Guidelines on

Urothelial Carcinomas of the Upper Urinary Tract

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European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

The last 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; urothelial carcinoma; renal pelvis; ureter; chemotherapy; nephroureterectomy; adjuvant treatment; 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 evaluation of the quality of information provided, levels of evidence (LE) and grades of recommendation (GR) were inserted according to general principles of evidence-based medicine (EBM) (2).

2.2 Publication history

A first guidelines publication on upper urinary tract tumours was presented in 2004 (3). This document was updated and included in the EAU Guidelines compilation print in 2011. The current 2013 publication presents a limited update of the 2011 document.

This document was peer reviewed prior to publication.

2.3 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

3. EVIDENCE SYNTHESIS

3.1 Epidemiology

Urothelial carcinomas 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 urothelial carcinomas and are the most common malignancy of the urinary tract (1,5). However, UTUCs are uncommon and account for only 5-10% of urothelial carcinomas (4,6). The estimated annual incidence of UTUCs in western countries is about two 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 non-polyposis 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 years of age, has a personal history of an HNPCC-associated cancer, a first-degree relative aged < 50 years 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 by 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 (e.g., 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 years, with a latency period of about 20 years 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 non-exposed population and is 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 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 inter-individual 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 **Histological types***

More than 95% of UCs are derived from the urothelium and correspond to UTUCs or bladder tumours (13,29). With regard to UTUCs, morphological 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 non-urothelial 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 histological 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 non-invasive 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).

3.3.2.1 Tumour Node Metastasis staging

Table 1 presents the Union Internationale Contre le Cancer (UICC) 2009 Tumour Node Metastasis (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 to use 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 pathological features and have a higher risk of recurrence (34,36).

Table 1: TNM classification 2009 for UTUC (35)*

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive 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 or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

**All EAU guidelines advocate the TNM system of tumour classification.*

3.3.2.2 Tumour grade

Until 2004, the most common classification used was the World Health Organization (WHO) classification of 1973, which distinguished only three grades (G1, G2 and G3) (37). In recent years, molecular biological 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 histological data into account to distinguish among three groups of non-invasive 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.

Computed tomography 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).

Computed tomography 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 pathological disease and poorer oncological 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). Magnetic resonance 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.

Computed tomography 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 (e.g., 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* (i.e., 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 uretero- and pyelography, because it may deteriorate cytological 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 upper UTUCs surveillance (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 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.

Table 2: Guidelines for the diagnosis of UTUC

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

CT urography = Computed tomography urography

3.6 Prognostic factors

UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 (67,68). This section briefly describes the currently recognised prognostic factors (69).

*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, chronologic 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 clinicopathological characteristics of tumours between Caucasian and Japanese patients. However, race and ethnicity are not so far recognised 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 (e.g., 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 oncological 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***

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 transsections, 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 (e.g., 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 Anesthesiologists (ASA) score also significantly correlates with cancer-specific survival after RNU (LE: 3) (96) but ECOG 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 (Ki67), 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 germ-line 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.

There are two available models 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).

Additionally there are two nomograms that can predict survival rates in a postoperative setting based on standard pathological 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

Radical nephroureterectomy 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 oncological principles, which 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 days and 3 months 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 anatomical 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).

Lymph node dissection appears to be unnecessary in cases of TaT1 UTUCs because it was reported to be retrieved in 2.2% T1 versus 16% 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, under-reporting 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 (i.e., right side: border vena cava and left side: border aorta) (116-118).

The 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 oncological 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 non-invasive UTUC (LE: 2) (127). In addition, it has been demonstrated that oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements (LE: 3) (128). Recommendations are listed in Table 3.

Table 3: Guidelines for radical management of UTUC: RNU

Indications for RNU for UTUC	**GR**
Suspicion of infiltrating UTUC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Non-invasive but large (i.e. > 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

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 anatomical 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).
- 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 pathological specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means (i.e., size or multiplicity) and for high-grade or invasive tumours when renal sparing surgery

(RSS) for preservation of renal function is a goal (LE: 3). High-grade tumours of the proximal ureter or mid-ureter should undergo RNU with excision of bladder cuff when possible. Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means (i.e., 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 non-invasive 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).

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

Table 4: Guidelines for conservative management of UTUC

Indications for conservative management of UTUC	**GR**
Unifocal tumour	B
Tumour size less than 1 cm	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on CT 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
Ureteroureterostomy is indicated for non-invasive low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means, and for high-grade or invasive tumours when RSS for preservation of renal function is a goal	C
Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means and for high-grade, locally-invasive tumours	C

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.

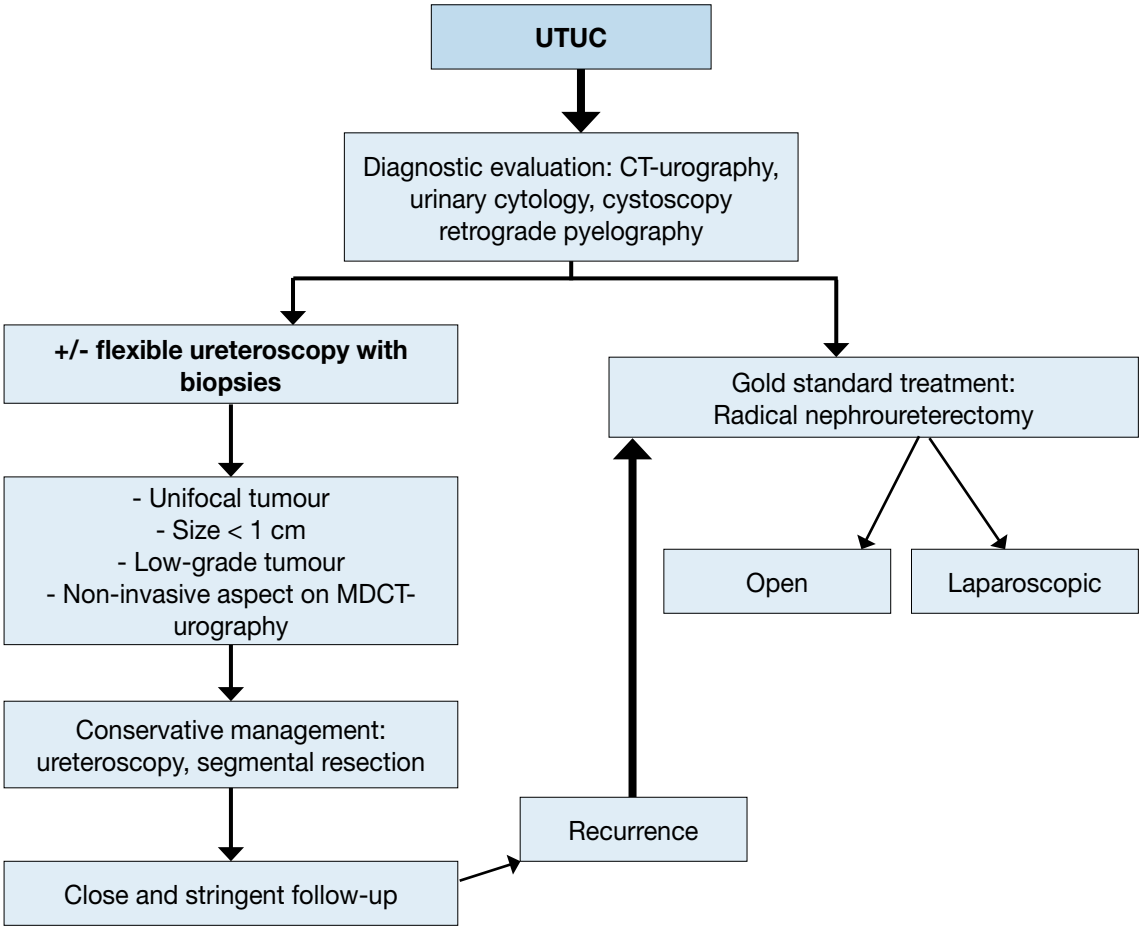
Contrary to what has been demonstrated for bladder cancer, there have been no reported effects of neoadjuvant chemotherapy for UTUCs in the only study published to date (147). Although survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the 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 POUT trial (PeriOperative chemotherapy or sUrveillance in upper Tract urothelial cancer) (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 nowadays both as a unique therapy and associated with chemotherapy as adjuvant therapy (Fig. 1).

Fig. 1: Proposed flowchart for the management of UTUC



MDCT = multidetector computed tomography

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 years (8-10). Bladder recurrence should not be considered as 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 endourological 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 UTUC patients after initial treatment

After RNU, over at least 5 years	**GR**
Non-invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT every year	C
Invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT urography every 6 months over 2 years and then yearly	C
After conservative management, over at least 5 years	
Urinary cytology and CT urography at 3 and 6 months, and then yearly	C
Cystoscopy, ureteroscopy and cytology *in situ* at 3 and 6 months, and then every 6 months over 2 years, and then yearly	C

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.

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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

EBM	evidence based medicine
CIS	carcinoma *in situ*
CT	computed tomography
EAU	European Association of Urology
EBM	evidence-based medicine
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence *in situ* hybridisation
GR	grade of recommendation
HIF	hypoxia-inducible factor
HNPCC	hereditary nonpolyposis colorectal carcinoma
LE	level of evidence
CT Urography	computed tomographic urography
MRI	magnetic resonance imaging
MSIs	microsatellite instabilities
RNU	radical nephroureterectomy
TNM	Tumour Node Metastasis
UTUC	upper tract urothelial carcinoma
WHO	World Health Organization
LND	Lymph node dissection

Conflict of interest

All members of the Upper Urinary Tract Urothelial Carcinomas Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.