

Chapter 2

Diagnosis and Evaluation of Upper Tract Urothelial Carcinoma (UTUC)

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Abstract Upper tract urothelial carcinomas (UTUC) are scarce and account for only 5–10 % of urothelial carcinomas. The estimated annual incidence of UTUC in Western countries is about 1–2 new cases per 100,000 inhabitants. Pyelocaliceal tumors are about twice as common as ureteral tumors. The diagnosis of a UTUC may be fortuitous or related to the exploration of symptoms. The symptoms are generally restricted. The most common symptom of UTUC is gross or microscopic haematuria (70–80 %). Flank pain occurs in 20–40 % of cases, and a lumbar mass is present in 10–20 %. In case of UTUC, a cystoscopy is mandatory to rule out a concomitant bladder tumor. 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

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by photodynamic diagnosis). Cytology is less sensitive for UTUC than for bladder tumors, even for high-grade lesions, and it should ideally be performed in situ (i.e., in the renal cavities). Retrograde ureteropyelography (through a ureteral catheter or during ureteroscopy) remains an option for the exclusion of a tumor in the upper urinary tract. 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. In addition, the possible advantages of ureteroscopy should be discussed in the preoperative assessment of any UTUC patient. Flexible ureteroscopy is used to visualize and biopsy the ureter, renal pelvis, and collecting system with a technical success approaching 95 %. Such ureteroscopic biopsies can determine tumor grade in 90 % of cases with a low false-negative rate regardless of the size of the sample. Ureteroscopy also facilitates selective ureteral sampling for cytology in situ. Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, in patients with a solitary kidney, or when conservative treatment is being considered.

Keywords Renal pelvis • Ureter • Urothelial carcinoma • Ureteroscopy • Computed tomography • Urinary cytology

Introduction

Because of their low incidence, upper tract urothelial carcinomas (UTUC) are often discovered during a symptomatic episode or during surveillance of bladder cancers. Over the past 10 years, technical advances in both imaging and endoscopy have improved the evaluation of these tumors preoperatively. We are entering a new era of preoperative assessment for both clinical imaging and endoscopy. This multimodal predictive assessment should lead, in the near future, to a more conservative treatment when possible or to a more intensive and multimodal adapted radical treatment (extended lymphadenectomy, neoadjuvant or adjuvant therapy).

Elements of Diagnosis

Clinical Revelation

Hematuria

Hematuria is the most common symptom found in the diagnosis of UTUC (75–82 % of cases) [1, 2]. However, among patients with isolated hematuria, the diagnosis of UTUC is rare involving only 0.32 % of cases. Hematuria may be gross or microscopic, often total, and sometimes terminal when a tumor of the lower

ureter is prolapsed at the meatus. Its abundance is variable, as is its frequency (intermittent, recurrent, and permanent). This typically painless disorder can sometimes be responsible for pain (renal colic) in cases of clotting or tumor-related obstruction in the upper tract.

Pain

Flank and lumbar pain is the second most frequent symptom of UTUC (20–30 % of cases). The most common disease etiology is ureteral obstruction by either intraluminal clotting or due to a bulky tumor. Progressive upper tract obstruction by the tumor is responsible for lumbar pain due to the dilatation of the proximal ureter and kidney [3]. Locoregional tumor extension is an infrequent cause of constant and poorly localized pain. Metastatic tumor dissemination to regions including the bone can also be responsible for pain.

Other Clinical Signs

Other clinical signs are present in approximately 10 % of cases. A palpable mass is correlated with very advanced tumors of the renal pelvis or the caliceal system or a hydronephrotic kidney. Due to the rising rates of obesity and location of the kidney behind the rib cage, a palpable mass is rarely noted.

Irritative or infectious symptoms may also be present at UTUC diagnosis. Urinary frequency can be caused by tumors in the lower ureter that are located in the intramural ureter or prolapsed at the meatus or due to concomitant bladder cancer (especially Carcinoma In Situ). Pyelonephritis may complicate the hydronephrosis caused by the tumor obstruction.

The deterioration of patients' general condition and development of constitutional symptoms (e.g., weight loss, anorexia) is possible but rare. When present, this deterioration often indicates advanced or metastatic tumors [3].

Asymptomatic Patients

In several recent series, the rate of asymptomatic tumors varies from 10 to 15 % of cases. However, these diagnoses are fortuitous because they are revealed following image analysis (including abdominopelvic CT) performed for other reasons.

Another circumstance of UTUC diagnosis in asymptomatic patients occurs after examination for non-muscle invasive bladder cancer (NMIBC). While upper tract tumor recurrence is a rare event (less than 5 %) for patients with NMIBC, a previous history of NMIBC was found in 10–30 % of UTUC cases.

Upper tract recurrence is a lifelong risk in patients with bladder cancer. A recent publication has described the practicality of routine surveillance by CT urography in this population to detect recurrence in the upper tract [4]. However, in case of

previous NMIBC, systematic routine upper tract imaging appears to have a low profitability and is not currently recommended (i.e., overall efficacy of less than 0.5 %) [5].

Conversely, after cystectomy for muscle invasive bladder urothelial carcinoma (MIBC), regular follow-ups with CT urography combine the advantage to explore the urinary tract functionally and oncologically [6]. While these recurrences are rare (0.75–6.4 %), routine follow-up investigations detect them in only 38 %. However, the use of CT urography was recommended to improve detection especially in high-risk patients after cystectomy (high-grade tumor, carcinoma in situ, multifocal disease, history of multiple urothelial recurrences, the presence of ureteral tumors/CIS, positive ureteral margins, positive urethral margins, urethral involvement, or history of upper urinary tract urothelial carcinoma) who undergo CT urography might more efficiently detect recurrence.

Imaging

CT Urography

The opacification of the urinary tract has been the most commonly used diagnostic tool for the diagnosis of UTUC. Urinary excretion of contrast or retrograde opacification of the urinary tract can usually locate the lesion in the urinary tract, given its size and endo-luminal characteristics, and help to objectify other lesions. Intravenous urography (IVU) has been the radiological standard for UTUC characterization. The opacification is achieved by the intravenous injection of a hypo-osmolar iodinated contrast agent and by simple radiographs of the abdomen. However, it is currently no longer recommended as a first-line procedure.

The development of CT urography using thin slices (<2 mm), various protocols to visualize the entire urinary tract (hyperhydration, diuretic injection), and excretory acquisition time (6–8 min after injection) now offers improved accuracy over IVU. Indeed, Wang et al. reported the sensitivity of IVU is 75 % vs. 95.8 % for CT urography and the specificity of IVU is 86 % vs. 100 % for CT urography [7].

Chlapoutakis et al. compiled the results of five studies in a meta-analysis and found that the sensitivity of CT urography for the diagnosis of UTUC was 96 % (88–100 %) and the specificity was 99 % (98–99 %) [8].

However, the cutoff for lesion detection by CT urography is 2–3 mm in terms of spatial resolution. For lesions <3 mm, the detection sensitivity drops to 40 %.

Moreover, CT urography facilitates a more comprehensive assessment of the lesion through MPR (multiplanar reformatted imaging) type reconstructions and the evaluation of its extension on the nodes and metastasis. Unfortunately, it is impossible to accurately determine the depth of tumor invasion (cT stage: cTa to cT2) due to insufficient spatial resolution.

Radiological appearance of intraluminal lesions is identical on IVU and CT urography:

- Within pelvicaliceal cavities, the CT images of these tumors depend on their growth (papillary or non-papillary invasive). Papillary tumors are seen as intraluminal masses with tissue density [40–50 Hounsfield units (HU)]. These mass lesions are sometimes heterogeneous but rarely calcified (<3 %). Their enhancement after injection of contrast is often discrete (50–60 HU), whereas during the excretory time, UTUCs appear as gaps with a sessile or pedunculated base. Infiltrative forms correspond to a nonspecific thickening of the wall that is more or less circumferential and/or irregular [9]. In case of hydronephrosis, it is sometimes possible to distinguish the UTUC due to higher density than the non-opaque urine.
- Within the ureter, UTUC can take the appearance of wall thickening or a filling defect. The radiographic images allow the detection of Bergman's sign (widening of the ureter below the lesion), which is not present with obstructions due to ureteral stones. In case of poor opacification of a dilated ureter, the suspicion of tumor presence is high, especially if there is an enhancement of the ureter wall at this level. It is then necessary to repeat the exam after placing the patient in the prone position [9].

The disadvantages of this technique include a relatively large radiation dose (16–35 mSv), the potential side effects associated with the injected iodinated contrast agent (anaphylaxis, acute tubular necrosis), and the high cost (approximately 3 times higher than the IVU).

Today, CT urography remains the gold standard for the diagnosis of UTUC (grade A recommendation) [2].

MR Urography

Magnetic Resonance Urography is the modality of choice in cases where CT urography is not recommended because of an allergy to iodinated contrast agents or moderate renal impairment. However, gadolinium contrast used for MRI is contraindicated in patients with severe chronic renal impairment with creatinine clearance <30 mL/min, due to the risk of nephrogenic systemic fibrosis. In those cases, retrograde pyelogram is preferred.

The radiological findings are identical to those described for CT urography. Usually, the lesions appear iso-attenuating on T1 and hyper-attenuating on T2 compared to the muscle. Enhancement of the lesion after the injection of gadolinium can distinguish a suspected lesion from a calculus (Fig. 2.1).

Several different sequences are needed to improve performance. Thus, it is possible to obtain reconstructions of urinary tracts comparable to IVU sequences with TSE (turbo spin-echo), HASTE (T2-weighted apnea), and MIP (3D T1-weighted gadolinium and furosemide). The MR urography has a lower spatial resolution and

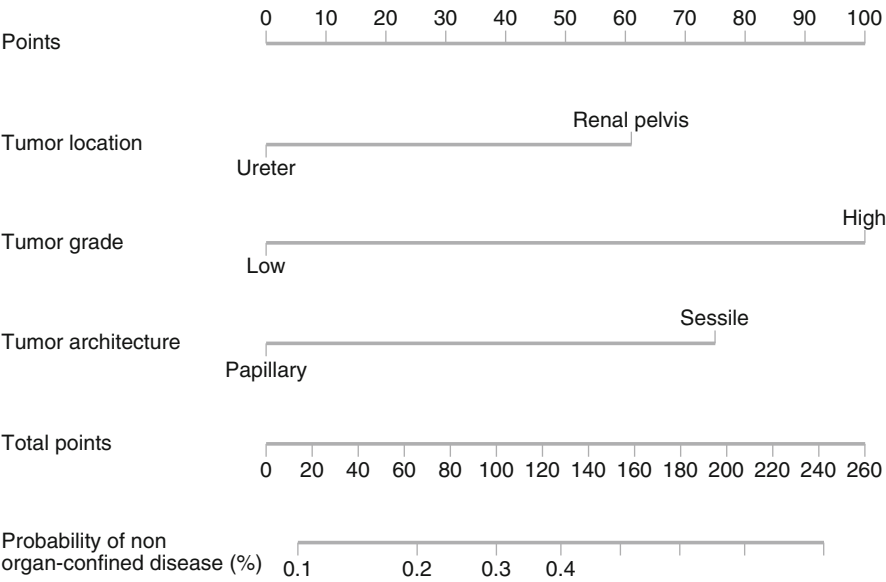


Fig. 2.1 Preoperative nomogram for prediction of organ-confined stage of the UTUC (adapted from Margulis V, et al.: Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. *J Urol.* 184: 453-8, 2010)

more artifacts by hematuria or the presence of a ureteral catheter than CT urography. Although only a few results have been published on this subject, the detection of UTUCs with MR urography has been demonstrated with a sensitivity of 70–80 % and specificity close to 100 % [10].

More recently, DWI (diffusion-weighted images) with calculation of apparent diffusion coefficient (ADC) was evaluated in the diagnosis of UTUC [11]. This technique, which does not require injection of gadolinium, is based on the diffusion of water molecules in tissue. This allows the calculation of the ADC for the renal parenchyma, dilated urinary system, and tumor. Several studies agree that the ADC of the pelvicaliceal cavities UTUC is significantly lower that of the adjacent tissue, making this sequence of interest for diagnosis in addition to conventional sequences [12]. The value of ADC in tumor staging is currently limited with conflicting data in the literature but appears to be associated with the tumor grade and proliferation markers [12, 13].

As with CT urography, MR urography has limited accuracy in staging cTa-cT2 grade tumors [14].

Endoscopy

Retrograde Ureteropyelography

Retrograde ureteropyelography (RUP) is usually performed during cystoscopy and/or flexible ureteroscopy under general anesthesia and is therefore not a diagnostic modality in its own right. This procedure consists of retrograde opacification by prior catheterization of the upper urinary tract with a ureteral catheter.

Using this approach, the delineation of the upper urinary tract following opacification demonstrates performance comparable to CT urography in terms of diagnostic sensitivity and specificity (96 % and 97 %, respectively) [15]. However, there is a bias since many patients already have a suspected lesion prior to going to the operating room for a RUP. This examination is recommended by several guidelines including that of the EAU (grade C) [2] and AUA.

Flexible Ureteroscopy and In Situ Biopsies

Technological advances have made ureteroscopy a valuable diagnostic tool for the evaluation of suspicious lesions in the upper urinary tract. Indeed, the use of flexible devices enables the complete examination of the upper tract, including the lower pole renal calices.

Ureteroscopy is particularly useful in cases of uncertain diagnoses, in cases of patients with a solitary kidney, or when conservative treatment is considered. Ureteroscopic examination is now recommended by the guidelines for the first-line screening of UTUC (recommendation of grade C) [2].

Flexible ureteroscopy allows a visual diagnosis in 95 % of cases [2]. Advances in image resolution with digital ureteroscopes reinforce the quality of this examination. The detection sensitivity could be improved by photodiagnosis using 5-aminolevulinic acid (5-ALA), especially for small lesions and carcinoma in situ, or Narrow Band Imaging (NBI) [16, 17]. The NBI system uses only a part of the visible spectra (between 415 and 540 nm), which enhances the contrast of the tumor neovascularization and thus the detection of the small lesion. The preliminary results are promising, with 22.7 % more lesions detected using this technique than with white light [17]. Further studies are warranted to evaluate whether tangential viewing within the ureter poses a limitation towards the use of these new technologies within the upper tract.

Morel et al. showed the limited applicability of rigid ureteroscopy in this context due to inability to explore the pyelocaliceal cavities [18].

However, the macroscopic visual diagnosis does not allow the infiltrating nature of the tumor to be determined. According to El-Hakim et al., the endoscopic appearance of tumors leads to errors of staging in at least 30 % of cases [19].

During the procedure, the surgeon can perform selective cytology and biopsy of a visualized suspicious lesion in addition to the visual macroscopic diagnosis. This pathologic biopsy can confirm the diagnosis with a sensitivity of 89–95 % and obtain a prognostic tumor grade and stage [20]. The reliability of biopsies for tumor staging is poor, with 45 % of tumors classified as Ta, but these are actually more invasive tumors. However, the biopsy grade is adequately correlated with the final histopathological grade in 69–91 % of cases and the final tumor stage. Often the grade of the tumor gives information about the likely stage. In fact, the detection of a grade 1 tumor on biopsy corresponds to a noninvasive tumor (\leq pT1) in 68–100 % and the detection of a grade 3 tumor on biopsy corresponds to an invasive tumor (\geq pT2) in 62–100 % cases [21–24]. Upper tract ureteroscopy may not identify any tumor up to 50 % of the time even in patients with positive urine cytology.

However, obtaining biopsies is not always possible. Indeed, the introduction of biopsy forceps through the working channel of the ureteroscope may limit deflection and therefore the accessibility of the lower calyx.

The assessment of UTUC depth invasion remains a challenging task in ureteroscopy. The use of endoscopic ultrasonography has been described for this task but has not been routinely used in daily practice [25]. New imaging techniques such as optical coherence tomography (OCT) or endoscopic confocal microscopy are now in development and could eventually be used for this specific evaluation and as a complement to lesion biopsies [26, 27].

The hypothesis of the possible “seeding” of cancer cells during the procedure (by hyperpressure of the cavities or trauma to the wall) is not currently discussed [28]. The delay attributable to the performance of a diagnostic ureteroscopy with biopsy does not significantly affect the long-term prognosis of the disease [29].

Although rare, complications associated with diagnostic ureteroscopy are possible (0.5–5 % of cases). These consist of perforations, stripping of the ureter, stenosis, or parenchymal infections.

Cystoscopy

This simple test is recommended (grade A) as a first-line screening to rule out any synchronous bladder tumors.

Urine Cytology

Urine cytology is based on the analysis of cells exfoliated in urine and remains recommended for the diagnosis of UTUC (grade A) [2].

The cells can be obtained following urination or samples taken by bladder wash during cystoscopy or in situ during ureteroscopy. Although easy and noninvasive, voided urinary cytology is limited by its variable sensitivity (35–65 %) according to the large interindividual variability in the interpretation and the increased level of false positives in cases of trauma of urothelium or inflammation. The specificity of this technique is also excellent (>90 %).

In cases of positive urine cytology with normal cystoscopy, the likelihood of UTUC is very high. However, urine cytology is poor at predicting final tumor stage and grade. Messer et al. reported that positive urine cytology predicts a high-grade tumor with a sensitivity of 56 % and an invasive tumor with a sensitivity of 62 % [30]. Additionally, a positive preoperative urine cytology appears to be a risk factor for intravesical recurrence [31].

This cytology examination can be optimized with the detection of chromosomal abnormalities by FISH (fluorescence in situ hybridization) [32, 33], but the results using this approach are still preliminary and the cost of this technique is high.

Predictive Tools

Currently, treatment decisions regarding UTUC are based on the clinician's ability to predict the risk of progression based on the individual pathology of each patient.

Therefore, predictive and prognostic statistical tools have been developed to assist the clinician in predicting the progression risk of the disease.

The combination of the various elements previously described should increase the prediction performance of such tools.

Margulis et al. developed a nomogram based on clinical criteria (biopsy grade, tumor architecture, and location) to estimate the probability of locally advanced disease [34]. Their tool showed an accuracy of 76.7 %.

Similarly, Favaretto et al. developed a tool to predict the invasiveness or locally advanced nature of UTUC based on the criteria of imaging data and ureteroscopy, which includes biopsy grade [35]. This tool predicts the infiltrating character with 71 % accuracy and the locally advanced nature with 70 % accuracy.

Currently, no molecular parameter has yet been incorporated into these nomograms, unlike with other pathologies such as colon cancer (K-ras status) and breast cancer (HER2 status).

These tools could be helpful for selected patients who require radical treatment and/or extensive lymphadenectomy and/or neoadjuvant chemotherapy; however, independent validation of these tools is required today as they are not currently used in clinical practice, external validation is not yet available, and these tools are not yet used in clinical practice.

We now propose the flowchart in Fig. 2.2 to summarize this chapter.

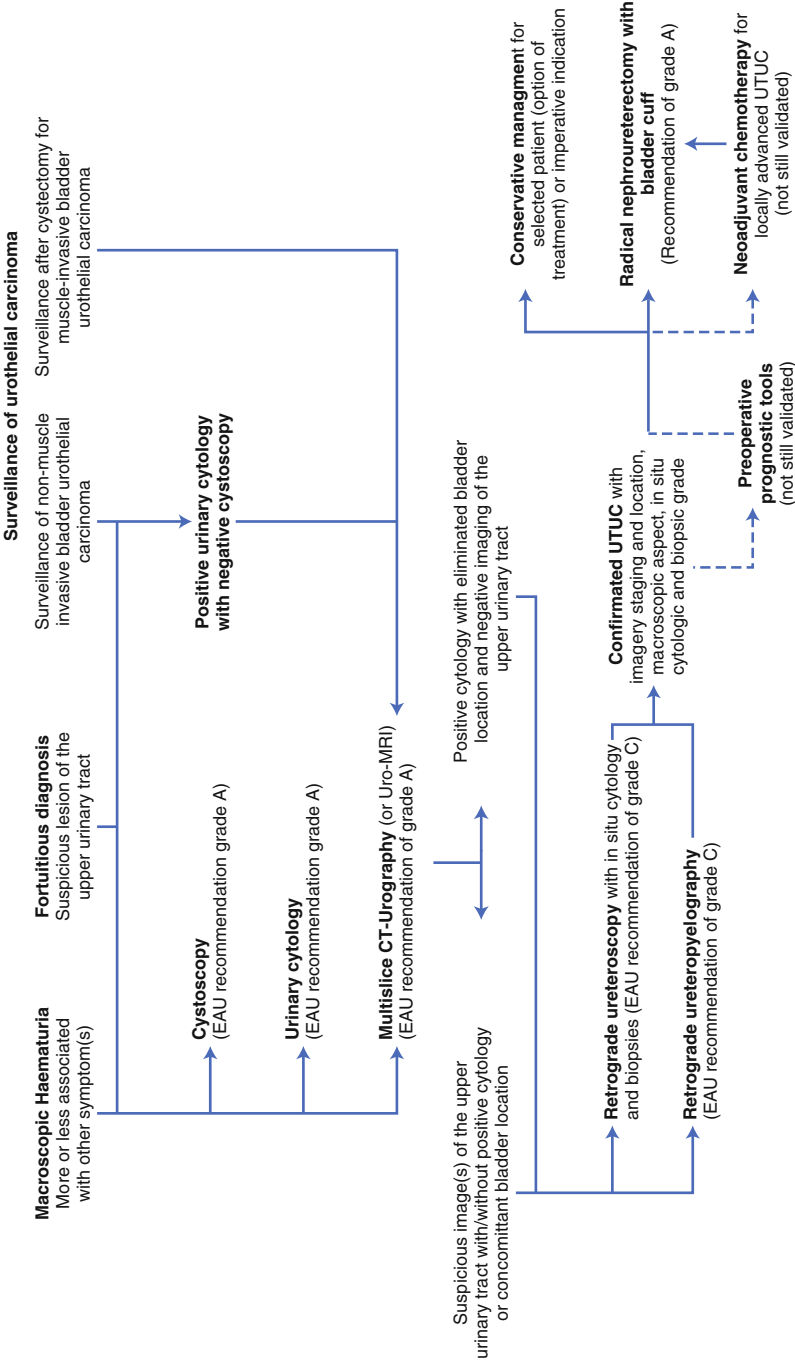


Fig. 2.2 Flowchart summarizing the diagnosis and evaluation of UTUC

Conclusion

Due to recent advances in imaging and endoscopy, the diagnostic management of UTUC has evolved in recent years. CT urography is now the tool for the detection of UTUC. Flexible ureteroscopy is often needed for the pretreatment patient evaluation. Future developments are expected to further refine the preoperative staging of these tumors.

Executive Summary

- The most common symptom of UTUC is gross hematuria (75–80 %).
- Systemic symptoms (i.e., weight loss, malaise, fever) associated with UTUC should prompt consideration of a rigorous metastatic evaluation.
- UTUC are diagnosed using imaging, cystoscopy, urinary cytology, and diagnostic ureteroscopy. The benefits of ureteroscopy in preoperative assessment should also be discussed with the patient.
- The diagnosis of UTUC may be fortuitous or related to the explorations of symptoms.
- Computed tomography (CT) urography is the imaging technique with the highest accuracy for UTUC.
- Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography (i.e., radiation or iodinated contrast media are contraindicated).
- Retrograde ureteropyelography through a ureteral catheter is an option for the exclusion of a UTUC.
- Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal and if CIS of the bladder has been ruled out.
- Flexible ureteroscopy is used to visualize and biopsy lesions in the ureter, which can be helpful to determine tumor grade in 90 % of cases.
- Ureteroscopy facilitates selective ureteral sampling for cytology in situ.

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Upper Tract Urothelial Carcinoma

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