

DISEASE MANAGEMENT:

1. Localised non-metastatic disease:

1.1 Kidney-sparing surgery: for low-risk UTUC **reduces the morbidity associated with radical surgery without compromising oncological outcomes.**

It can also be considered in selected high-risk patients with a serious renal insufficiency or having a solitary kidney.

- **Ureteroscopy (URS):** Complete tumour resection or destruction is necessary. The patient should be informed of the need and be willing to comply with an early second-look URS and stringent surveillance. A risk of disease progression remains due to the suboptimal performance of imaging and biopsy for risk stratification.
- **Percutaneous Access:** Can be considered for low-risk UTUC in the renal pelvis and may be offered for tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. A risk of tumour seeding remains with a percutaneous access.
- **Ureteral resection:** Adequate pathological specimens for staging and grading while preserving the ipsilateral kidney. Distal ureterectomy with ureteroneocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically and for high-risk tumours when kidney-sparing surgery for renal function preservation is desired.

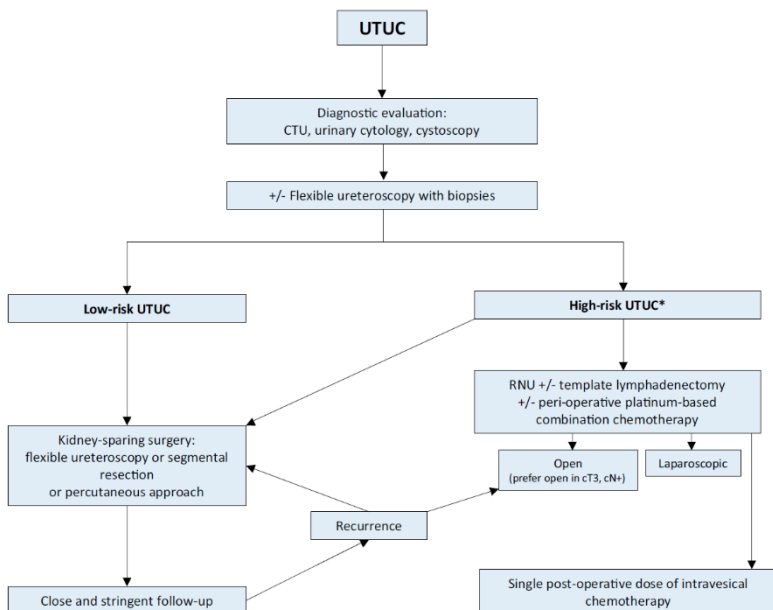
1.2 Management of high-risk non-metastatic UTUC

- **Surgical approach:** Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location. Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC. Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence. Lymphadenectomy improves survival in muscle-invasive UTUC.
- **Peri-operative chemotherapy:** Post-operative chemotherapy improves disease-free survival and a single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.

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

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.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with high-risk non-metastatic UTUC.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Proposed flowchart for the management of UTUC



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
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.	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
Offer erdafitinib in platinum-refractory tumours with FGFR alterations.	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; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

2. Metastatic disease:

- **Radical nephroureterectomy:** Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.
- **Metastasectomy:** In patients with metastases limited to lung and/or lymph nodes, whose disease responded to systemic chemotherapy, metastasectomy can improve oncological outcomes in individual cases.
- **Systemic treatments:**
 - Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin.
 - Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy. Non-platinum combination chemotherapy has not been tested against standard chemotherapy.
 - Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin.
 - PD-1 inhibitors pembrolizumab, atezolizumab and nivolumab have been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III, II and III trials respectively.
 - PD-1 inhibitors pembrolizumab and atezolizumab have been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trials but their use are restricted to PD-L1 positive patients.
 - Erdafitinib improves OS in in platinum-refractory patients with locally advanced or metastatic UC and FGFR DNA genomic alterations (FGFR2 or 3 mutations, or FGFR3 fusions).