European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update

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Abstract

Context: The European Association of Urology (EAU) guidelines panel on upper urinary tract urothelial cell carcinoma (UTUC) has prepared updated guidelines to aid clinicians in the current evidence-based management of UTUC and to incorporate recommendations into clinical practice.

Objective: To provide a brief overview of the EAU guidelines on UTUC as an aid to clinicians.

Evidence acquisition: The recommendations provided in the current guidelines are based on a thorough review of available UTUC guidelines and articles identified following a systematic search of Medline. Data on urothelial malignancies and UTUC were searched using these keywords: urinary tract cancer; urothelial carcinomas; upper urinary tract, carcinoma; renal pelvis; ureter; bladder cancer; chemotherapy; nephroureterectomy; adjuvant treatment; instillation; neoadjuvant treatment; recurrence; risk factors; and survival. References were weighted by a panel of experts.

Evidence synthesis: Due to the rarity of UTUC, there are insufficient data to provide strong recommendations (ie, grade A). However, the results of recent multicentre studies are now available, and there is a growing interest in UTUC. The 2009 TNM classification is recommended. Recommendations are given for diagnosis and risk stratification as well as radical and conservative treatment, and prognostic factors are discussed. A single postoperative dose of intravesical mitomycin after nephroureterectomy reduces the risk of bladder tumour recurrence. Recommendations are also provided for patient follow-up after different therapeutic strategies.

Conclusions: These guidelines contain information on the management of individual patients according to a current standardised approach. Urologists should take into account the specific clinical characteristics of each patient when determining the optimal treatment regimen, based on the proposed risk stratification of these tumours.
1. Introduction

The previous European Association of Urology (EAU) guidelines on upper urinary tract urothelial cell carcinoma (UTUC) were published in 2013 [1]. The EAU guidelines panel has prepared updated guidelines to provide evidence-based information on the management of these tumours in clinical practice.

2. Methodology

2.1. Data identification

A Medline search was performed using combinations of the following terms: urinary tract cancer; urothelial carcinomas, upper urinary tract, urothelial carcinoma, renal pelvis, ureter, chemotherapy, nephroureterectomy, adjuvant treatment, neoadjuvant treatment, recurrence, risk factors, nomogram, and survival. The publications identified were mainly retrospective including some large multicentre studies. Due to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant. To facilitate evaluation of the quality of information provided, levels of evidence (LEs) and grades of recommendation were included according to the general principles of evidence-based medicine [2].

3. Epidemiology, aetiology, and pathology

3.1. Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours [1]. They can be located in the lower urinary tract (bladder and urethra) or the upper (pyelocaliceal cavities and ureter). Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy [3]. However, UTUCs are uncommon and account for only 5–10% of UCs [1,4], with an estimated annual incidence in Western countries of almost 2 cases per 100 000 inhabitants. Pyelocaliceal tumours are approximately twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer (BCa) is present [5]. Recurrence in the bladder occurs in 22–47% of UTUC patients [1,6] compared with 2–6% in the contralateral upper tract [1,7].

Overall, 60% of UTUCs are invasive at diagnosis compared with 15–25% of bladder tumours [1,8]. UTUCs have a peak incidence in individuals aged 70–90 yr and are three times more common in men [1,9].

Familial/hereditary UTUCs are linked to hereditary nonpolyposis colorectal carcinoma (HNPCC) [10], and these patients can be screened during an interview (Fig. 1) [11]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic [10,12].

3.2. Risk factors

Many environmental factors contribute to the development of UTUC [1,13]. Tobacco exposure increases the relative risk from 2.5 to 7 [1,13]. Historically, UTUC “amino tumours” were related to occupational exposure to carcinogetic aromatic amines including benzidine and β-naphthalene, both of which have been banned since the 1960s in most industrialised countries.

UTUC is secondary to an amino tumour of the bladder. The average duration of exposure before the development of UTUC is approximately 7 yr, with a latency of almost 20 yr following termination of exposure. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [1,13]. UTUCs caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [13].

Several studies have demonstrated the carcinogenic potential of aristolochic acid contained in Aristolochia fangchi and Aristolochia clematis. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139 that occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC [1,13,14]. Although the incidence of Balkan endemic nephropathy is also on the decline, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the pathophysiology and induction of this nephropathy, respectively.

There is a high incidence of UTUC in Taiwan, especially on the southwest coast, which represents 20–25% of UCs in the region [1,13]. There is a possible association between UTUC, blackfoot disease, and arsenic exposure in drinking water in this population [1,13].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the interindividual susceptibility to the risk factors previously mentioned. UTUC may share some risk factors or molecular disruption pathways with bladder UC. Only two UTUC-specific polymorphisms have been reported [1,15].
3.3. **Histology and classification**

3.3.1. **Histologic types**
Morphologic variants of UTUC are more often observed in urothelial kidney tumours. These variants correspond to high-grade tumours associated with squamous cell or glandular differentiation [16]. Sarcomatoid and micropapillary are the most commonly observed with classic UC aspects [1]. Collecting duct carcinoma can have similar characteristics to UTUC due to its common embryologic origin [1].

UTUC with pure nonurothelial histology is an exception [1], but variants are present in almost 25% of cases [16,17]. Squamous cell carcinoma of the upper urinary tract represents <10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious diseases arising from urolithiasis [1]. Other histologic subtypes are adenocarcinoma (<1%), small cell carcinoma, and sarcoma.

4. **Staging and classification systems**

4.1. **Classification**

The classification and morphology of UTUC and bladder carcinoma are similar [1]. It is possible to distinguish between noninvasive papillary tumours (papillary urothelial tumours of low malignant potential and low-grade and high-grade papillary UC), flat lesions (carcinoma in situ [CIS]), and invasive carcinoma.

4.2. **Tumour node metastasis staging**

The TNM classification is shown in Table 1 [18]. The regional lymph nodes to be considered are the hilar, abdominal para-aortic, and paracaval nodes, and for the ureter, the intrapelvic nodes. Laterality does not affect N classification.

Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b). Subclassification of pT3a and pT3b UTUC has been suggested [16,19,20]; pT3b UTUC is more likely to have aggressive pathology and a higher risk of recurrence [16,19].

4.3. **Tumour grade**

Until 2004, the 1973 World Health Organisation (WHO) classification was used for tumour grading and distinguished only three grades (G1–G3) [1,21]. The 2004 WHO classification considers histologic data to distinguish noninvasive tumours: papillary urothelial neoplasia of
low malignant potential, and low-grade and high-grade carcinomas (low grade vs high grade).

5. Diagnosis

5.1. Symptoms

The diagnosis of UTUC may be fortuitous or related to the evaluation of symptoms that are generally limited [1]. The most common symptom is visible or nonvisible haematuria (70–80%) [1]. Flank pain occurs in 20–40% of cases, and a lumbar mass is present in 10–20% [22,23]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt more rigorous metastatic evaluation [22,23].

5.2. Diagnosis

5.2.1. Imaging

5.2.1.1. Computed tomography urography. Computed tomography (CT) urography has the highest diagnostic accuracy in high-risk patients [1]. The sensitivity of CT urography for UTUC is 0.67–1.0; specificity is 0.93–0.99 [1,24]. Conventional CT urography usually includes at least one series of images acquired during the excretory phase of contrast enhancement [1]. Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution [1]. Flat lesions are undetectable unless they exert a mass effect or cause urothelial thickening [1].

The secondary sign of hydronephrosis is associated with advanced disease and poor oncologic outcome [1,25,26]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [1].

5.2.1.2. Magnetic resonance urography. Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [1]. The sensitivity of MR urography is 75% after contrast injection for tumours <2 cm [1]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (<30 ml/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis. CT urography is generally preferred to MR urography for diagnosing UTUC.

5.2.2. Cystoscopy and urinary cytology

Positive urine cytology is highly suggestive of UTUC when bladder cytoscopay is normal, provided no CIS in the bladder or prostatic urethra has been detected [1]. Cytology is less sensitive for UTUC than bladder tumours and should be performed in situ in the renal cavities [27]. Retrograde ureteropyelography remains an option to detect UTUCs [1,24]. Urinary cytology of the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography because it may cause deterioration of cytologic specimens [1,27].

The sensitivity of fluorescence in situ hybridisation (FISH) for molecular abnormalities characteristic of UTUCs parallels its performance in BCa. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs [1]. FISH appears to have limited value in the surveillance of UTUCs [1].

5.2.3. Diagnostic ureteroscopy

Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis, and collecting system. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [28]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if renal-sparing treatment is selected [1]. Ureteroscopy also facilitates selective ureteral sampling for cytology in situ [1,29].

Flexible ureteroscopy is particularly useful in diagnostic uncertainty, when conservative treatment is considered, or in patients with a solitary kidney. Ureteroscopy and biopsy should be performed in the preoperative assessment of UTUC. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology may help in the decision between radical nephroureterectomy (RNU) and endoscopic treatment [1,29].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions. Narrow-band imaging is a promising technique, but results are preliminary [1]. Recommendations are listed in Table 2.
6. Prognosis

6.1. Prognostic factors

UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-yr specific survival is <50% for pT2/pT3 and <10% for pT4 [1,30]. The main prognostic factors are briefly listed here. Figure 2 shows an exhaustive list.

6.1.1. Preoperative factors

6.1.1.1. Age and sex. Sex is no longer considered an independent prognostic factor influencing UTUC mortality [1,9,30]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [1,30] (LE: 3). Many elderly patients can be cured following RNU [1], suggesting that age alone is an inadequate indicator of outcome [1,31]. Advanced age is linked with survival, but it should not be considered an absolute exclusion criterion in treatment decision making for potentially curable UTUC.

6.1.1.2. Ethnicity. A multicentre study showed no difference in outcome between races [32], but population-based studies have indicated that African American patients have worse outcomes than other racial groups [31] (LE: 3).

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Table 2 – Diagnostic guidelines for upper urinary tract urothelial cell carcinoma

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary cytology should be performed as part of a standard diagnostic work-up</td>
<td>A</td>
</tr>
<tr>
<td>Cystoscopy should be performed to rule out concomitant bladder tumour</td>
<td>A</td>
</tr>
<tr>
<td>CT urography must be part of the diagnostic work-up</td>
<td>A</td>
</tr>
<tr>
<td>Diagnostic ureteroscopy and biopsy should be performed, especially in cases where additional information will have an impact on treatment decisions</td>
<td>C</td>
</tr>
<tr>
<td>Retrograde ureteropyelography is an optional tool for the detection of UTUC</td>
<td>C</td>
</tr>
</tbody>
</table>

CT = computed tomography; GR = grade of recommendation; UTUC = upper urinary tract urothelial cell carcinoma.

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Fig. 2 – Upper urinary tract urothelial cell carcinoma: prognostic factors. ASA = American Society of Anesthesiologists; BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; UTUC = upper urinary tract urothelial cell carcinoma.
6.1.1.3. Tobacco consumption. Being a smoker at diagnosis increases the risk of poor oncologic outcome [1,33] and recurrence within the bladder [34] (LE: 3).

6.1.1.4. Tumour location. Initial location of the tumour within the upper urinary tract is a prognostic factor [1,35,36] (LE: 3). Following adjustment for tumour stage, ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours [30,35–38].

6.1.1.5. Surgical waiting time. A delay between diagnosis and tumour removal may increase the risk of disease progression. The cut-off for removal of tumours >3 cm is controversial and ranges between 30 d and 3 mo [1,39–41] (LE: 3).

6.1.1.6. Other factors. The American Society of Anesthesiologists score also significantly correlates with cancer-specific survival after RNU [42] (LE: 3), but the Eastern Cooperative Oncology Group performance status correlates only with overall survival (OS) [43]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [44] (LE: 3).

6.1.2. Postoperative factors

6.1.2.1. Tumour stage and grade. The primary recognised prognostic factors are tumour stage and grade [1,29,30].

6.1.2.2. Lymph node involvement. Extraneural extension is a powerful predictor of clinical outcome in UTUCs and positive lymph node metastases [1]. Lymph node dissection (LND) associated with RNU allows optimal tumour staging [1,45] (LE: 3). Lymph node invasion is an important prognostic factor, indicating metastatic spread to the lymph nodes.

6.1.2.3. Lymphovascular invasion. Lymphovascular invasion is present in approximately 20% of UTUCs and is an independent predictor of survival [1]. Lymphovascular invasion status should be systematically included and specifically reported in the pathologic reports of all RNU specimens [1,46] (LE: 3).

6.1.2.4. Surgical margins. A positive surgical margin after RNU is a significant factor in the development of UTUC metastases. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour if \( T > 2 \) [47] (LE: 3).

6.1.2.5. Pathologic factors. Extensive tumour necrosis (>10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [1,48] (LE: 3). Tissue architecture of UTUC is associated with prognosis after RNU. The poorest outcome is associated with a sessile growth pattern [49,50] (LE: 3). Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [1,51,52] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of a poor outcome in organ-confined disease [1].

6.2. Molecular markers

Several studies have investigated the prognostic impact of markers related to cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor), angiogenesis (hypoxia inducible factor \( \alpha \) and metalloproteinases), cell proliferation (Ki-67), epithelial-mesenchymal transition (Snail), mitosis (Aurora A), apoptosis (Bcl-2 and survivin), vascular invasion (RON), and c-met protein (MET) [1,30,53,54]. Microsatellite instability (MSI) is an independent molecular prognostic marker [55]. MSI can help detect germline mutations and hereditary cancers [10]. None of these markers have fulfilled the criteria necessary to support their introduction in daily clinical decision making.

6.3. Predictive tools

There are two models in the preoperative setting: one for predicting LND of locally advanced cancer that could guide the extent of LND at the time of RNU [1] and one for the selection of non–organ-confined UTUC that is likely to benefit from nephroureterectomy [56]. Four nomograms predict survival rates postoperatively based on standard pathologic features [1,57,58].

6.4. Risk stratification

As with non–muscle-invasive BCa, it is necessary to risk-stratify UTUC before treatment to identify tumours that are more suitable for kidney-sparing treatment than radical extirpative surgery [1] (Fig. 3).

7. Disease management

7.1. Localised disease

7.1.1. Kidney-sparing surgery

Conservative management of UTUC can be carried out in low-risk cases when the contralateral kidney is functional [1]. Kidney-sparing surgery for low-risk UTUC (Table 3) prevents the morbidity associated with open radical surgery without compromising oncologic outcome and kidney function [59]. In addition, it can also be considered in all serious cases (ie, renal insufficiency or solitary kidney) (LE: 3).

7.1.1.1. Ureteroscopy. Endoscopic ablation can be considered in highly selected cases and in the following situations [1,60]:

- Laser generator [1] and pliers are available for biopsies [1,60] (LE: 3).
- Flexible rather than rigid ureteroscope is used.
- The patient is informed of the need for closer, more stringent, surveillance.
- Complete tumour resection is strongly advocated.

However, there is a risk of understaging and undergrading with endoscopic management only.
7.1.1.2. Percutaneous access. Percutaneous management can be considered for low-risk UTUCs in the renal cavities [1,60,61] (LE: 3). This may be offered for tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible ureteroscopy. This approach is used infrequently due to the availability of enhanced materials and advances in distal-tip deflection of current ureteroscopes [1,60,61].

7.1.1.3. Segmental resection. Segmental ureteral resection with wide margins provides adequate pathologic specimens for staging and grading while preserving the ipsilateral kidney.

- Ureteroureterostomy is indicated for noninvasive low-grade tumours of the proximal or midureter that cannot be completely removed endoscopically, and for high-grade or invasive tumours when renal-sparing surgery for renal function preservation is a goal.

- Patients with high-grade tumours of the proximal or midureter should undergo RNU with bladder cuff excision. Complete distal ureterectomy with neocystostomy is indicated for noninvasive low-grade tumours in the distal ureter that cannot be completely removed endoscopically and for high-grade locally invasive tumours [62–64] (LE: 3).

- Segmental resection of the iliac and lumbar ureter is associated with a greater failure rate than segmental resection of the distal pelvic ureter [62–64].

- Open resection of tumours of the renal pelvis or calices is rarely performed.

- Resection of pyelocaliceal tumours is technically difficult and has a higher recurrence rate than resection of ureteral tumours.

7.1.1.4. Adjuvant topical agents. The antegrade instillation of bacillus Calmette-Guérin vaccine or mitomycin C in the

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**Table 3 – Guidelines for kidney-sparing management of low-risk upper urinary tract urothelial cell carcinoma**

<table>
<thead>
<tr>
<th>Indications for endourologic management</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unifocal tumour</td>
<td>B</td>
</tr>
<tr>
<td>Tumour &lt;1 cm</td>
<td>B</td>
</tr>
<tr>
<td>Low-grade tumour</td>
<td>B</td>
</tr>
<tr>
<td>No evidence of infiltrative lesion on CT urography</td>
<td>B</td>
</tr>
<tr>
<td>Understanding of close follow-up</td>
<td>B</td>
</tr>
<tr>
<td>Techniques used according to location:</td>
<td></td>
</tr>
<tr>
<td>- Laser should be used for endoscopic treatment</td>
<td>C</td>
</tr>
<tr>
<td>- Flexible is preferable to rigid ureteroscopy: renal pelvis, distal, mid- and proximal ureter</td>
<td>C</td>
</tr>
<tr>
<td>- Percutaneous approach remains an option for low-grade tumours not accessible by the ureteroscopic approach</td>
<td>C</td>
</tr>
<tr>
<td>Surgical open approach</td>
<td></td>
</tr>
<tr>
<td>- Renal pelvis or calyces:</td>
<td>C</td>
</tr>
<tr>
<td>- Partial pylectomy or partial nephrectomy is seldom indicated</td>
<td>C</td>
</tr>
<tr>
<td>- Ureteroureterostomy is indicated for tumours that cannot be completely removed endoscopically</td>
<td>C</td>
</tr>
<tr>
<td>- Distal:</td>
<td>C</td>
</tr>
<tr>
<td>Complete distal ureterectomy and neocystostomy are indicated for tumours in the distal ureter that cannot be completely removed endoscopically</td>
<td>C</td>
</tr>
</tbody>
</table>

CT = computed tomography; GR = grade of recommendation.
upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete tumour eradication) is feasible after conservative treatment of UTUC or for the treatment of CIS [65] (LE: 3). Retrograde instillation through a ureteric stent is also used, but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used [1] but is not advisable because it may not reach the renal pelvis.

7.1.2. Radical nephroureterectomy

Open RNU with bladder cuff excision is the standard for high-risk UTUC, regardless of tumour location [8] (LE: 3) (Table 4). RNU must comply with oncologic principles that consist of preventing tumour seeding by avoiding entry into the urinary tract during resection [8].

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy. Removal of the distal ureter and bladder cuff is beneficial after RNU [1,66]. Regardless of the technique, the surgeon must be confident that the bladder is closed appropriately.

Several techniques have been considered to simplify distal ureter resection (eg, the pluck technique, stripping, transurethral resection of the intramural ureter) [1,7]. Endoscopy is associated with a higher risk of subsequent bladder recurrence [67,68] (LE: 3).

7.1.2.1. Laparoscopic radical nephroureterectomy. Metastatic dissemination in the retroperitoneum and along the trocar pathway following manipulation of large tumours in the pneumoperitoneal environment has been reported in only a few cases [1].

The following precautions are necessary to avoid tumour spillage:

- Entering the urinary tract should be avoided.
- Direct contact between instruments and tumour should be avoided.

Table 4 - Guidelines for radical nephroureterectomy in upper urinary tract urothelial cell carcinoma

<table>
<thead>
<tr>
<th>Indications for RNU</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of infiltrating UTUC on imaging</td>
<td>B</td>
</tr>
<tr>
<td>High-grade tumour (urinary cytology)</td>
<td>B</td>
</tr>
<tr>
<td>Multifocality (with two functional kidneys)</td>
<td>B</td>
</tr>
<tr>
<td>Noninvasive but large (≥1 cm) UTUC</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Techniques for RNU</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Open and laparoscopic access has equivalent efficacy in T1–T2/N0 tumours</td>
<td>B</td>
</tr>
<tr>
<td>Bladder cuff removal is necessary</td>
<td>A</td>
</tr>
<tr>
<td>Several techniques for bladder cuff excision are acceptable, except stripping</td>
<td>C</td>
</tr>
<tr>
<td>Lymphadenectomy is recommended for invasive UTUC</td>
<td>C</td>
</tr>
<tr>
<td>Postoperative instillation is recommended after RNU to avoid bladder recurrence</td>
<td>B</td>
</tr>
</tbody>
</table>

GR = grade of recommendation; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial cell carcinoma.

7.1.2.2. Lymph node dissection. Anatomic sites for LND have not been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed [1].

LND appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2–4 tumours [1]. An increase in the probability of lymph node–positive disease is related to pT classification [1]. However, it is likely that the true rate of node-positive disease has been underreported because these data are retrospective.

It is not possible to standardise the indication or extent of LND. LND can be achieved following lymphatic drainage as follows: LND medial to the ureter in ureteropelvic tumours, retroperitoneal LND for higher ureteral tumours and/or tumours of the renal pelvis (ie, right side: border vena cava or right side of the aorta; and left side: border aorta) [1,45].

7.1.2.3. Bladder instillation of chemotherapy. One prospective randomised study demonstrated that a single postoperative dose of intravesical mitomycin on the day of catheter removal reduces the risk of bladder tumour within the first year post-RNU [73] (LE: 2). This therapeutic strategy was confirmed in another prospective trial with pirarubicin [74] and in a meta-analysis [75]. Management is outlined in Figure 4.

7.2. Advanced disease

7.2.1. Radical nephroureterectomy

RNU in metastatic disease does not result in benefits, although it can be considered as palliative [1,8] (LE: 3).

7.2.2. Systemic chemotherapy

UTUCs are urothelial tumours; therefore, platinum-based chemotherapy is expected to have similar efficacy to that in BCa. However, data are currently insufficient to provide recommendations. There are several platinum-based regimens [1], but the risk of impaired postoperative function means that neoadjuvant chemotherapy is only optional. Not all patients can receive chemotherapy due to comorbidity and impaired renal function after radical surgery.
Chemotherapy-related toxicity, particularly nephrotoxicity due to platinum derivatives, may significantly reduce survival in patients with postoperative renal dysfunction [1,76].

In the only study published to date, no adverse effects were noted due to neoadjuvant chemotherapy for UTUCs [77], although survival data and longer follow-up are awaited. Adjuvant chemotherapy can achieve a recurrence-free rate ≤50% [1,78]. From available studies, cisplatin-based adjuvant chemotherapy appears to have a beneficial effect on OS and disease-free survival [79] (LE: 3). However, a definitive statement is unlikely until further evidence from an ongoing prospective trial is available [1].

7.2.3. Radiotherapy

Radiotherapy is no longer relevant, either alone or as an adjunct to chemotherapy [1] (LE: 3).

7.3. Follow-up

The risk of recurrence and death evolves during the follow-up period after surgery [80]. Stringent follow-up (Table 5) is mandatory to detect metachronous bladder tumours, local recurrence, and distant metastases.

Surveillance regimens are based on cystoscopy and urinary cytology for >5 yr [1,6]. Bladder recurrence should not be considered distant recurrence. When conservative treatment is undertaken, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence [1]. Despite endourologic improvements, follow-up after kidney-sparing management is difficult, and frequent, repeated endoscopic procedures are necessary.

Author contributions: Morgan Roupé had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Rouprêt.
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Drafting of the manuscript: Rouprêt.
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