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.

Disease Management

1. 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.

1.2 Management of high-risk non-metastatic UTUC

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Proposed flowchart for the management of UTUC

UTUC

Diagnostic evaluation: CTU, urinary cytology, cystoscopy

+/− flexible ureteroscopy with biopsies

Low-risk UTUC

Kidney-sparing surgery, flexible ureteroscopy or segmental resection or percutaneous approach

High-risk UTUC

RNU/+ template lymphadenectomy

+/− perioperative platinum-based combination chemotherapy

Open (prefer via open cystotomy)

Laparoscopic

Recurrence

Close and stringent follow-up

Single post-operative dose of intravesical chemotherapy

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
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<tbody>
<tr>
<td>Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer kidney-sparing management (distal ureterectomy) to patients with high-risk tumours limited to the distal ureter.</td>
<td>Weak</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

First-line treatment for cisplatin-eligible patients

- Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.
- Do not offer carboplatin or non-platinum combination chemotherapy.
- Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.
- Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.
- Perform a radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).
- Perform open RNU in non-organ-confined UTUC.

Second-line treatment

- Offer checkpoint inhibitor (pembrolizumab or atezolizumab) or pembrolizumab depending on PD-L1 status.
- Offer carboplatin combination chemotherapy if PD-L1 is negative.
- Offer maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.
- 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.

GC = gemcitabine plus cisplatin; FGF = f rocablast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, Adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; POG = pancitaxel, 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 combination 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).