Emerging strategies: conservative management of upper tract urothelial carcinoma

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Purpose of review
Upper tract urothelial carcinoma (UTUC) is a rare yet aggressive malignancy, representing 5–10% of urothelial cancers. While radical nephroureterectomy (RNU) has traditionally offered excellent oncological control, it compromises renal function. Recent advancements have shifted the paradigm toward kidney-sparing strategies in select cases. This review highlights innovations in UTUC diagnosis and conservative management, focusing on emerging imaging techniques, noninvasive biomarkers, and minimally invasive treatments.

Recent findings
Advances in multiparametric MRI and radiomics have improved diagnostic accuracy and risk stratification. Moreover, noninvasive biomarkers – including circulating tumor DNA, microRNAs, and urinary methylation assays – provide promising tools for early detection and surveillance. Kidney-sparing approaches such as endoscopic laser ablation and segmental ureterectomy have demonstrated comparable oncologic outcomes in low-risk patients. Moreover, topical therapies, including intracavitary treatments like UGN-101, offer a promising minimally invasive option.

Summary
The conservative management of UTUC is evolving, driven by advancements in imaging, molecular diagnostics, and minimally invasive treatments. While kidney-sparing approaches are increasingly utilized in low-risk patients, further prospective studies are needed to validate their efficacy.

Keywords
kidney-sparing surgery, topical treatment, upper tract urothelial carcinoma, ureteroscopy

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare but aggressive malignancy, accounting for 5–10% of urothelial cancers, with an incidence of one to two cases per 100 000 annually [1]. Radical nephroureterectomy (RNU) has long been the standard treatment, offering excellent oncological control at the cost of renal function [1–3]. However, recent advancements have led to a paradigm shift towards kidney-sparing strategies in select cases, aims to preserve renal function without compromising oncologic outcomes [1–3].

Diagnosis and management of UTUC have evolved with novel technologies, improving accuracy and risk stratification. Advances in imaging, including multiparametric MRI and radiomics, enhance tumor characterization, while noninvasive blood and urine biomarkers show promise for early detection and monitoring. Diagnostic ureteroscopy (URS) remains crucial for preoperative tumor evaluation, providing insights into grade and stage to guide treatment decisions.

Despite these advances, managing UTUC remains challenging, particularly in optimizing treatment for high-risk cases and minimizing recurrences. Kidney-sparing surgery (KSS), including endoscopic techniques and topical therapies, are increasingly used for low-risk UTUC, offering comparable outcomes with reduced morbidity. However, these approaches require rigorous surveillance due to high recurrence rates.

This review summarizes recent innovations in UTUC diagnosis and management, emphasizing emerging imaging, biomarkers, and conservative

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KEY POINTS

- CT urography and ureteroscopy remain the standard for UTUC diagnosis, while emerging imaging and noninvasive biomarkers may enhance accuracy.
- Kidney-sparing strategies, including endoscopic treatment and topical therapies, are increasingly utilized in select UTUC patients.
- Radiomics and liquid biopsy technologies show promise for improving UTUC risk stratification and treatment decision-making.
- Bladder recurrence after diagnostic ureteroscopy remains controversial, with ongoing research into mitigation strategies.
- Further prospective studies are needed to validate the long-term oncologic outcomes of conservative UTUC management.

treatments. By exploring the latest evidence, it provides a comprehensive update and insights into future directions in this evolving field.

LITERATURE REVIEW

Upper tract urothelial carcinoma diagnosis

Computed tomography urography (CTU) and ureteroscopy remain the standard diagnostic tools for UTUC, yet emerging imaging and noninvasive biopsy techniques are being explored to improve diagnostic accuracy.

Imaging

Computed tomography

CTU remains a cornerstone in UTUC diagnosis, with recent advancements enhancing its diagnostic capabilities. Multidetector CT (MDCT) provides a more detailed visualization of the urinary tract than standard CTU, with 92% sensitivity and 95% specificity [4]. Recent CTU-based machine-learning models show promise in predicting tumor grade, aiding selection for conservative management [5▪].

MRI

MRI urography has lower sensitivity than CTU (69 vs. 96%) [6] but is an alternative for patients unable to undergo CTU. Multiparametric MRI (mpMRI), widely used in bladder cancer [7], is under investigation for UTUC. Messina *et al.* [8] reported 95% sensitivity and 71% specificity for muscle invasion detection. Almas *et al.* [9] found the diffusion-weighted imaging (DWI) series predictive of muscle invasion (area under the curve (AUC) 0.88), with the apparent diffusion coefficient (ADC) value predictive of tumor grade.

Radiomics

Radiomics enhances imaging by extracting quantitative data beyond human perception.

CTU-based radiomics models differentiate UTUC from infiltrative renal-cell carcinoma [10], predict survival and recurrence [11], and tumor stage and grade, with high sensitivity and specificity [12]. A CT-based perirenal fat model improves prognosis prediction when integrated with clinical data [13▪].

MRI-based radiomic, particularly ADC analysis, also aids tumor grading. The Nai *et al.* [14] ADC-based model outperformed the mean ADC value in tumor grade classification accuracy (AUC 0.786 vs. 0.628, $P = 0.07$).

In summary, integrating radiomics and artificial intelligence models in imaging for UTUC holds great promise for enhancing our ability to diagnose and predict grade and stage. However, the current accuracy of imaging is still insufficient, and ureteroscopic biopsy remains essential for clinical decision-making.

Noninvasive biopsy techniques

Blood biomarkers

Blood-based liquid biomarkers, including circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) offer promising noninvasive diagnostic tool for UTUC. Shishido *et al.* [15] reported a significant difference in CTCs between UTUC patients and healthy volunteers, identifying unique rare-cell categories linked to disease state. Ghoreifi *et al.* [16▪] showed that oncosome levels correlate with recurrence-free survival post-RNU. Huelster *et al.* [17] found pre-RNU ctDNA detection predictive of tumor invasiveness and poor oncological outcomes.

Mu *et al.* [18] demonstrated that plasma ctDNA alterations, particularly in high-grade tumors, may aid in genetic profiling.

MicroRNAs (miRNAs) are small, single-stranded RNA molecules (18–24 nucleotides) that regulate gene expression posttranscriptionally and emerge as novel UTUC biomarkers, with miR-1343-5p and miR-6087 identified as robust diagnostic markers, validated across independent cohorts [19]. A review by Cinque *et al.* [20] highlighted the potential of various miRNAs for prognosis and detection.

Urine biomarkers

EpiCheck, a DNA methylation urine test initially developed for bladder cancer, is now being evaluated for UTUC detection. A single-center prospective study reported 83% sensitivity and 79% specificity, with high-grade UTUC samples achieving 96% sensitivity and a 97% negative-predictive value (NPV) [21]. Palermo *et al.* [22] found overall sensitivity of 65% and specificity of 83%, but for high-grade UTUC, sensitivity reached 100%, suggesting EpiCheck could aid decision-making and potentially reduce unnecessary ureteroscopic biopsies.

Bladder CARE, which measures three cancer biomarker methylation level, achieves sensitivity, specificity, positive-predictive value (PPV) and NPV of 96, 88, 89 and 96%, respectively, for detecting UTUC, and has a strong correlation with tumor grade [23].

Metabolomics-based urine analysis using liquid chromatography-high-resolution mass spectrometry (LC-HRMS) detects UTUC with high accuracy [24], with specific metabolite panels (e.g. prostaglandin I2, 5′-methylthioadenosine) achieving AUC values at least 0.8 [24]. Xpert-BC, a real-time PCR measuring the level of five target mRNAs, has a 100% sensitivity but low specificity of 4.5% [25].

A multitarget urine DNA test detecting FGFR3 and TERT mutations alongside methylation markers demonstrated over 90% sensitivity for both bladder and UTUC detection [26].

While these methods perform well for high-grade UTUC, overall detection remains a challenge. Techniques such as Bladder CARE, LC-HRMS, and multitarget urine DNA testing combine high sensitivity and specificity, offering advantages over cytology (Table 1). Further studies are needed to confirm clinical utility.

The role of diagnostic ureteroscopy and the risk of bladder recurrence

The role of diagnostic URS in UTUC management remains debated. The American Urological Association/Society of Urologic Oncology (AUA/SUO) and National Comprehensive Cancer Network (NCCN) recommend URS for any lesion suspected to be UTUC in imaging [2,3], while the European Association of Urology (EAU) advises performing it only when imaging and/or urine cytology is inconclusive, or kidney-sparing approach is considered [1].

Efforts to refine UTUC diagnosis without URS include a study by Trail *et al.* [27], which identified macrohematuria, solid imaging lesions, and smoking history as strong predictors, with a 96.2% predictive value in patients undergoing RNU.

The ROBUUST collaborative group provided updated data on the accuracy of ureteroscopic biopsy (URSBx) in high-grade UTUC. Compared to RNU histology, preoperative URSBx demonstrated 81.3% sensitivity, 75.3% specificity, 93% PPV, and 50% NPV, with an 80.1% concordance rate for tumor grade ($\kappa = 0.47$, $P < 0.001$). Notably, no significant difference in recurrence-free survival was found between patients who underwent pre-RNU URSBx and those who did not [28▪].

The impact of URS on bladder recurrence following RNU remains controversial (Table 2). Some report an increased risk [29–32], whereas others refute this association [28▪,33▪▪]. Additionally, evidence suggests bladder recurrence may be linked more to endoscopic biopsy than URS itself [34,35].

Various techniques have been proposed to mitigate the potential risk, yet conflicting results persist. Wong *et al.* [31] reported lower 24-month bladder recurrence-free survival in patients undergoing URS before RNU (52 vs. 64%, $P = 0.02$), with URS being the only significant factor in a multivariant analysis.

Table 1. Urine-based tests for the diagnosis upper tract urothelial carcinoma

		Overall		High grade	
		Sensitivity	**Specificity**	**Sensitivity**	**NPV**
Selective Cytology	Pycha *et al.* [25]	41.9%	93.9%	100%	77.5%
EpiCheck	Territo *et al.* [21]	83%	79%	96%	97%
	Palermo *et al.* [22]	65%	81.2%	100%	Not reported
	Pycha *et al.* [25]	64.5%	78.8%	100%	82.5%
Bladder CARE	Ghoreifi *et al.* [23]	96%	88%	Not reported	Not reported
LC-HRMS	Yang *et al.* [24]	83.3%	80.6%	Not reported	Not reported
Xpert-BC	Pycha *et al.* [25]	100%	4.5%	100%	100%
Multitarget urine DNA testing	Wu *et al.* [26]	92.9%	95.09%	96.5%	Not reported

LC-HRMS, liquid chromatography-high-resolution mass spectrometry; NPV, negative predictive value; PPV, positive-predictive value.

Table 2. Intravesical recurrence post-RNU by preoperative endoscopy and biopsy status

Reference	Pre-RNU intervention	Intravesical recurrence rate	Median time to IVR	Hazard ratio
Sharma *et al.* [34], 2021	No URS	2 years, 15%		
	URS (with/without Bx)	2 years, 18.4%		1.15, $P=0.54$
	URS+Bx	2 years, 21.9%		1.4, $P=0.04$
Douglawi *et al.* [29], 2022	No URS	7.7%	12.1 months	
	URS (with/without biopsy)	30.8%	9 months	5.6, $P<0.004$
Nowak *et al.* [35], 2021	URS (with/without biopsy)			1.44, $P<0.001$
	URS without Bx			1.28, $P=0.16$
	URS with Bx			1.38, $P<0.001$
Wong *et al.* [31], 2024	Upfront RNU	2 years, 36%		
	URS	2 years, 48%		1.705, $P=0.02$
Nakano *et al.* [37], 2024	No URS	3 years, 36.8%		
	URS without Bx	3 years, 53.4%		1.45, $P=0.013$
	URS+ Bx	3 years, 46.4%		1.56, $P=0.009$
Liedberg *et al.* [32], 2023	URS (with/without biopsy)/ pyelography			1.24, 95% CI 1.03–1.52
Chen *et al.* [33▪▪], 2024	No URS/URS without Bx	26.2%		
	URS+Bx	28.6%		
Ditonno [28▪] *et al.*, 2024	No URS		8 months	
	URS+Bx		7 motnhs	0.96, 95% CI 0.62–1.5

Bx, biopsy; IVR, intravesical recurrence; RNU, radical nephroureterectomy; URS, ureteroscopy.

Yonese *et al.* [36] found ureteral catheter placement post-URS significantly increased bladder recurrence risk (hazard ratio = 17.8).

Nakano *et al.* [37] demonstrated a significantly higher bladder recurrence rate in patients who underwent URS, with or without biopsy. Three-year recurrence-free survival was 63.2% in the no-URS group, compared to 46.6% in the URS-alone group and 53.6% in the URSBx group. Multivariate Cox regression identified URS (hazard ratio= 1.56, $P=0.009$) and URSBx (hazard ratio = 1.45, $P=0.013$) as independent risk factors for recurrence. Positive cytology (hazard ratio = 1.41, $P=0.007$) further increased recurrence risk, while adjuvant chemotherapy significantly reduced it (hazard ratio = 0.57, $P=0.025$), reinforcing its protective role in UTUC management.

Prophylactic intravesical chemotherapy following URS is an emerging strategy to reduce bladder recurrence. While its efficacy after RNU is well established [38], its role post-URS remains under investigation. Currently, evidence supporting this approach is indirect, based on findings from existing studies suggesting a potential benefit of upper tract instillations in reducing bladder recurrence. Gallioli *et al.* [39] reported a 10% reduction in bladder recurrence with a single mitomycin instillation post-URS. The Olympus trial [40], evaluating the ablative effects of a Mitomycin gel for UTUC, observed only 9% bladder recurrence at 1 year, suggesting potential prophylactic effects from upper tract excretion. Several clinical trials are currently recruiting patients to explore the benefit of bladder instillation following URS, with a potential to reduce the recurrence rates and hence the morbidity and costs of treatment.

Upper tract urothelial carcinoma risk stratification

Multiple organizations, including the EAU [1], AUA/SUO [2], NCCN [3], Japanese Urological Association (JUA) [41] and French Association of Urology (AFU) [42] have published UTUC management guidelines with broadly similar framework, but key differences, particularly in risk stratification, highlight variations in classification and subsequent treatment approaches.

The NCCN relies primarily on tumor histology, whereas the other organizations have more elaborate guidelines that categorize UTUC into distinct risk groups. The EAU, AFU, and JUA use a standardized system incorporating histology, cytology,

and radiologic/endoscopic features, including size and multiplicity, to classify tumors as high risk or low risk. The AUA/SUO further subcategorizes into favorable and unfavorable low-risk and high-risk groups, allowing for more nuanced treatment decisions.

One major divergence is multifocality – classified as high-risk by the EAU, but considered 'unfavorable low-risk' by the AUA/SUO if low-grade, potentially influencing the choice of kidney-sparing management. Similarly, the AUA/SUO takes a more flexible approach to hydronephrosis, obstruction, and bladder involvement, permitting a less aggressive management strategy compared to EAU.

Tumor size thresholds also differ; the EAU and AFU set a 2 cm cutoff for low-risk vs. high-risk categorization, whereas the AUA/SUO lacks a strict size criterion [43].

Treatment

Although RNU remains the gold-standard, kidney-sparing approaches, including endoscopic treatment and topical therapy, are gaining interest.

Radical nephroureterectomy vs. kidney-sparing surgery

Historically, KSS, including endoscopic treatment and segmental or distal ureterectomy, was reserved for selected cases with imperative indication, such as solitary kidney or bilateral UTUC, with RNU remaining the gold standard. Recent studies demonstrated that patients with low-risk UTUC exhibit comparable overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS), between RNU and endoscopic treatment [44,45]. Other studies have also reported similar results regarding upper tract and intravesical recurrence-free survival (RFS) [46].

When analyzing for patients with high-risk UTUC, several studies have reported conflicting findings. In a review by Giulioni *et al.* [44], patients with high-risk UTUC demonstrated lower 5-year OS when treated endoscopically compared to those undergoing RNU. Conversely, Wang *et al.* [47], in their retrospective study, reported noninferior OS in the KSS group compared to the RNU group, albeit with a higher recurrence rate observed in the former.

In a large population-based retrospective study, Ye *et al.* [48] compared RNU with endoscopic treatment for UTUC, and found significantly worse 5-year OS for the latter group. However, after stratifying by anatomic location and tumor grade, they observed a comparable 5-year OS between RNU and endoscopic treatment for low-grade ureteral tumors. In contrast, endoscopic treatment continued to show poorer outcomes for high-grade tumors and those located in the renal pelvis.

Overall, the evidence for endoscopic treatment in high-risk UTUC is conflicting and emphasizes the need for further prospective, randomized trials before utilizing this approach in nonimperative indications.

Endoscopic treatment

Several aspects of endoscopic treatment have been studied recently, aiming to improve the safety profile and oncological outcomes. One key area of investigation is the approach to the affected upper tract, comparing the antegrade and retrograde techniques. In a meta-analysis by Laukhtina *et al.* [49], the antegrade approach was associated with lower bladder and upper tract recurrence rates but resulted in a higher rate of any-grade complications.

Another area of interest is the tumor ablation technique, particularly the various lasers available for achieving effective tumor treatment. A new player in this field is the thulium fiber laser (TFL), with promising preliminary results regarding early recurrence rates (17.7–21.7%) with an acceptable postoperative complication rate (10%) [50]. In a systematic review by Candela *et al.* [51] on using either TFL or Thulmium:YAG for endoscopic tumor ablation, they found a recurrence rate of 17.7–44%.

Jue and Armenakas detailed their experience with en-bloc enucleation and specimen retrieval technique of UTUC tumor using TFL low-ablation laser settings and nitinol basket [52]. Overall, TFL holds promise as a superior laser for the treatment of UTUC.

Chen *et al.* [53] reported their endoscopic cryoablation technique and compared it to RNU in high-risk UTUC patients. They found comparable 2-year OS, progression-free survival, and intravesical RFS. Of note, the cryoablation group had a small sample size, questioning its validity, and the technique required using an 8/9.8Fr ureteroscope, limiting its applicability to accessible ureteral tumors.

Surveillance protocols following endoscopic treatment

UTUC is known for its high rate of local or intravesical recurrence, and its high risk of progression. Therefore, several surveillance protocols have been suggested in recent years, highlighting the need to tailor the protocol based on the individual patients perceived risk, yet there is little evidence on how to do so as reflected in the variability between the different guidelines' recommendations (Table 3). Notably, guidelines – particularly regarding upper

Table 3. Follow-up approach in low-risk upper tract urothelial carcinoma patients after endoscopic treatment

	Cystoscopy and cytology	Upper tract endoscopy	Upper tract imaging
EAU guidelines [1] (2023)	At 3 and 6 months, then annually for 5 years	At 3 months	At 3 and 6 months, then annually for 5 years
AUA/SUO guidelines [2] (2023)	At 3–6 months, then every 6–9 months for 2 years, then at least annually.	At least at 6 and 12 months	Every 6–9 months for 2 years, then annually up to 5 years
NCCN guidelines [3] (2024)	Every 3 months for 1 year, then at longer intervals	At 3–12 months intervals	At 3–12 months intervals
JUA Guidelines [41] (2023)	At 3 and 6 months, then annually for 5 years	At 3 months	Not mandatory
AFU guidelines [42] (2024)	At 3 and 6 months, then annually at least for 5 years	At 3 and 6 months	At 3 and 6 months, then annually for5 years

tract endoscopy – aim to balance the morbidity and cost of surveillance with recurrence risk. While these recommendations represent a minimum standard, clinicians often escalate surveillance intensity based on individual risk assessment and shared decision-making.

Figaroa *et al.* [54] examined 71 UTUC patients with a follow-up protocol including endoscopy every 3 months in the first year, then 6-month intervals up to year 3, and yearly thereafter. Endoscopy included also cystoscopy, and patients underwent CTU as well. The overall 2-year RFS rate was 22%.Twenty-three patients were referred to RNU in a median time of 9.9 months. Thirteen patients who initially presented with low-grade UTUC have upgraded to high-grade UTUC in a median time of 21.9 months. All of this data rationalizes the extended endoscopic follow-up for UTUC patients.

Carmona *et al.* [55] found that selective urine cytology had a minimal impact on decision-making during UTUC follow-up, with only one case (0.17%) where the urine cytology report altered the follow-up regimen. They also demonstrated the added value of performing FISH analysis as both a diagnostic tool and for surveillance, particularly in cases with strong initial clinical suspicion of UTUC but no visible lesion detected during endoscopy.

Linder *et al.* [56] recommended semi-annual cystoscopy for up to 5 years, due to the continuous risk of bladder recurrence, and regular URS for 3 years, as well as strict imaging protocol in the first 2 years following yearly intervals to exclude distant metastasis.

Topical therapy

In order to improve kidney-sparing endoscopic management techniques, topical treatment for UTUC has been recently explored.

UGN-101

The Olympus trial assessed the response to UGN-101 (UroGen Pharma, Ra'anana, Israel), a reverse thermal gel formulation of mitomycin, in patients with low-grade UTUC who received six once-weekly retrograde instillations of UGN-101 into the renal pelvis and calyces. The trial found that 59% of patients achieved a complete response at the 3-month URS evaluation [40]. A recent update highlighted the long-term safety and durability of response to UGN-101, including a maintenance protocol of up to 11 monthly instillations for patients who achieved a complete response after the initial induction regimen. Fifty-six percent were in complete response at 12 months, with or without maintenance treatment. Ureteric stenosis was reported in 44% of patients, with an increasing number of instillations appearing to be associated with an increased incidence of urinary adverse events [57]. The AUA/SUO guidelines also support the use of UGN-101 for low-grade tumors [2].

Padeliporfin vascular-targeted photodynamic therapy (TOOKAD soluble)

Padeliporfin is an experimental short-acting photodynamic drug designed for a novel vascular-targeted photodynamic therapy (VTP) (Steba Biotech, Luxembourg City, Luxembourg), demonstrated to be effective against various malignancies in preclinical investigations and clinical trials. In a Phase 1 study [58▪▪], patients received up to two endoscopic VTP treatments at a maximum dose of 200 mW/cm. At a 30-day follow-up, the response rate to treatment was 94% (50% complete, 44% partial). Among the patients who received the second treatment, the complete response rate of 68% after the second treatment. Observed side effects primarily included transient renal colic and hematuria. A Phase 3 study, the ENLIGHTED trial, is currently ongoing.

CONCLUSION

Advances in imaging, radiomics, and liquid biopsy have improved UTUC diagnosis and risk stratification. Kidney-sparing treatments, including endoscopic techniques and topical therapies, offer alternatives to RNU in select cases. However, challenges remain in managing high-risk disease and recurrence. Further research is needed to refine these strategies and expand access to innovativetherapies.

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There are no conflicts of interest.

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