EUROPEAN ASSOCIATION OF UROLOGY

Guidelines

European Guidelines on Upper Tract Urothelial Carcinomas: 2013 Update

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Article info

Abstract

Context: The European Association of Urology (EAU) guideline group for upper tract urothelial carcinoma (UTUC) has prepared updated guidelines to aid clinicians in assessing the current evidence-based management of UTUC and to incorporate present recommendations into daily clinical practice.

Objective: To provide a brief overview of the EAU guidelines on UTUC as an aid to clinicians in their daily clinical practice.

Evidence acquisition: The recommendations provided in the current guidelines are based on a thorough review of available UTUC guidelines and articles identified using a systematic search of Medline. Data on urothelial malignancies and UTUCs in the literature were searched using Medline with the following 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; nomogram*; and *survival.* References were weighted by a panel of experts.

Evidence synthesis: There is a lack of data in the current literature to provide strong recommendations (ie, grade A) due to the rarity of the disease. A number of recent multicentre studies are now available, and there is a growing interest in UTUC in the recent literature. Overall, 135 references have been included here, but most of these studies are still retrospective analyses. The TNM 2009 classification is recommended. Recommendations are given for diagnosis as well as radical and conservative treatment (ie, imperative and elective cases); additionally, prognostic factors are discussed. Recommendations are also provided for patient follow-up after different therapeutic options.

Conclusions: These guidelines contain information for the management of individual patients according to a current standardised approach. Physicians must take into account the specific clinical characteristics of each individual patient when determining the optimal treatment regimen including tumour location, grade, and stage; renal function; molecular marker status; and medical comorbidities.

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1.   Introduction

The prior version of the European Association of Urology (EAU) guidelines on upper urinary tract tumours known as upper tract urothelial carcinomas (UTUCs) were published in 2011 [1]. The EAU Guidelines Working Panel for UTUCs has prepared the current guidelines to provide evidence-based information for the clinical management of these rare tumours and to help clinicians incorporate these recommendations into their practice. The current update is based on a structured literature search.

2.   Methodology

2.1.   Data identification

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

2.2.   Publication history

The first guidelines publication on upper urinary tract tumours was presented in 2004 [3]. This document was updated and included in the EAU guidelines compilation printed in 2011. The current 2013 publication presents a limited update of the 2011 document. This document was peer reviewed prior to publication.

3.   Evidence synthesis

3.1.   Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours after prostate (or breast), lung, and colorectal cancer [4,5]. They can be located in the lower urinary tract (bladder and urethra) or upper urinary tract (pyelocaliceal cavities and ureter). Bladder tumours account for 90–95% of UCs and are the most common malignancy of the urinary tract [1,5]. In contrast, UTUCs are uncommon and account for only 5–10% of UCs [4,6]. The estimated annual incidence of UTUCs in Western countries is about 2 new cases per 100 000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present [7]. Recurrence of disease in the bladder occurs in 22–47% of UTUC patients [8–10], whereas recurrence in the contralateral upper tract is observed in 2–6% [11,12].

The natural history of UTUCs differs from that of bladder cancer: 60% of UTUCs are invasive at diagnosis compared with only 15–25% of bladder tumours [13,14]. UTUCs have a peak incidence in people in their 70s and 80s, and they are three times more prevalent in men than in women [15,16].

There are familial/hereditary cases of UTUCs linked to hereditary nonpolyposis colorectal carcinoma (HNPCC) [17]. Among patients with UTUCs, HNPCC cases can be screened during a medical interview [18]. There is a suspicion of hereditary UTUC if the patient is <60 yr of age, has a personal history of an HNPCC-associated cancer, a first-degree relative <50 yr of age with HNPCC-associated cancer, or two first-degree relatives with HNPCC-associated cancer [18]. These patients should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers due to insufficient clinical data [19]. The presence of other HNPCC-associated cancers should also be evaluated. These patients should be closely monitored, and genetic counselling is advocated [17,19].

3.2.   Risk factors

Many environmental factors contribute to the development of UTUCs [20,21]. Some are similar to those associated with bladder cancer, whereas others are more specific for UTUC. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Exposure to tobacco increases the relative risk of developing UTUC from 2.5 to 7 [20,21]. UTUC *amino tumours* are related to occupational exposure to certain aromatic amines. These aromatic hydrocarbons are used in many industries (eg, dyes, textiles, rubber, chemicals, petrochemicals, and coal). They are responsible for the carcinogenicity of certain chemicals including benzidine and β-naphthalene. These two chemicals have been banned since the 1960s in most industrialised countries. In most cases, UTUCs are secondary to an amino tumour of the bladder. The average duration of exposure needed to develop a UTUC is approximately 7 yr, with a latency period of about 20 yr following the termination of exposure. The estimated risk (odds ratio) of developing UC after exposure to aromatic amines is 8.3 [21,22]. Upper urinary tract tumours resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s [21].

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, respectively, of this nephropathy [23–26]. Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* (plants endemic to the Balkans). This acid contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action due to their ability to make up covalent

links with cell DNA. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the nonexposed population and predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC [21,23,24].

A high incidence of UTUC has also been described in Taiwan, especially in the population on the southwest coast of the island, and it represents 20–25% of UCs in the region [21,24]. The association of UTUC with blackfoot disease and arsenic exposure remains unclear in this patient population [21,24]. Differences in the ability to counteract carcinogens may contribute to host susceptibility and the risk of developing UC. Although it is not unusual that a genotype confers protection for an organ and increases the risk for another, UTUC may share some risk factors or molecular disruption pathways with bladder UC, but each has its own specific features. Certain genetic polymorphisms are associated with an increased risk of cancer or faster disease progression; thus there is variability in interindividual susceptibility to the risk factors just mentioned. Only two polymorphisms specific to UTUC have been reported so far [27,28]. A variant allele, SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC.

3.3. Histology and classification

3.3.1. Histologic types

More than 95% of UCs are derived from the urothelium and correspond to UTUCs or bladder tumours [13,29]. With regard to UTUCs, morphologic variants have been described that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours, and such UCs are associated with one of the following variants: micropapillary, clear cell, neuroendocrine, and lymphoepithelial [29,30]. Collecting duct carcinoma has similar characteristics to UTUC because of its common embryologic origin [31]. Upper urinary tract tumours with pure nonurothelial histology are exceptions [32,33], but a variant can be seen in nearly 25% of cases [34]. Squamous cell carcinomas of the upper urinary tract represent <10% of pyelocaliceal tumours and are even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious disease arising from stones in the urinary tract [29,30]. Other histologic subtypes are adenocarcinomas (<1%), small cell carcinomas, and sarcomas.

3.3.2. Classification

The classification and morphology of UTUCs are similar to those of bladder carcinomas [13]. It is possible to distinguish between noninvasive papillary tumours (papillary urothelial tumours of low malignant potential, low-grade papillary UC, high-grade papillary UC), flat lesions (carcinoma in situ [CIS]), and invasive carcinomas. All variants of urothelial tumours described in the bladder can also be observed in the upper urinary tract [34].

Table 1 – TNM 2009 classification for upper tract urothelial carcinoma [35]

T: Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Noninvasive papillary carcinoma
Tis CIS
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
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 in the greatest dimension
N2 Metastasis in a single lymph node >2 cm but not >5 cm in the greatest dimension, or multiple lymph nodes, none >5 cm in the greatest dimension
N3 Metastasis in a lymph node >5 cm in the greatest dimension

M: Distant metastasis
M0 No distant metastasis
M1 Distant metastasis

CIS = carcinoma in situ.
All European Association of Urology guidelines advocate the TNM system of tumour classification.

3.3.2.1. TNM staging. Table 1 presents the Union Internationale Contre le Cancer 2009 TNM classification used throughout these guidelines [35]. According to the TNM classification, the regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect the N classification.

There is an interest in using a renal pelvic pT3 subclassification to discriminate between microscopic infiltration of the renal parenchyma (pT3a) versus macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b) [34,36]. pT3b UTUCs are more likely to have aggressive pathologic features and have a higher risk of recurrence [34,36].

3.3.2.2. Tumour grade. Until 2004, the most common classification used was the World Health Organisation (WHO) classification of 1973 that distinguished only three grades (G1, G2, and G3) [37]. In recent years, molecular biologic data have allowed for further distinction between different tumour groups and the development of a new classification system that better reflects the potential growth of these tumours [38]. Thus the 2004 WHO classification now takes histologic data into account to distinguish among three groups of noninvasive tumours: papillary urothelial neoplasia of low malignant potential, low-grade carcinomas, and high-grade carcinomas. There are almost no tumours of low malignant potential in the upper urinary tract [29,30].

3.4. Symptoms

The diagnosis of UTUC may be fortuitous or related to the exploration of symptoms. The symptoms are generally restricted [39]. The most common symptom of UTUC is gross or microscopic haematuria (70–80%) [40]. Flank pain occurs in 20–40% of cases, and a lumbar mass is present in 10–20% [41,42]. However, systemic symptoms (altered health condition including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt consideration of a more rigorous metastatic evaluation [41,42].

3.5. Diagnosis

3.5.1. Imaging

3.5.1.1. Computed tomography urography. Computed tomography (CT) urography is the imaging technique with the highest diagnostic accuracy for UTUC and has replaced intravenous excretory urography and ultrasonography as the first-line imaging test for investigating high-risk patients [40]. The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used [43–50]. Attention to technique is therefore very important for optimum results.

CT urography of the urinary tract acquires at least one image series during the excretory phase, usually 10–15 min, following the administration of intravenous contrast medium [51]. Rapid acquisition of thin sections allows high-resolution isotropic images to be produced that can be viewed in multiple planes to assist with diagnosis without degradation of resolution [52,53].

CT urography can also detect wall thickening of the renal pelvis or ureter, which is a sign of UTUC, even when there is no luminal mass effect, but flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening [54]. The secondary sign of hydronephrosis on imaging in the presence of UTUC is associated with advanced pathologic disease and poorer oncologic outcomes [51,55].

3.5.1.2. Magnetic resonance imaging. Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography usually when radiation or iodinated contrast media are contraindicated [56]. The sensitivity of MR urography is 75% after contrast injection for tumours <2 cm [56]. MR urography with certain gadolinium-based contrast media is contraindicated in selected 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 UTUCs in terms of greater diagnostic accuracy, lower cost, and greater patient acceptability.

3.5.2. Cystoscopy and urinary cytology

Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal and if CIS of the bladder or prostatic urethra has been largely excluded (eg, by biopsies of any suspicious lesion, possibly guided by photodynamic diagnosis) [13,57]. Cytology is less sensitive for UTUC than for bladder tumours, even for high-grade lesions, and it should ideally be performed *in situ* (ie, in the renal cavities) [58]. Retrograde ureteropyelography (through a ureteral catheter or during ureteroscopy) remains an option for the exclusion of a tumour in the upper urinary tract [44,59]. However, urinary cytology of the renal cavities and ureteral lumina should preferably be performed prior to application of larger amounts of contrast agent for retrograde ureteropyelography because it may deteriorate cytologic specimens.

The sensitivity of fluorescence *in situ* hybridisation (FISH) for the identification of molecular abnormalities characterising UTUCs parallels its performance in bladder cancer; however, the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs may limit its usefulness [60,61]. In addition, FISH appears to have limited value for the surveillance of UTUCs [60,61].

3.5.3. Diagnostic ureteroscopy

Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis, and collecting system with a technical success approaching 95%. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate regardless of the size of the sample [62]. Undergrading may occur from the diagnostic biopsy, making intensive follow-up a requirement if renal-sparing treatments are selected [63]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [59,64,65].

Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney. If available, ureteroscopy and biopsy should be performed in the preoperative assessment of any UTUC patient. Combining ureteroscopic biopsy grade, diagnostic imaging findings such as hydronephrosis, and urinary cytology may help decision making on radical nephroureterectomy (RNU) versus endoscopic treatment [64,66].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve the visualisation and diagnosis of flat lesions. Narrow band imaging appears to be the most promising technique, but results are still preliminary [66,67]. Table 2 lists the recommendations.

3.6. 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 [67,68]. This section briefly describes the currently recognised prognostic factors [69].

Table 2 – Guidelines for the diagnosis of upper tract urothelial carcinoma

Recommendations	Grade
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
Computed tomography urography	A
Diagnostic ureteroscopy and biopsy	C
Retrograde ureteropyelography	C

3.6.1. Tumour stage and grade

According to the most recent classifications, the primary recognised prognostic factors are tumour stage and grade [64,69–71]. Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with UTUCs and positive lymph node metastases [72].

3.6.2. Age and sex

Sex is no longer considered an independent prognostic factor that influences UTUC mortality [15,69,73]. Conversely, patient age is still considered an independent prognostic factor because older age at the time of RNU is associated with decreased cancer-specific survival (LE: 3) [69,74]. However, chronological age alone should not be an absolute exclusion criterion for the treatment of potentially curable UTUC but rather overall life expectancy. A significant proportion of elderly patients can still be cured with RNU [74]. This suggests that chronological age alone is an inadequate indicator of outcomes in older UTUC patients [74,75].

3.6.3. Ethnicity

There are differences in clinicopathologic characteristics of tumours between white and Japanese patients. However, race and ethnicity are not recognised so far as independent factors for survival (LE: 3) [76].

3.6.4. Tumour location

According to the most recent findings, the initial location of the tumour within the upper urinary tract (eg, ureter vs renal pelvis) is a prognostic factor [77–79] (LE: 3). There is a prognostic impact of tumour location when adjusted for tumour stage: Ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours [69,78–80].

3.6.5. Tobacco consumption

Smoking intensity (long-term exposure) and being a smoker at diagnosis increases the risk for poor oncologic outcomes (LE: 3) [81–83].

3.6.6. Lymphovascular invasion

Lymphovascular invasion is present in approximately 20% of UTUCs and an independent predictor of survival [84,85]. Lymphovascular invasion status should be systematically included and specifically reported in the pathologic report of all RNU specimens (LE: 3) [84,86].

3.6.7. Surgical margins

A positive surgical margin after RNU appears to be a significant factor for developing subsequent UTUC metastases (LE: 3). Pathologists should look for, and report on, positive margins at the level of ureter transections, bladder cuff, and around the tumour if the tumour is >T2 [87].

3.6.8. Other factors

Extensive tumour necrosis is an independent predictor of clinical outcomes in patients who undergo RNU. Extensive tumour necrosis can be defined as >10% of the tumour area (LE: 3) [88,89]. The tumour architecture (eg, papillary vs sessile) of UTUCs appears to be associated with the

prognosis after RNU. A sessile growth pattern is associated with the worst outcomes (LE: 3) [90,91]. The presence of concomitant CIS in patients with organ-confined UTUC is associated with a higher risk of recurrent disease and cancer-specific mortality (LE: 3) [92,93]. Similar to lower tract urothelial carcinoma, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [94]. A previous history of bladder CIS is associated with increased risk of recurrence and death from UTUCs (LE: 3) [95].

The American Society of Anaesthesiologists score also correlates significantly with cancer-specific survival after RNU (LE: 3) [96], but Eastern Cooperative Oncology Group performance status correlates only with overall survival [97]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients with UTUCs (LE: 3) [98].

3.6.9. Molecular markers

Several research groups are working on UTUC characteristics and carcinogenesis pathways. Several studies have investigated the prognostic impact of various tissue-based markers that are related to cellular processes such as cell adhesion (E-cadherin and CD24), cell differentiation (snail and epidermal growth factor receptor), angiogenesis (hypoxia inducible factor-1α and metalloproteinases), cell proliferation (Ki-67), epithelial mesenchymal transition (snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin), and vascular invasion (récepteur d'origine nantais [RON]) and c-met protein (MET) [69,99–102]. However, because of the rarity of the disease, the main limitations shared by these studies are their retrospective nature and their small sample size. Microsatellite instability (MSI) is an independent molecular maker used for tumour prognosis [103]. In addition, MSI can help detect germline mutations, allowing for the detection of possible hereditary cancers [17].

To date, none of the markers has fulfilled the clinical and statistical criteria necessary to support their introduction in daily clinical decision making.

3.7. Prediction and risk stratification

Available accurate predictive tools are rare in UTUCs. Two models are available in a preoperative setting: one for the prediction of locally advanced cancer that could guide the extent of lymph node dissection at the time of RNU [104], and one for selection of non–organ-confined UTUCs that are likely to benefit from nephroureterectomy [105]. Two nomograms can predict survival rates in a postoperative setting based on standard pathologic features: one coming from an international group [106] and the other one built from a European population only [107].

3.8. Treatment

3.8.1. Localised disease

3.8.1.1. Radical nephroureterectomy. RNU with excision of the bladder cuff is the gold standard treatment for UTUC,

regardless of the location of the tumour in the upper urinary tract (LE: 3) [14]. The RNU procedure must comply with oncologic principles that consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection [14]. Resection of the distal ureter and its orifice is performed because it is a part of the urinary tract with considerable risk of tumour recurrence. After removal of the proximal part, it is almost impossible to image or approach it by endoscopy during follow-up. Recent publications on survival after RNU have concluded that removal of the distal ureter and bladder cuff is beneficial [108–110].

McDonald et al. presented the pluck technique in 1952, but it was not until 1995 [111] that the usefulness of an endoscopic approach to the distal ureter was emphasised, and then several other alternative techniques were reconsidered to simplify resection of the distal ureter: stripping, transurethral resection of the intramural ureter, and intussusception techniques [11,109]. Apart from ureteral stripping, none of these techniques is inferior to excision of the bladder cuff (LE: 3) [74–76,78]. Nevertheless, the endoscopic approach is clearly associated with a higher risk of subsequent bladder recurrence [112].

A delay between diagnosis and removal of the tumour may increase the risk of disease progression. However the cut-off has been disputed between 45 d and 3 mo, and it remains a moot point (LE: 3) [113–115].

Lymph node dissection (LND) associated with RNU is of therapeutic interest and allows for optimal staging of the disease (LE: 3) [116,117]. However, the anatomic sites of LND have not yet been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed [118]. LND appears to be unnecessary in cases of TaT1 UTUCs because it was reported to be retrieved in 2.2% of T1 versus 16% of pT2–4 tumours [117]. In addition, a continuous increase in the probability of lymph node–positive disease related to pT classification has been described [117]. However, these data are retrospective; consequently, underreporting of the true rate of node-positive disease is likely. It is not yet possible to standardise either indication or extent of LND. However, LND can be achieved according to lymphatic drainage as follows: LND medially to the ureter in ureteropelvic tumour, retroperitoneal LND in case of higher ureteral tumour and/or tumour of the renal pelvis (ie, right side: border vena cava, and left side: border aorta) [116–118].

Laparoscopic RNU has not yet achieved final proof of its safety. There are early reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway when large tumours were manipulated in a pneumoperitoneal environment [119,120].

Several precautions must be taken when operating with a pneumoperitoneum because it may increase tumour spillage:

- Entering the urinary tract should be avoided.
- Direct contact of the instruments with the tumour should be avoided.

- Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided, and an endobag is necessary to extract the tumour.
- The kidney and ureter must be removed en bloc with the bladder cuff.
- Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.

Recent data show a tendency towards equivalent oncologic outcomes after either laparoscopic or open RNU [121–126]. In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes (LE: 3) [121–126]. Only one prospective randomised study of 80 patients has provided evidence that laparoscopic RNU is not inferior to open RNU for noninvasive UTUC (LE: 2) [127]. In addition, it has been demonstrated that oncologic outcomes after RNU have not changed significantly over the past 3 decades despite staging and surgical refinements (LE: 3) [128]. Recommendations are listed in Table 3.

3.8.1.2. Conservative surgery. Conservative surgery for low-risk UTUCs allows preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery. Conservative management of UTUCs can be considered in imperative cases (renal insufficiency or solitary functional kidney) or in elective cases (when the contralateral kidney is functional) for low-grade, low-stage tumours (LE: 3) [110,129,130]. The choice of technique depends on technical constraints, the anatomic location of the tumour, and the experience of the surgeon.

3.8.1.2.1. Ureteroscopy. Endoscopic ablation can be considered in highly selected cases and in these situations [131–133]:

- A flexible rather than a rigid ureteroscope, laser generator [134], and pliers (pluck) for biopsies are available (LE: 3) [132,135].

Table 3 – Guidelines for radical management of upper tract urothelial carcinoma: radical nephroureterectomy

Indications for RNU for UTUC	Grade
Suspicion of infiltrating UTUC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Noninvasive but large (ie, >2 cm) UTUC	B
Techniques for RNU for UTUC	
Open and laparoscopic access are equivalent in terms of efficacy	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable except stripping	C
Lymphadenectomy is recommended in case of invasive UTUC	C
Postoperative instillation (chemotherapy) is recommended after RNU to avoid bladder recurrence	B
RNU = radical nephroureterectomy; UTUC = upper tract urothelial carcinoma.	

- The patient is informed of the need for closer, more stringent surveillance.
- A complete resection of the tumour is strongly advocated.

However, there is a risk of understaging and undergrading the disease with pure endoscopic management.

3.8.1.2.2. Segmental resection. Segmental ureteral resection with wide margins provides adequate pathologic specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Ureteroureterostomy is indicated for noninvasive low-grade tumours of the proximal ureter or midureter that cannot be removed completely by endoscopic means (ie, size or multiplicity) and for high-grade or invasive tumours when renal-sparing surgery for preservation of renal function is a goal (LE: 3). High-grade tumours of the proximal ureter or midureter should undergo RNU with excision of the bladder cuff when possible. Complete distal ureterectomy and neocystostomy is indicated for noninvasive low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means (ie, size or multiplicity) and for high-grade locally invasive tumours (LE: 3) [136–138]. For both ureteroureterostomy and complete distal ureterectomy and neocystostomy, it is necessary, however, to ensure that the area of tissue around the tumour is not invaded. Segmental resection of the iliac and lumbar ureter is associated with a failure rate greater than that for the distal pelvic ureter [136–138]. Open resection of tumours of the renal pelvis or calices has almost disappeared. Resection of pyelocaliceal tumours is technically difficult, and the recurrence rate is higher than for tumours of the ureter.

3.8.1.2.3. Percutaneous access. Percutaneous management can be considered for low-grade or noninvasive UTUCs in the renal cavities (LE: 3) [132,139,140]. This treatment option may be offered to patients with low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by ureteroscopy. A theoretical risk of seeding exists in the puncture tract and in perforations that may occur during the procedure. This approach, however, is being progressively abandoned due to enhanced materials and advances in distal-tip deflection of recent ureteroscopes [132,139,140].

3.8.1.3. Adjuvant topical agents. The antegrade instillation of bacillus Calmette-Guérin vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete eradication of the tumour) is technically feasible after conservative treatment of UTUCs or for the treatment of CIS (LE:3) [141]. Retrograde instillation through a ureteric stent or with the help of the reflux obtained from a double J stent have also been used [142], but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The medium-term results are similar to those observed for the treatment of bladder tumours but have not been confirmed in long-term studies (LE: 3) [141,142].

Table 4 – Guidelines for conservative management of upper tract urothelial carcinoma

Indications for conservative management of UTUC	Grade
Unifocal tumour	B
Tumour size <1 cm	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on computed tomography urography	B
Understanding of close follow-up	B
Techniques used in conservative management of UTUC	
Laser should be used in case of endoscopic treatment	C
Flexible ureteroscopy is preferable over rigid ureteroscopy	C
A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment	C
RSS = renal-sparing surgery; UTUC = upper tract urothelial carcinoma.	

One prospective randomised study of 144 patients provided evidence that a single postoperative dose of intravesical mitomycin reduces the risk (ie, absolute risk 11%) of a bladder tumour within the first year following RNU (LE: 2) [143]. Table 4 lists the recommendations.

3.8.2. Advanced disease

3.8.2.1. Nephroureterectomy. There are no benefits of RNU in metastatic (M+) disease, although it can be considered a palliative option (LE: 3) [14,117].

3.8.2.2. Chemotherapy. UTUCs are urothelial tumours; therefore, platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer. Several platinum-based chemotherapy regimens have been proposed [144]. However, adding chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, to a population with already impaired postsurgical renal function may also be related to the reduced survival in these patients [145,146]. In addition, not all the patients receive this treatment because of comorbidity and impaired renal function after radical surgery.

Contrary to what has been demonstrated for bladder cancer, there have been no reported effects of neoadjuvant chemotherapy for UTUCs in the only study published to date [147]. Although survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the sustained support of trials using this strategy in UTUCs.

Adjuvant chemotherapy can somehow achieve a recurrence-free rate of up to 50% but has clearly no impact on survival [148,149]. Further data are awaited from the ongoing prospective randomised Peri-operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer trial [150]. Data are currently insufficient to provide any recommendations.

3.8.2.3. Radiotherapy. Adjuvant radiotherapy may improve local control of the disease [151]. When given in combination with cisplatinum, it may result in longer disease-free and overall survival [152] (LE: 3). Radiotherapy appears to be scarcely relevant today both as a unique therapy and associated with chemotherapy as adjuvant therapy (Fig. 1).
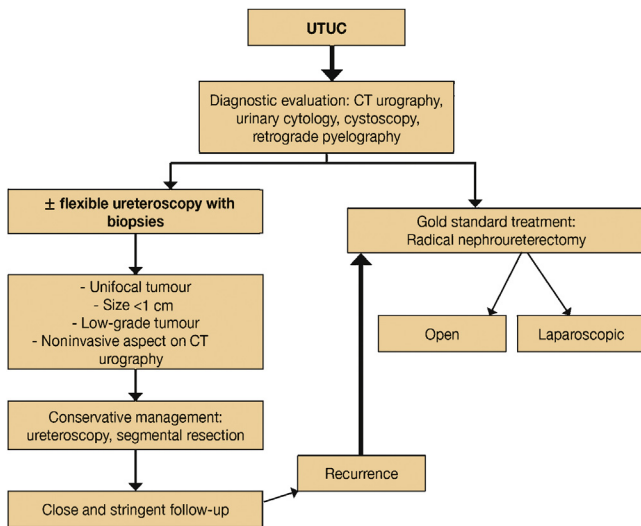
Fig. 1 – Radical nephroureterectomy treatment. CT = computed tomography; UTUC = upper tract urothelial carcinoma.

3.9. Follow-up

Stringent follow-up of UTUC patients after surgical treatment is mandatory to detect metachronous bladder tumours (in all cases), local recurrence, and distant metastases (in the case of invasive tumours). When RNU is performed, local recurrence is rare, and the risk of distant metastases is directly related to the risk factors listed previously. The reported recurrence rate within the bladder after treatment of a primary UTUC varies considerably from 22% to 47% [8,10]. Thus the bladder should be observed in all cases.

The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 yr [8–10]. Bladder recurrence should not be considered as a distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence [129,133,135]. Despite notable improvements in endourologic technology, the follow-up of patients treated with conservative therapy is difficult, and frequent and repeated endoscopic procedures are necessary. Table 5 lists the recommended follow-up schedules.

Table 5 – Guidelines for follow-up of patients with upper tract urothelial carcinoma after initial treatment

After RNU, over at least 5 yr	Grade
Noninvasive tumour	
Cystoscopy/urinary cytology at 3 mo and then yearly	C
CT every year	C
Invasive tumour	
Cystoscopy/urinary cytology at 3 mo and then yearly	C
CT urography every 6 mo over 2 yr and then yearly	C
After conservative management, over at least 5 yr	
Urinary cytology and CT urography at 3 and 6 mo, and then yearly	C
Cystoscopy, ureteroscopy, and cytology *in situ* at 3 and 6 mo, and then every 6 mo over 2 yr, and then yearly	C
CT = computed tomography; RNU = radical nephroureterectomy.	

4. Conclusions

These renewed UTUC guidelines contain information for the diagnosis and treatment of individual patients according to a current standardised approach. When determining the optimal treatment regimen for their patients, urologists must take into account each individual patient's specific clinical characteristics with regard to renal function including medical comorbidity; tumour location, grade, and stage; and molecular marker status.

Slawin K, Kattan M, Shariat S, Stephenson A, Scardino P, inventors. Nomogram for predicting outcome of salvage radiotherapy for suspected local recurrence of prostate cancer after radical prostatectomy. US patent Fi. 2003.

Shariat S, inventor. Solube Fas: a promising novel urinary marker for the detection of bladder transitional cell carcinoma (UTSD: 1666). US patent application in process.

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