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

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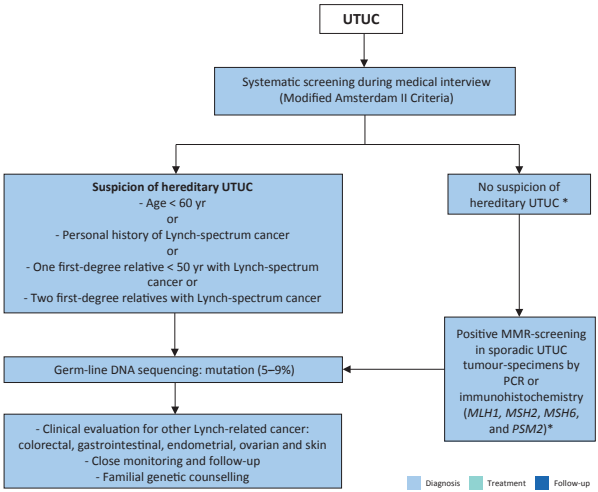
Figure 1: Selection of patients with UTUC for Lynch syndrome screening during the first medical interview



**These patients may benefit from MMR deficiency screening using PCR or IHC. Positive result should prompt subsequent testing for germline DNA sequencing mutations.*
MMR = mismatch repair; mismatch repair genes = MLH1, MSH2, MSH6, and PSM2; UTUC = upper urinary tract urothelial carcinoma.

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 to screen patients for Lynch syndrome using modified Amsterdam II criteria.	Strong
Perform germline DNA sequencing in patients with clinical suspicion of hereditary upper urinary tract urothelial carcinomas (UTUC).	Weak
Offer testing for mismatch repair (MMR) proteins or microsatellite instability in patients without clinical suspicion of hereditary UTUC.	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

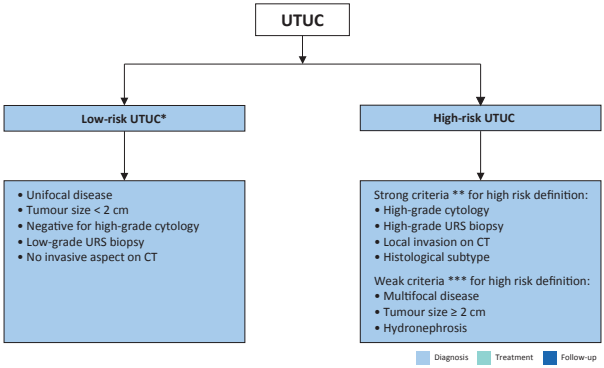
UTUCs are diagnosed using imaging, cystoscopy, urinary cytology and diagnostic ureteroscopy. Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques. In case conservative management is considered, a pre-operative ureteroscopic assessment is needed.

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform chest, abdominal and pelvis computed tomography (CT) with urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy (URS) 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 (UTUC).	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/CT may be used when CT is contraindicated.	Weak

Prognosis

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

Figure 2: 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.*
**** In the presence of low-grade tumour these factors are not strong predictors of invasive disease.*

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 and those who should be treated by radical nephroureterectomy. These factors can be used to counsel patients regarding follow-up and administration of peri-operative chemotherapy (see Figure 2).

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

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 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

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.
- 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.

Peri-operative systemic treatments

- Neoadjuvant chemotherapy has been associated with significant downstaging at surgery in phase 2 trials but no randomised data is available regarding potential' survival benefit as compared to RNU alone.
- In a phase 3 randomised trial, adjuvant gemcitabine platinum-based chemotherapy was associated with a significant improvement in disease-free survival (DFS) in patients with pT2–pT4 N (any) or pT any N1–3, M0, UTUC.
- Adjuvant nivolumab improved DFS compared to placebo in a cohort of high-risk muscle-invasive UC who had muscle invasive or node positive disease after surgery, were not eligible to cisplatin based adjuvant chemotherapy and expressed PDL-1. A small proportion of patients in the study had UTUC.

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
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 (BC).	Strong
Discuss adjuvant nivolumab with 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
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Discuss kidney-sparing management to 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

Metastatic disease

- Radical nephroureterectomy has no benefit in metastatic (M+) disease but may be used in palliative care.
- Platinum-based first-line chemotherapy has been the standard of care for decades.
- In the recent EV302 phase 3 trial, first-line Enfortumab Vedotin significantly improved both PFS and OS as compared to platinum-based chemotherapy.
- Sequencing of treatment after Ev+Pembro is currently unclear and later line treatments will depend upon what agents the patient has previously received.
- Maintenance Avelumab offers overall survival benefits for patients who did not have disease progression after first-line chemotherapy.
- In the phase 3 THOR trial, Erdafitinib improved overall survival in pretreated patients (chemo +/- immunotherapy) compared to the investigator's choice of chemotherapy and who harboured an FGFR DNA genomic alterations (FGFR2/3 fusions or FGFR3 mutations).

Recommendations	**Strength rating**
Offer Enfortumab vedotin in combination with pembrolizumab as first line treatment to patients with advanced/metastatic disease.	Strong
First-line treatment for platinum-eligible patients who are unsuitable/ineligible for Enfortumab + Pembrolizumab	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine-cisplatin + 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 checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Later line treatment	
Offer platinum-based combination chemotherapy as the second-line treatment of choice if it is not received in the first-line setting.	Strong
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab.	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

Test upper tract urothelial carcinoma (UTUC) patients for FGFR alterations (FGFR2/3 mutations or FGFR3 fusions) prior to erdafitinib treatment.	Strong
Offer erdafitinib as an alternative subsequent-line therapy to patients who: - have been previously treated with platinum-containing chemotherapy; - experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor; - harbour FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 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 nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak

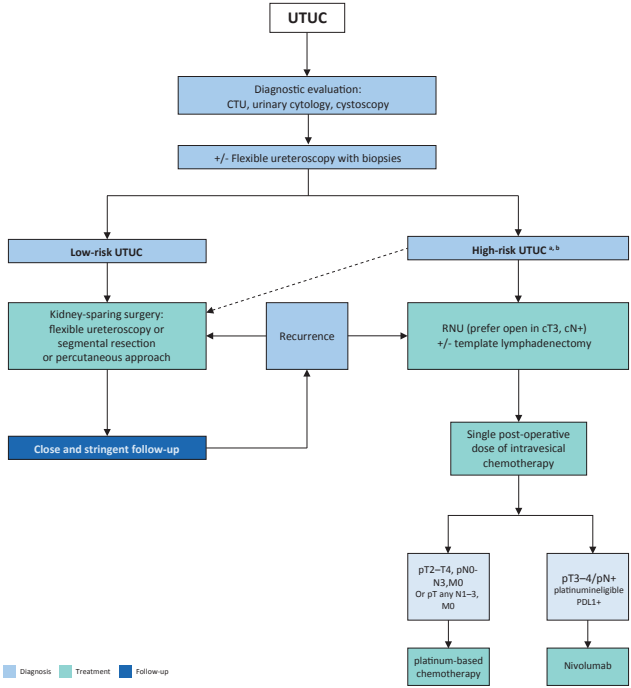
DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1.

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 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 if no second-look ureteroscopy was performed.	Weak
High-risk tumours	
Perform second-look URS and cytology in six weeks. If no residual tumour follow similar follow-up principles as for high-risk disease treated with radical nephroureterectomy.	Weak

Figure 3: Proposed flowchart for the management of UTUC

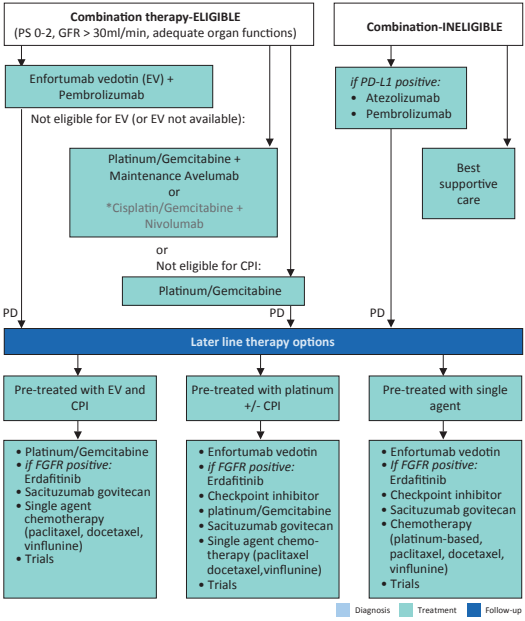


a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
CTU = computed tomography urography;
RNU = nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

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.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

Figure 5: Flowchart for the management of metastatic upper tract urothelial carcinoma



**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

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-23-3) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.