatic (M+) disease. Enfortumab vedotin plus pembrolizumab is the standard of care treatment for metastatic UTUC based on the EV302 study. In patients that are ineligible for EV + P, platinum-based chemotherapy should be offered, followed by maintenance avelumab in case of response.

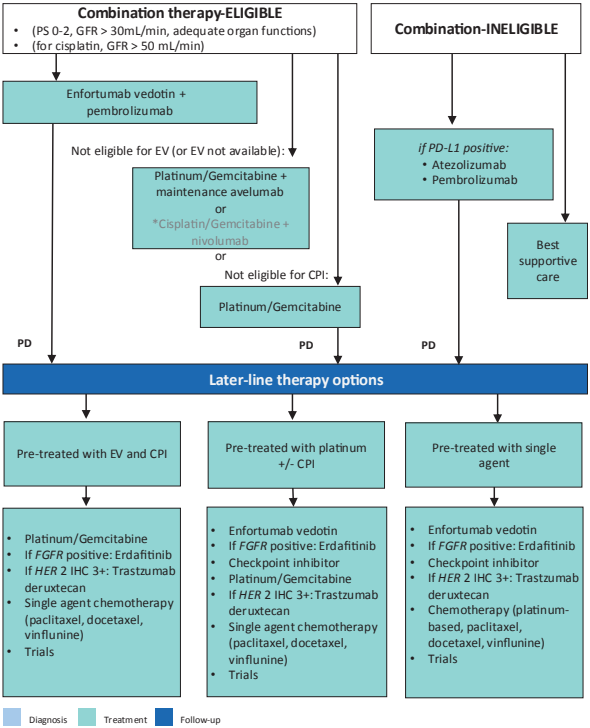
Recommendations for the treatment of metastatic upper urinary tract urothelial carcinoma	**Strength rating**
Offer EV + P as first-line treatment to patients with advanced/metastatic disease.	Strong
First-line treatment for platinum-eligible patients who are unsuitable/ineligible for EV + P	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine-cisplatin plus nivolumab in cisplatin-eligible patients.	Weak
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong

Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after four to six cycles of platinum-based combination chemotherapy.	Strong
First-line treatment in patients ineligible for any combination therapy	
Offer CPIs pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Later lines of treatment	
Offer platinum-based combination chemotherapy as second-line treatment of choice if not received in the first-line setting.	Strong
Offer CPI (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab.	Strong
Offer EV 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

Offer erdafitinib as an alternative subsequent-line therapy to patients: • previously treated with platinum-containing chemotherapy; • who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor; • who harbour *FGFR* DNA genomic alterations (*FGFR* 2/3 mutations or *FGFR* 3 fusions).	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 RNU as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak

CPI = checkpoint inhibitors; DNA = deoxyribonucleic acid; EV = enfortumab vedotin; EV + P = enfortumab vedotin plus pembrolizumab; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; RNU = radical nephroureterectomy.

Figure 5: Flowchart for the management of metastatic UTUC



**In view of lack of subgroup analysis data for UTUC*
EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PS = performance status; CPI = checkpoint inhibitor; PD-L1 = programmed death-ligand 1; PD = programmed death.

Follow-up

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. Follow-up should be based on risk stratification and the type of treatment.

Recommendations for follow-up	Strength rating
After radical nephroureterectomy (RNU)	
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	
In patients with previous history of non-muscle-invasive bladder cancer (NMIBC), perform cystoscopy and voided 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
In patients without a prior history of NMIBC, perform cystoscopy and voided urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every six months for a period of two years, and every year thereafter until five years.	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	
For bladder follow-up, perform cystoscopy at three and six months, and then yearly for five years.	Weak
For upper tract follow-up, after negative second-look ureteroscopy (URS), perform CT urography at three and six months and then yearly for five years with or without URS*.	Weak
High-risk tumours	
In patients with a prior history of NMIBC, perform cystoscopy and voided urine cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for two years, then every six months for five years, and then yearly.	Weak
In patients without a prior history of NMIBC, perform cystoscopy and voided urine cytology at three months. If negative, repeat subsequent cystoscopy and cytology every six months for two years, then every year for five years (same follow-up schedule as for high-risk tumours after RNU).	Weak

For upper tract follow-up, after negative second-look URS, perform cross-sectional imaging urography and URS at three and six months and then CT urography every six months for two years and then every year for five years, with or without URS*.	Weak

**The role of URS of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment versus CT urography and voided urinary cytology is unknown.*

This short booklet text is based on the more comprehensive EAU Guidelines accessible on the website: http://www.uroweb.org/guidelines/.