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SPECIAL SECTION: UROTHELIAL DISEASE

Diagnosis, management, and follow-up of upper tract urothelial carcinoma: an interdisciplinary collaboration between urology and radiology

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Abstract

Upper tract urothelial carcinoma (UTUC) is a common and lethal malignancy. Patients diagnosed with this illness often face invasive workups, morbid therapies, and prolonged post-operative surveillance. UTUC represents approximately 5–10% of urothelial malignancies in the United States and affect 4600–7800 new patients annually. Various environmental exposures as well as smoking have been implicated in the development of UTUC. The diagnosis and workup of UTUC relies on heavily on imaging studies, a close working relationship between Urologists and Radiologists, and invasive procedures such as ureteroscopy. Treatments range from renal-sparing endoscopic surgery to radical extirpative surgery depending on the specific clinical situation. Follow-up is crucial as UTUC has a high recurrence rate. Here we review the epidemiology, diagnosis, management strategies, and follow-up of UTUC from an interdisciplinary perspective.

Keywords Urothelial carcinoma · Upper tract urothelial carcinoma · Radical nephroureterectomy · Ureteral neoplasm

Introduction

Urothelial carcinoma (UC) is a prevalent and lethal malignancy, representing the fourth most common tumor in the United States as well as the fourth leading cause of cancer death in the U.S. [1]. Approximately 90–95% of UC occurs in the bladder (UCB) while upper tract urothelial carcinoma (UTUC) represents the remaining 5–10% [2, 3]. Nonetheless, UTUC is diagnosed at a higher stage and carries a poorer prognosis compared to UCB; while only 15–25% of UCB presents with muscle invasion at diagnosis, that number is as high as 60% for patients diagnosed with UTUC [4]. Here, we provide an overview of the epidemiology and risk factors, as well as the current diagnostic strategies and basic management principles of UTUC.

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Epidemiology

UTUC comprise 6–10% of kidney and ureteral malignancies, and 10% of urothelial carcinomas overall [2, 5, 6]. In 2018, it is estimated that between 4600 and 7800 new cases in the United States UTUC were diagnosed with 24,200–40,300 new cases globally [2, 7, 8]. Patients diagnosed with UTUC have an average age of 73 years and are twice as likely to be men than women [9, 10]. A large number of patients with primary UTUC are found to have concomitant UCB at diagnosis, and the two diseases share many risk factors [11]. In a retrospective analysis of 470 patients with primary UTUC, Cosentino et al. found that 17% of patients had concurrent lower tract disease, and that proportion increases to 33% if the primary lesion is in the lower ureter as opposed to the renal pelvis or upper ureter [11]. On the other hand, bilateral, synchronous UTUC is relatively rare, at 1.6% of cases [10, 12].

Like UCB, there are several important environmental risk factors for the development of UTUC. The most important among these is cigarette smoke. Smokers have a relative risk as high as 7 for the development of UTUC in some series, as well as having a poorer prognosis following therapy compared to their nonsmoking counterparts [10, 13]. This is thought to be primarily driven by specific compounds in smoke, such as aromatic amines, which are metabolized into carcinogenic byproducts by a series of enzyme systems including the Cytochrome P450s and others [14, 15]. The increase in UTUC risk in this group appears to be dose related and is increased with number of exposure years [14, 16].

Other important environmental hazards contribute to increases in risk of UTUC as well. Non-tobacco sources of aromatic amines, primarily industrial dyes, textiles, rubber, coal, and others have been identified as occupational risks for UTUC [14, 17]. Still other carcinogens can be found in various Chinese herbs carrying aristocholic acid, for example, which has been described as mutating key oncogenes [18, 19].

Staging

Staging of UTUC is classified using the tumor, node, metastasis (TNM) system (Table 1). The TNM staging system was recently updated in 2017. Browne et al. conducted a retrospective analysis of 48,845 UTUC cases from the national cancer data base and extracted staging percentages at presentation, which have been placed into Table 1 [20] where applicable.

Diagnosis

The diagnosis of UTUC generally occurs in the context of known UCB or because of a heralding symptom and is not generally a screened malignancy [6]. The majority of patients (70–80%) diagnosed with UTUC present with hematuria [21, 22]. Others may have local flank or lumbar

Table 1 TNM staging for upper tract urothelial carcinoma, with percentages at diagnosis

T	Primary tumor	Staging percentage [20]
TX	Primary tumor cannot be assessed	43.2
T0	No evidence of primary tumor	0.4
Ta	Non-invasive papillary carcinoma	19.4
Tis	Carcinoma *in situ*	2.9
T1	Tumor invades subepithelial connective tissue	15.7
T2	Tumor invades muscle	5.7
T3	Renal pelvis—tumor invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumor invades beyond muscularis into periureteric fat	9.3
T4	Tumor invades adjacent organs or through the kidney into perinephric fat	3.3
N	**Regional lymph nodes**	**Staging percentage [20]**
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	–
N2	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**	**Staging percentage [20]**
M0	No distant metastasis	93.5
M1	Distant metastasis	6.5

pain. A small proportion of patients present with systemic symptoms such as fatigue, lethargy, weight loss, anorexia, fevers, or night sweats. In a review of pre-operative symptoms in over 400 patients with UTUC, Raman et al. noted that 6% of patients presented with systemic symptoms and that systemic symptoms pre-operatively carried a significantly worse overall prognosis compared to those with GU specific symptoms or those found incidentally to have UTUC [9]. Still, approximately 60% and 12.6% of patients are found to have muscle invasive disease and high grade T3a+ disease at presentation, respectively [20]. Thus, patients with UTUC are being diagnosed at a comparatively late stage [4].

Fig. 1 CT urogram obtained during the nephrographic (**a**) and delayed (**b**) phase demonstrates soft tissue with filling defect within the lower pole calyces of the right kidney (arrows). Retrograde pyelogram shows lack of filling of lower pole calices (black arrow) due to an obstructing mass (**c**). Urothelial carcinoma was found at pathology

Imaging studies

CT urogram

The reference standard for UTUC diagnostic imaging today is the computer tomography urogram (CT urogram), as it has the highest reported diagnostic accuracy of available imaging modalities [6, 23]. Jinzaki et al. reported a sensitivity, specificity, and accuracy of CT urography fall between 93.5–95.8%, 94.8–100%, and 94.2–99.6%, respectively [23].

Upon analysis of the images, small filling defects, mass lesions, ureteral wall thickening, or renal parenchyma-infiltrating lesions are indicative of UTUC (Figs. 1, 2) [23]. CT urography can be used to help predict staging, as a radiologist or clinician would be able to potentially visualize the extent, or lack thereof, of local invasion, nodal, or distant metastases. Generally, small and large masses are correlated with low and high grade malignancy, but that is not definitive. Benign diseases such as endometriosis, amyloidosis, or chronic inflammation or infections can be difficult to distinguish from UTUC on CT urogram alone. To assist with finding a diagnosis in these cases, urine cytology can help narrow down the differential [23].

A significant downside of this form of imaging is the amount of radiation to the patient. For a three-phase CT urography (non-contrast, nephrographic and delayed), the patient is exposed to 15–35 mSv of radiation, compared to a standard chest X-ray that is 0.1 mSv [23]. Efforts to decrease this dose come at a cost of compromised specificity and thus must be balanced with clinical needs [24]. Another downside of CT urography is its limitation in detecting carcinoma *in situ* or localizing any superficial extensions of the tumor. This is because chronic inflammation often results in false positive findings during image analysis [23]. Renal function may limit the ability to give intravenous contrast and get a complete study via CT urogram. Furthermore, patients with

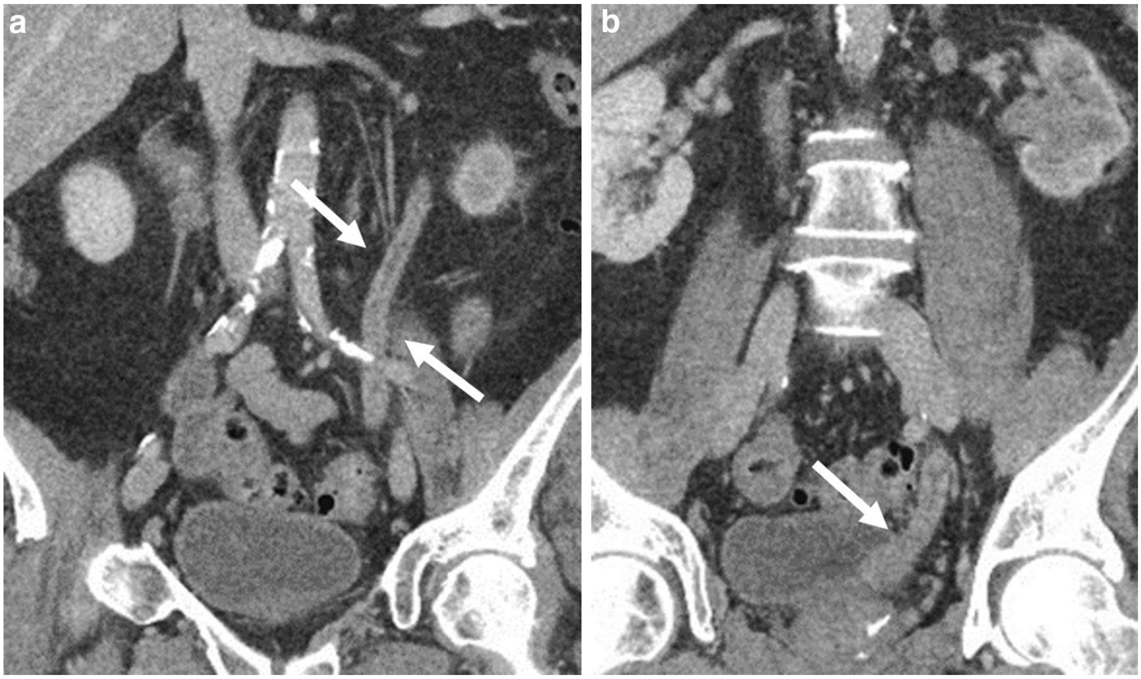

Fig. 2 CT urogram obtained during the nephrographic phase (**a**, **b**) demonstrated diffuse urothelial thickening involving the entire left ureter and left renal pelvis (arrows) consistent with urothelial carcinoma

history of severe contrast allergy to iodinated intravenous contrast material may not b candidates for CT urography due to an increased risk of a repeated severe allergic reaction.

MR urogram

Use of MR urogram in the diagnosis of UTUC is secondary and supplemental in nature. The European Association of Urology (EAU) guidelines recommend it for patients who have contraindications to radiation or iodinated contrast media required during a CT urogram. Takahashi et al. conducted a retrospective analysis of 91 MR urogram studies of patients with suspected UTUC using two reviewers. Sensitivity, specificity, and accuracy calculated from the results of reviewer 1 were 74.3%, 96.8%, and 93.7%, respectively, while those of reviewer 2 were 62.9%, 96.3%, and 91.7%, respectively [25]. Due to the higher comparative values of sensitivity, specificity, and accuracy, CT urogram is stated as the prominent and most effective diagnostic imaging technique for UTUC [6, 23, 24].

However, new studies have introduced evidence supporting MR urography as a possible first line imaging modality. A recent prospective study involving 20 patients and 39 UUT's by Sudah et al. demonstrated the efficacy of a 3.0T-MRU protocol that involved multiple contract-enhanced and excretory sequences. They came to the conclusion that this protocol has the potential to be just as effective as CT urogram, but without the need to expose the patient to radiation [26] (Fig. 3). Due to the limited size of the patient population, more research needs to be done on comparison between CT and MR urography.

Contrast enhanced ultrasound

A less commonly used imaging modality for the diagnosis of UTUC is contrast enhanced ultrasound. Advantages of this modality include decreased radiation exposure to the patient, relatively lower cost, and therefore higher access in limited resource regions. Drudi et al. conducted a small retrospective analysis of 18 patients and compared the accuracy of CEU to that of MRU and CTU. While MRU and CTU identified all 18 lesions, CEU was able to identify 17/18, resulting in a sensitivity of 94.4% [27]. Still, larger studies need to be carried out, and the use of this diagnostic modality has been quite limited in our clinical experience.

Tissue diagnosis

Endoscopic diagnosis and management

Ureteroscopy (URS) with biopsy or endoscopic resection is a cornerstone of the management of UTUC. In addition to direct visualization of neoplasm, ureteroscopic biopsy

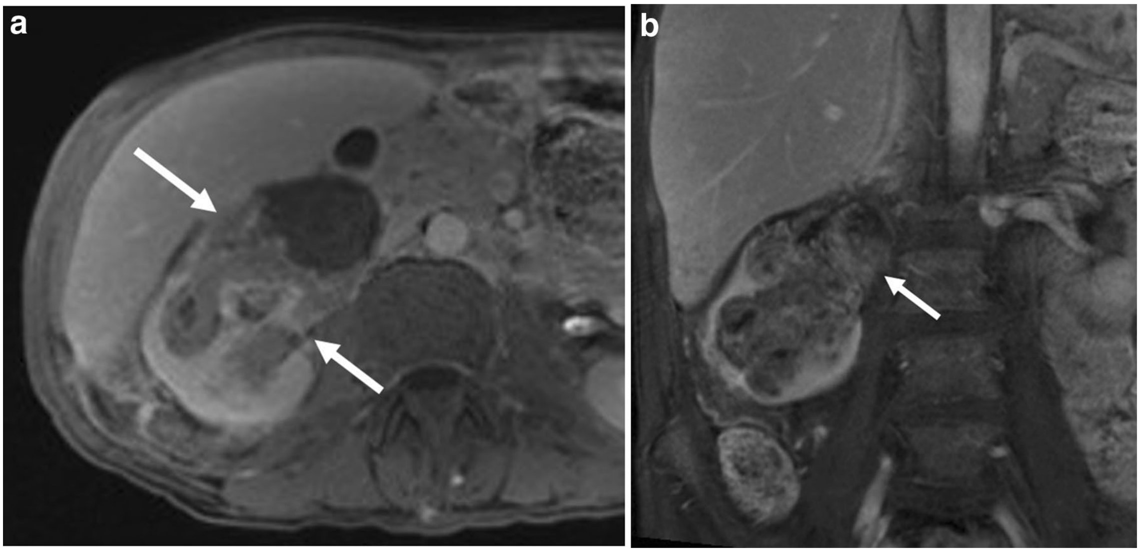

Fig. 3 MR urogram obtained during the delayed phase in axial (**a**) and coronal (**b**) plane demonstrates large infiltrative mass involving the entire renal pelvis including calyces also extending towards the ureter (arrows)

and/or fulguration has important diagnostic, prognostic, and therapeutic role. Tumor visualization often includes the performance of a retrograde pyelogram intraoperatively (Fig. 1c). This technique provides anatomic information for URS, and about the degree of ureteral obstruction and lumen caliber. If the cystoscopy is unremarkable, but correlated urine cytology is positive, the indication for UTUC in the patient is high [6]. Direct visualization of the malignancy can be used to help inform tumor staging prediction alongside CT urography pre-operatively [23]. Ureteroscopy may be performed utilizing semi-rigid or flexible instruments.

The predictive ability of ureteroscopic biopsy for tumor grade is high. Rojas et al. conducted a retrospective analysis of 54 patients who underwent ureteroscopic biopsy followed by nephroureterectomy and noted that pre-operative biopsy grading was in concordance with post-surgical excision grading 92.6% of the time, with a low upgrading rate of 5.6% [28]. In a systematic review, Jinzaki et al. noted a range of grading concordance of 69–91% between ureteroscopy and nephroureterectomy [23]. Endoscopy has been found to influence the treatment path toward more conservative options.

There are several important limitations to diagnostic ureteroscopy and biopsy. Firstly, technical limitations coupled with complex anatomy make this technique challenging. One large meta-analysis comparing endoscopic management of UTUC to radical nephroureterectomy (RNU) found a pooled complication rate of 14% with URS and ureteral stricture rate of 11% [29]. In the urolithiasis literature, complications including ureteral mucosal abrasions, ureteral perforations, ureteral avulsions, sepsis, hematuria, and aborted cases have been well documented, though care must be taken to extrapolate directly the rates of such events from stone disease to UTUC management [30–32].

URS carries risk of inadequate or inaccurate diagnosis. Relatively small instruments are utilized to minimize ureteral trauma and thus the amount of specimen that can be biopsied can be limited [33]. As discussed above, however, data are reassuring regarding the diagnostic reliability of even small volume biopsies, though undergrading remains a concern [28, 34]. A recurring problem with interpreting the endoscopic data is with undergrading, especially in low grade malignancies. Wang et al. analyzed 184 patients and noted that 96% of clinical grade 1 tumors were upgraded on the final pathologic evaluation of the excised tumor specimen [34]. As such, caution is advised with respect to requirement for close endoscopic surveillance in patients who undergo ureteroscopic ablative management for presumptive low grade UTUC.

Finally, some reports have suggested that diagnostic URS is associated with increased oncologic risk, specifically increased recurrence of UBC following definitive nephroureterectomy [35], but several more robust and recent reports have provided compelling data to the contrary and it is not currently felt that URS poses an increased oncologic risk to patients with UTUC [36, 37].

Percutaneous renal mass biopsy

A percutaneous biopsy is often indicated in patients with large volume upper tract tumors which may be more easily accessed via a percutaneous approach than a retrograde ureteroscopic approach or in patients in whom urinary reconstruction (such as a urinary diversion) may adversely

Fig. 4 Axial (**a**) and coronal (**b**) images through the left kidney obtained during the nephrographic phase demonstrate large infiltrative lesion occupying most of the left kidney and renal pelvis. It was unclear on imaging whether this lesion originated in the renal parenchyma or the urothelial tract, therefore percutaneous biopsy was performed which confirmed the diagnosis of urothelial carcinoma

impact retrograde access [33]. This technique is particularly important when cross-sectional imaging fails to clearly distinguish UTUC from renal tumors such as renal cell carcinoma. Figure 4 presents an example of a case with such a diagnostic uncertainty. These procedures provide very reliable diagnostic information and often allow more extensive tumor resection than can be performed with more limited retrograde instrumentation. An important study by Huang et al. of 26 percutaneous renal biopsies found a diagnostic accuracy of 85% [38]. Moreover, questions have been raised regarding oncologic benefit to an antegrade rather than a retrograde approach which has been hypothesized to encourage antegrade tumor spread. One study found a lower rate of recurrence with an anterograde approach (37%) compared to retrograde (52%), though this is an area of relative controversy [29]. Nonetheless, the diagnostic accuracy comes at a cost of morbidity and potential complications.

Percutaneous antegrade biopsy carries standard periprocedural risks and morbidity including bleeding and kidney damage. A systematic review by Cutress et al. describes a rate of blood transfusion of 17–37% and acute hemorrhage of 1%, and kidney failure in 2% of patients [29]. Accessing malignant tumors via percutaneous approaches raises concern for tumor seeding, as well, though data with respect to this have been encouraging [33]. Huang et al., for example, did not identify a single instance of tumor seeding in their cohort after undergoing an independent review [38]. Examples of tumor seeding through the percutaneous tracts have been described in case reports but the risk has not been born out in large cohort analyses [39, 40].

Management

While nephroureterectomy with complete excision of a bladder cuff whenever present remains the cornerstone of management of localized or locally advanced disease, increasing understanding of the differential outcomes based on tumor grade, as well as the deleterious consequences of surgical nephron loss has led to investigation of nephron sparing modalities. A proposed management algorithm encapsulating treatment of UTUC from presentation onward is described in Fig. 5.

Nephron preserving modalities

Historically, once an UTUC malignant mass was identified, patients underwent radical nephroureterectomy (RNU) as a standard treatment [4]. Renal-sparing therapy was reserved exclusively for patients who could not tolerate a RNU, had a solitary kidney, severe renal insufficiency, bilateral malignancy, or some other strong imperative [41]. In recent years, however, renal-sparing therapy has emerged as the standard treatment for low grade UTUC [6, 41]. This approach combines the oncologic benefits of surgical extirpation, with the benefits of renal function preservation [41].

Several series have demonstrated no significant differences in outcomes for low grade UTUC managed with renal-sparing approaches. Daneshmand et al. reported on 41 patients with low grade UTUC on biopsy managed radical surgery ($n=11$) and endoscopic therapy ($n=30$) and found no difference in recurrence rate or progression [42]. Seisen et al. performed a systematic review that included 1923 patients and found that in low grade, non-invasive UTUC, patient survival is similar after 5- and 10-year follow-up in nephron sparing surgery (NSS) when compared with RNU [41]. A decrease in overall length of survival and an increase

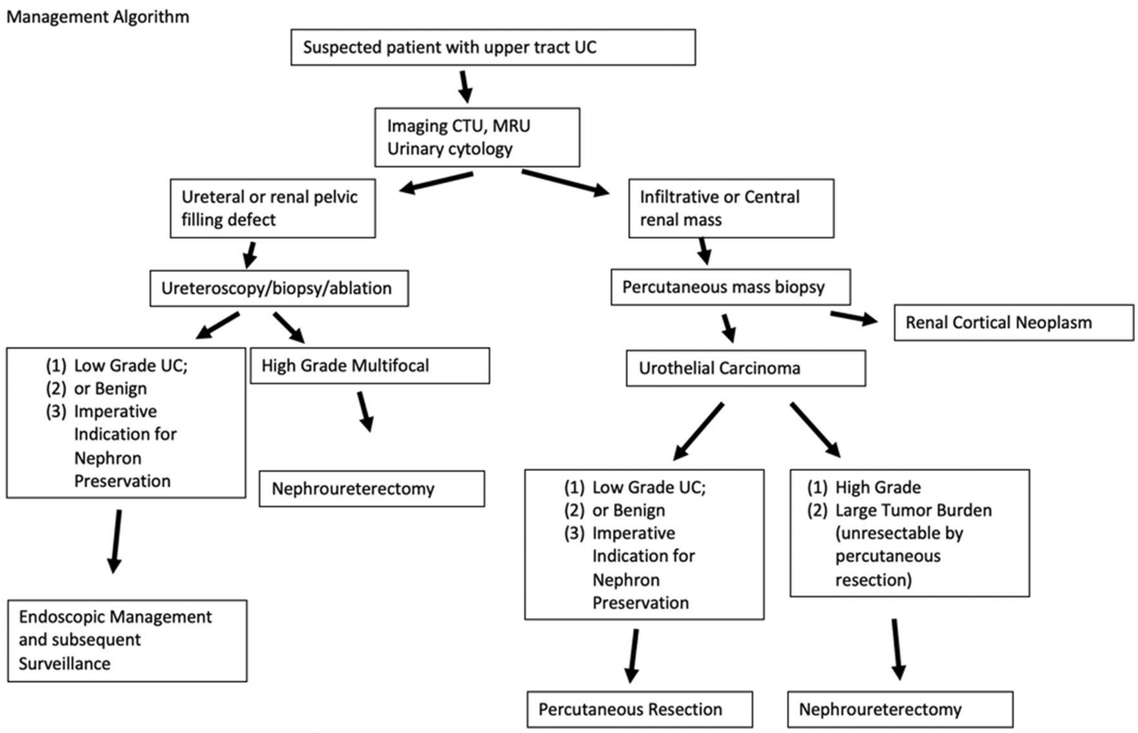

Fig. 5 Management algorithm for the treatment of UTUC

Table 2 Comparison of nephron sparing surgery to radical nephroureterectomy through retrospective analyses

Study	Number of patients	Type of management	Follow-up (median months)	Recurrence	CSS	OS	Complications
Simham et al. [63]	1227	(URS + SU + obs.) RNU	61	n/a	Cancer sp. mort RNU HR: 0.89 $p = 0.50$	All cause mortality RNU HR: 0.78 $p = 0.009$	n/a
Cutress et al. [64]	129	URS&PC (endo) LNU	50	5 yr: RFS Endo: 49.3% LNU: 100% $p \leq 0.0001$	5 yr: URS/PC, LNU − 85.6%, 92.1% 10 yr: URS/PC, LNU − 68.3%, 92.1% $p = 0.215$	5 yr: URS/PC, LNU − 64.1%, 74.8% 10 yr: URS/PC, LNU − 31.9%, 74.8% $p = 0.018$	n/a
Fukushima et al. [65]	129	SU RNU	50	9/43 24/86	SU HR 1.61 $p = 0.28$	n/a	n/a
Colin et al. [66]	468	SU RNU	26	5 yr: RFS SU: 37% RNU: 47.9%	5 yr: SU, RNU 87.9%, 86.3% $p = 0.99$	n/a	n/a
Roupret ert al [67]	97	URS PC RNU	URS: 51.5 PC: 57.5 RNU: 60	URS: 44.4% RC: 31.13% RNU: 50%	URS: 80.7 RC: 80 RNU: 84 $p = 0.89$	n/a	URS: 11.1% RC: 12.5% RNU: 14.8%

URS ureteroscopy, *SU* segmental ureterectomy, *RNU* radical nephroureterectomy, *HR* hazard ratio, *LNU* laparoscopic nephroureterectomy, *RFS* recurrence-free survival, *Endo* endoscopy, *n/a* not available

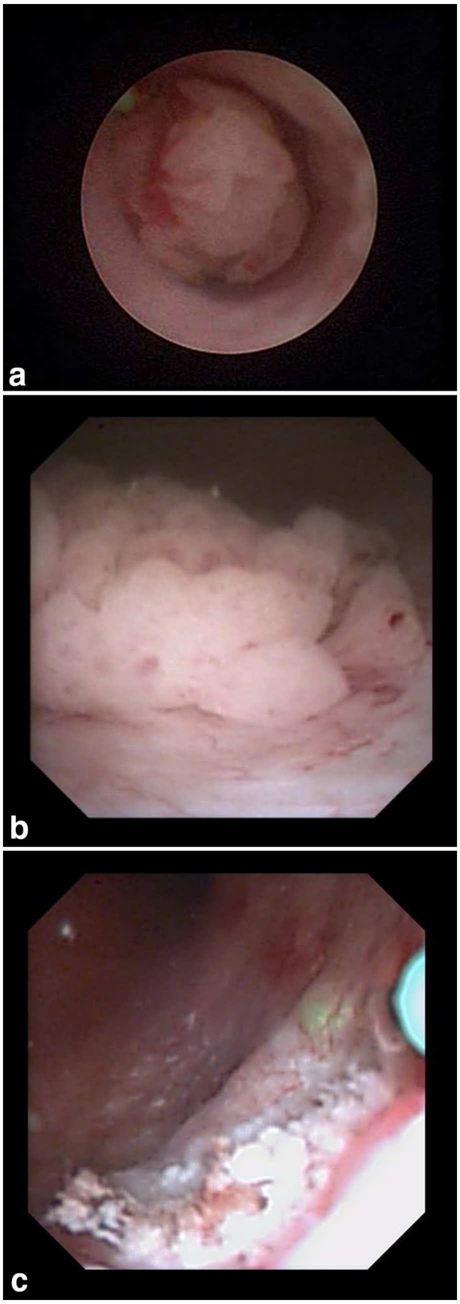

Fig. 6 **a** Urothelial cell carcinoma of the ureter visualized with ureteroscopy. **b** Papillary tumor found to be Urothelial cell carcinoma of the renal pelvis tumor. **c** Ureteroscopic laser ablation of renal pelvis tumor

in bladder recurrence was found in patients who underwent NSS with grade 2 or 3 disease.

The three nephron sparing approaches that are commonly used, and studied in Seisen et al., are segmental ureterectomy, ureteroscopy, and percutaneous management. Table 2 provides a summary of relevant retrospective studies comparing these techniques to RNU. While head-to-head randomized trials are lacking in the comparison of RNU to NSS, it is an accepted standard to offer patients with low grade disease renal-sparing surgery when surgically feasible [6].

When a patient is taken into the operating room for a diagnostic ureteroscopy and biopsy, supplemental laser ablation will often be performed if feasible. Figure 6 depicts representative images from this nephron sparing modality. The indications for ablation include a low grade, non-invasive malignancy, where due to the anatomy and the location of the mass, complete tumor resection or destruction can be achieved [6, 29]. The recurrence rate in these cases is high, and the patients need to be monitored closely. Villa et al. found that a 2nd look ureteroscopy in patients 6–8 weeks after the primary ureteroscopic procedure yielded the reveal of a tumor recurrence rate of 51.2%, which impacted the course of treatment for those patients moving forward [44]. A limiting factor on the ability to ablate the tumor is regarding treatment center resources, as both a laser generator and flexible ureteroscope are needed [43].

Nephroureterectomy

The gold standard treatment for high grade UTUC is the open nephroureterectomy (NU) with bladder cuff excision. This stands true regardless of tumor location [4, 6]. Perioperatively, tumor seeding can be prevented by not puncturing the urinary tract during resection [4, 6]. Although open NU is the current standard, promising results have been found on laparoscopic (LNU) and robotic-assisted (RANU) techniques (Table 3). Stills from a RANU with bladder cuff excision are shown in Fig. 7. LNU has been found in multiple studies to be associated with a decrease in estimated blood loss and blood transfusion rates, along with diminished pain, and a shorter recovery with less complications [45–48]. Stonier et al. performed a systematic review comparing LNU and RANU, and found that the two approaches were equal in perioperative and oncologic performance, with RANU suggesting a lower overall complication rate and post-operative mortality [49]. As comparative data continue to shed light on the efficacy of LNU and RANU, these approaches should continue to become more prevalent, which should improve patient outcomes.

A radical extirpation of the kidney, ureter, and bladder cuff excision is performed in high grade malignancies due to the high degree of recurrence [50]. Even still, considering the large amount of excised tissue, in a meta-analysis by Seisen et al., it was found that out of 8275 patients, 29% had intravesical recurrence after a median time of 22.2 months [50]. The EAU guidelines estimate recurrence at 22–47%. The bladder cuff excision (BCE) helps to reduce this recurrence. Ha et al. performed a retrospective analysis and found that patients who underwent NU without BCE had significantly worse cancer specific survival [51].

Table 3 Comparison of open, laparoscopic, and radical nephroureterectomy through retrospective analyses

Study	Number of patients	Approach	Follow-up	Intravesical recurrence (median months)	CSS	OS	Complication rate
Kim et al. [68]	1693	ONU LNU	37.8 44.3	IVRFS LNU vs. ONU HR: 0.832 $p=0.039$	LNU vs. ONU HR: 0.545 $p\leq0.001$	LNU vs. ONU HR: 0.524 $p\leq00.001$	n/a
Kim et al. [69]	1521	ONU LNU	62 48.9	IVRFreeSurv ONU: 51 LNU: 57.7 $p=0.010$	5 yr 76.4% 80.4% $p=0.032$	5 yr 71.4% 75.8% $p=0.026$	n/a
Lee et al. [70]	422	ONU LNU RANU	41.7 38.1 23.7	IVR HR-ONU vs. LNU: 0.803 $p=0.270$ RANU: 0.665 $p=0.107$	HR-ONU vs. LNU: 0.364 $p=0.116$ RANU: 0.336 $p=0.172$	HR-ONU vs. LNU: 0.537 $p=0.115$ RANU: 0.335 $p=0.084$	No complications 81.1% 85.4% 86.3% $p=0.664$
Hu et al. [71]	36	LNU RANU	47.8 6.1	55.6% 33.3% $p=0.720$	CS death 16.7% 5.6% $p=0.729$	Overall death 27.8% 11.1% $p=0.781$	n/a
Trudeau et al. [72]	1450	LNU RANU	n/a	n/a	n/a	n/a	18.2 11.9 $p\leq0.001$

ONU open nephroureterectomy, *LNU* laparoscopic nephroureterectomy, *RANU* robotic-assisted nephroureterectomy, *IVR* intravesical recurrence, *IVRFS* intravesical recurrence-free survival, *HR* hazard ratio, *5 yr* survival at the 5-year post-operative mark, *CS death* cancer specific death, *n/a* not available

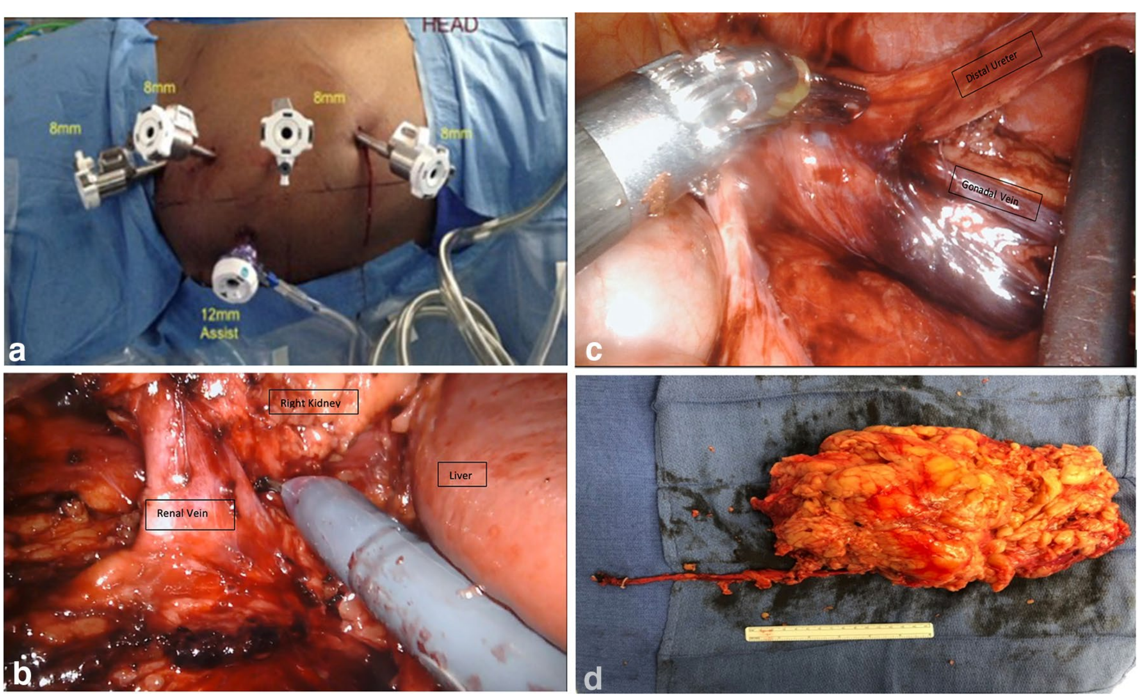

Fig. 7 **a** Port placement for Robotic-assisted right nephroureterectomy. **b** Hilar preparation prior to vessel ligation during nephrectomy portion of nephroureterectomy. **c** Isolation of the distal ureter during nephroureterectomy. **d** Excised right kidney and ureter with bladder cuff

Kidney sparing surgery is indicated for high grade malignancy in cases where a NU is contraindicated. As stated above, this includes solitary kidney, severe renal insufficiency, or a bilateral malignancy [41]. In the previously referenced study by Seisen et al., segmental ureterectomy (SU) was not found to negatively impact cancer specific survival, even in high grade cases with invasive features [41]. Although more research needs to be done, SU stands as an option for NSS in select patients carrying contraindications for radical NU.

Other emerging modalities

Emerging reports have examined the feasibility of new treatment modalities for UTUC such as stereotactic ablative radiation therapy (SBRT), radiofrequency ablation (RFA), cryoablation, and mitomycin gel. A case report by Evans et al. tells of a 95-year-old patient with pT2 stage UTUC who was deemed inoperable who received SBRT. At the 31-month follow-up the patient had no apparent adverse effects and imaging showed no metastatic disease [52]. SBRT has been shown to be a safe and effective treatment for a variety of neoplasms [53]. Although more research needs to be done on this treatment modality in regard to UTUC, this case report shows potential as a future treatment. Another recent case report by Molina et al. discussed a case of a 73-year-old man with recurrent local metastasis after being diagnosed with pT2 UTUC and undergoing a RNU 5 years prior. RFA was performed, and 2 years later the patient had no signs of malignancy [54]. Metcalfe et al. conducted a retrospective analysis of 27 patients who underwent adjuvant mitomycin c therapy for Ta/T1 UTUC that was treated endoscopically. They reported 3-year recurrence-free, progression free, and NU-free survival rates of 60%, 80%, and 76%, respectively, alongside a cancer specific mortality of 0% [55]. Results on this modality appear promising as well.

Follow-up and surveillance

Local recurrence of UTUC following treatment is high and requires persistent surveillance. Following RNU with bladder cuff excision, studies estimate the rate of intravesical recurrence (IVR) to be between 22 and 47%, [35, 56, 57] with a recent 2016 retrospective analysis of 664 patients by Liu et al. estimating IVR to be 33.7% [35]. For this reason, following a RNU, EAU guidelines recommend a cystoscopy and urinary cytology at 3 months, then annually. Specifically, for non-invasive they recommend a CT urogram annually, and for invasive tumors the recommendation is CTU every 6 months for 2 years, then annually [6]. Shigeta et al. conducted a retrospective analysis of 364 patients who underwent RNU and found that IVR most often occurs between 6 and 12 months. They performed cystoscopy at 3 months, and every 6 months thereafter, and recommend closer surveillance for at least the first 2 years [58].

Patients undergoing NSS, rather than RNU, require a more stringent follow-up protocol. The following has been recommended: cystoscopy, URS, and cytology *in situ* at 3 months, followed by every 6 months for 2 years, then annually assuming no recurrence. In addition, urine cytology and CTU should be performed at 3 months, 6 months, then annually [6].

Distant metastatic recurrence is unfortunately also very common in patients following RNU. Data from two large retrospective analyses demonstrate 55.8% and 54.1% metastatic recurrence rate following RNU at 29.8 months and 60 months follow-up respectively [59, 60]. Unsurprisingly, depth of invasion on final pathology, pT3 or higher, was most predictive of recurrence [60]. For this reason, invasive tumors are surveilled aggressively per EAU guidelines with CTU every 6 months for two years, and then annually thereafter. Distant metastases tend to occur in liver and bone as well as lungs, specifically with a primary tumor site in the renal pelvis [61]. Thus, chest imaging following surgery is also warranted although this is interestingly left out of the EAU recommendations. Generally, our practice is performing chest X-ray every 6 months following surgery for the first 2 years, and yearly afterwards. For patients with particularly high-risk disease, difficult to interpret chest X-ray, suspicious lesions, or some other clinical imperative, Chest CT is employed.

The use of conservative treatment for UTUC should be seen as an indication for more stringent surveillance. Following URS ablation, it is recommended to perform a second look URS at the 6–8 week mark [62]. *In situ* cytology, cystoscopy, URS, and CTU should be performed along the same protocol as for NSS [62]. Overall, follow-up and surveillance need to be meticulous and persistent.

Conclusion

UTUC is a lethal disease requiring a complex treatment algorithm and nuanced patient selection in diagnosis, management, and follow-up. A combination of imaging and ureteroscopy are often used for diagnosis and tissue attainment. Though multiple treatment modalities exist currently, including radical surgery and NSS, emerging modalities such as SBRT and RFA are currently being investigated and warrant future study. Follow-up should be stringent given the high rate of recurrence.

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