Gold standard nephroureterectomy, chemoprophylaxis and surveillance in upper tract urothelial carcinoma

Giuseppe Basile[a], *Marco Bandini*[a], *Roger Li*[b], *Michael A. Poch*[b], *Andrea Necchi*[c] *and Philippe E. Spiess*[b]

Purpose of review
The purpose of this review is to summarize the most recent evidence on surgical management, strategies to reduce tumor recurrence, and surveillance regimens in patients diagnosed with upper tract urothelial carcinoma (UTUC) and elected for radical treatment.

Recent findings
Minimally invasive surgery is gaining momentum in the surgical management of UTUC. Chemoprophylaxis is still the gold standard to reduce intravesical recurrence after radical nephroureterectomy (RNU). Novel surveillance strategies have been proposed to adapt follow-up regimens to patients' characteristics.

Summary
Minimally invasive surgery has been associated with comparable oncological outcomes to the open approach while improving postoperative morbidity. In these cases, bladder cuff excision (BCE) is mostly performed by an extravesical approach, that demonstrates a noninferiority compared to the intravesical one in terms of oncological outcomes. Although lymphadenectomy is recommended in patients with high-risk tumors, its benefits are still unclear. Currently, there is a lack of recent prospective trials on chemoprophylaxis to reduce intravesical recurrence post RNU, making single-dose postoperative chemotherapy instillation the standard treatment. Although novel risk stratification models were released by international urological guidelines, their validity is mainly nonevidence-based. Risk-adapted follow-up strategies incorporating cystoscopy and cross-sectional imaging accounting for individual patient factors should be implemented.

Keywords
chemoprophylaxis, nephroureterectomy, surveillance, upper tract urothelial carcinoma

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) comprises only 5–10% of all urothelial carcinomas. It is a relatively rare disease due to an estimated annual incidence of nearly two cases per 100 000 inhabitants in Western countries [1]. However, UTUC poses significant clinical challenges due to its characteristics, aggressive biology, and treatment-related morbidity. Multifocality represents an important clinical feature as it is recognized in almost 20% of cases, while around 20% of UTUCs are diagnosed with concurrent bladder cancer (BCa), further complicating the clinical course and treatment strategies [2–4]. Finally, although advances in imaging modalities and refinements in endoscopic armamentarium have led to more accurate and timely diagnoses, approximately two-thirds of patients continue to be diagnosed with muscle-invasive disease, and nearly 10% harbor metastatic disease [2,4–6]. Hence, early diagnosis and accurate definition of disease characteristics are crucial when treating patients with UTUC aiming at balancing oncological and functional outcomes. In this review, we delve into the treatment paradigms of UTUC,

[a]Vita-Salute San Raffaele University, IRCCS Ospedale San Raffaele, Milan, Italy, [b]Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, Florida, USA and [c]Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy

Correspondence to Philippe E. Spiess, MD, MS, FACS, FRCS(C), Assistant Chief of Surgical Services, Senior Member, Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL 33612, USA. Tel: +1 813 745 8343; e-mail: Philippe.spiess@moffitt.org

Curr Opin Urol 2025, 35:75–82

DOI:10.1097/MOU.0000000000001247

KEY POINTS

- Radical nephroureterectomy with bladder cuff excision is the gold-standard treatment of patients with high-risk or low-risk upper tract urothelial carcinoma with unfavorable characteristics.
- Open, laparoscopic and robot-assisted approaches demonstrated comparable oncological outcomes, however, due to lower postoperative morbidity, the robotic approach is currently the most used worldwide.
- Template-based lymphadenectomy is recommended in high-grade, high-risk disease, but evidence on its benefit is weak.
- Single-dose intravesical chemoprophylaxis is still the main tool to reduce intravesical recurrence after radical treatment.
- Risk-adapted follow-up strategies incorporating cystoscopy and cross-sectional imaging should also consider individual patient factors.

aiming to provide evidence-based updates on surgical management, strategies to reduce tumor recurrence, and surveillance regimens in patients elected for radical treatment.

RADICAL NEPHROURETERECTOMY

The combination of CT scan and urinary cytology represents the gold standard in the diagnostic work-up of UTUC [3,4]. However, CT scan showed reduced accuracy in disease staging and low specificity in flat lesions or small upper tract thickening characterization [7]. When imaging and urinary cytology do not provide a definitive diagnosis, ureteroscopy, either with or without biopsy, can aid clinicians in better assessing tumor characteristics. This procedure can enhance the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing treatments by providing additional insights into the tumor's risk profile [8,9]. This is noteworthy, as tumor multifocality, architecture, hydronephrosis, tumor size, high-grade biopsy or cytology have been identified as predictors of ≥pT2 disease. Based on such data and expert opinion, international urological guidelines released risk stratification models to support patient risk stratification tailoring RNU for high-risk (HR) patients [3,4]. However, the predictive performance of the full set of variables used to stratify patients has not been fully investigated. Two recent multicenter studies by Foerster *et al.* and Marcq *et al.* tried to identify new parameters strongly associated with tumor invasiveness. A new category of patients with an intermediate risk of progression has been proposed, possibly expanding the role of nephron-sparing surgery (NSS) to this group [10,11▪]. Although this novel intermediate risk category has not been included, the last update of the European Association of Urology (EAU) and the American Urological Association (AUA) risk models on UTUC marked an important turning point [3,4]. The expanded EAU criteria consider patients with high-grade or invasive tumors at CT scan or histological subtypes as those having the highest risk of progression and thus suitable for RNU. Notably, other criteria such as multifocality, dimension ≥2 cm and hydronephrosis, previously considered important determinants of invasiveness have been underrated, consequently expanding the role of NSS. Similarly, the AUA guidelines identify all high-grade tumors as HR, however, patients with no tumor invasion, no hydronephrosis, unifocal and papillary tumors are those with favorable features for which RNU remains the gold standard treatment, but NSS may be proposed.

SURGICAL APPROACH

RNU with bladder cuff excision (BCE) with possible regional lymph node dissection (LND) is the standard of care for patients with nonmetastatic HR UTUC or low-risk disease with unfavorable features [3,4]. Although advanced age has been considered an independent predictor of worse oncological outcomes in surgically treated patients with UTUC [12], RNU has been demonstrated to be feasible also in elderly populations without increased morbidity [13,14].

pen, laparoscopic, and robot-assisted approaches have been used to perform RNU [15,16]. With the growing body of evidence supporting minimally invasive surgery, distinct nuances in perioperative and oncological outcomes have come to light, warranting further discussion. A recent systematic review conducted by the EAU panel on UTUC guidelines, encompassing 42 studies, revealed that laparoscopic RNU is associated with inferior oncological outcomes relative to the open approach, particularly in patients with locally advanced high-risk disease. However, the evidence supporting this finding is weak [17]. Furthermore, despite the robotic approach being associated with longer operative time, it has been related to fewer postoperative complications, shorter hospitalization, and higher lymph node yield, compared to laparoscopy [18,19▪]. The superiority of the robotic approach in perioperative outcomes has been summarized by the ROBUUST group, demonstrating a lower achievement of tetrafecta (1 – occurrence of bladder cuff excision, 2 – better LND, 3 – no complications, and 4 – negative surgical margins) in the

laparoscopic group [20]. Conversely, a recent study by Grossmann *et al.* showed that despite similar oncological outcomes, both laparoscopic and robotic approaches are associated with significantly worse bladder recurrence-free rates compared to the open approach [21▪]. However, only about one-eighth of patients in the included studies received perioperative intravesical chemotherapy. Therefore, both EAU and AUA guidelines still consider open, laparoscopic, and robot-assisted as equivalent approaches [3,4]. A summary of studies comparing robot-assisted vs. laparoscopic vs. open RNU is reported in Table 1 [21▪,22–27].

RNU can also be performed using both transperitoneal and retroperitoneal approaches, with the transperitoneal being associated with shorter procedure time and prolonged intestinal function recovery [28]. Novel robotic platforms have entered the market allowing for a wider availability of minimally invasive surgery worldwide. Single-position RNUs using the DaVinci Xi robotic platform were demonstrated to be safe techniques and slightly associated with lower complication rates and better cosmetic outcomes [29,30]. The supine anterior retroperitoneal access (SARA) technique has been also developed using the Single-Port robotic platform, and its feasibility has been demonstrated in a small cohort of patients [31]. Similarly, novel robotic systems such as KangDuo and Hinotori have been recently used for RNU [32,33]. Thus, different techniques, surgical approaches, and platforms can be used to perform RNU. The choice among these options should be tailored to individual patient needs and consider surgeons' experience and skills. Nevertheless, as also demonstrated in muscle-invasive BCa, patient referral to high-volume centers is recommended to enhance both short-term surgical and long-term oncological outcomes [34].

BLADDER CUFF EXCISION

Management of the distal ureter and ureteral orifice during RNU is a crucial step to improve bladder recurrence-free survival. Several techniques of BCE have been described. The transvesical is mostly used in open surgery while the extravesical during minimally invasive approaches. Alternative techniques have also been proposed (i.e. the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception) [35]. However, there is no Level 1 evidence supporting one approach over another. The transvesical has been considered for a long time the standard approach, as it may provide the most radical ureteral resection. However, the increasing use of robotic surgery has currently changed the surgical management of UTUC, as the extravesical technique is the most frequent technique used [36]. In the first meta-analysis published by Lai *et al.* comprising nine studies and involving 4683 patients, the transvesical technique was associated with better recurrence-free survival (RFS) ($P < 0.01$) and intravesical RFS ($P < 0.01$) [37▪]. Since then, more recent series have been published. An updated meta-analysis including 19 non-randomized studies, 15 of which used minimally invasive approaches, demonstrated that the risk of bladder recurrence, metastasis and cancer-related death did not differ significantly between approaches (all $P > 0.05$) [38]. Therefore, since RCTs are missing, the most important element is to perform a complete and high-quality BCE, regardless of the approach chosen. Furthermore, other factors should be considered. One of the most important is the tumor location. Therefore, the endoscopic technique should not be recommended in patients with distal ureteral tumors. Second, the use of the endoscopic approach is losing its rationale, since robotic surgery eases the performance of a less invasive BCE approach (extravesical), sparing the endoscopic time of the surgery.

REGIONAL LYMPH NODE DISSECTION

Currently, international clinical practice guidelines advocate for performing LND during RNU in patients diagnosed with UTUC. The EAU guideline advises templated-based LND for all patients diagnosed with high-risk UTUC [4]. Similarly, the AUA guideline recommends LND at the time of RNU for high-grade UTUC and it may be considered for low-grade UTUC [3]. However, the main point of performing LND in UTUC lies in the unclear and challenging quantification of its staging, prognostic, and therapeutic benefits [39]. Data regarding LND in UTUC is limited, and one of the main reasons is the insufficient number of LND performed worldwide [40]. However, regional lymph node metastases are present in up to one-third of UTUC patients at the time of diagnosis, but the majority are recognized at final pathology since cross-sectional imaging performance is poor in detecting N+ disease (sensitivity 25%, specificity 91%) [41▪]. Nevertheless, some predictors associated with lymph node involvement in UTUC have been considered. Lughezzani *et al.* found that the incidence of N+ disease varies significantly based on the T stage ($P < 0.001$) and tumor grade ($P = 0.002$) [42]. Conversely, Venkat *et al.* created a nomogram that identified high-grade disease, lymphovascular invasion (LVI), cN+ status, and tumor size >5 cm as predictors of lymph node involvement (AUC 0.87) [43].

Table 1. Perioperative and oncological outcomes of studies comparing open vs. laparoscopic vs. robotic nephroureterectomy in patients with upper tract urothelial carcinoma

Author	Study design	Number of patients, *N*	Postoperative complications, %	LOS, days	PSM	CSS	OS
Pearce *et al.* 2015	Retrospective	ONU 11698 LNU 2638 RoNU 2286	ONU 30% LNU 23% RoNU 19%	ONU 5 (4-7) LNU 4 (3–6) RoNU 4 (3–5)	NA	NA	NA
Tinay *et al.* 2015	Propensity score matched analysis	ONU 17254 LNU 13317 RoNU 3774	ONU 38% LNU 36% RoNU 42%	Lower after LNU and RoNU ($P<0.001$)	NA	NA	NA
Lenis *et al.* 2017	Retrospective	ONU 969 LNU 1385 RoNU 762	NA	NA	ONU13% LNU 7% RoNU 8%	NA	RoNU HR 0.93 (0.77–1.12, $P=0.4$) LNU HR 0.97 (0.83–1.13, $P=0.7$) (ref. ONU)
Rodriguez *et al.* 2017	Retrospective	ONU 3199 LNU 4104 RoNU 2098	NA	NA	RoNU HR 0.73 (95%CI: 0.54–0.98, $P=0.04$) LNU HR 0.86 (95%CI: 0.68–1.10, $P=0.2$) (ref. ONU)	NA	RoNU HR 0.88 (95%CI: 0.71–1.09, $P=0.2$) LNU HR 0.84 (95%CI: 0.70–1.00, $P=0.06$) (ref. ONU)
Lee *et al.* 2018	Retrospective	ONU 161 LNU 137 RoNU 124	ONU 15% LNU 15% RoNU 14%	ONU 12.8 ± 5.0 LNU 10.4 ± 3.7 RoNU 10.3 ± 4.9	NA	RoNU HR 0.34 (0.07–1.6, $P=0.2$) LNU HR 0.36 (0.1–1.28, $P=0.1$) (ref. ONU)	RoNU HR 0.33 (0.09–1.16, $P=0.08$) LNU HR 0.54 (0.25–1.16, $P=0.11$) (ref. ONU)
Bae *et al.* 2022	Retrospective	ONU 61 LNU 185 RoNU 119	ONU 16% LNU 17% RoNU 21%	ONU 7.5 ± 1.9 LNU 7.2 ± 2.4 RoNU 7.3 ± 3.4	ONU 3% LNU 5% RoNU 2%	ONU HR 1.12 (0.35–3.54) LNU HR 0.98 (0.22–4.40) (ref. RoNU)	ONU HR 1.28 (0.45–3.61) LNU HR 0.77 (0.18–3.30) (ref. RoNU)
Grossmann *et al.* 2023	Propensity score matched analysis	ONU 252 LNU 252 RoNU 252	ONU 61% LNU 64% RoNU 75%	ONU 10 (6–15) LNU 8 (5–14) RoNU 4 (2–6)	ONU 6% LNU 4% RoNU 2%	RoNU HR 0.65 (0.39–1.10, $P=0.1$) LNU HR 0.92 (0.59–1.41, $P=0.8$) (ref. ONU)	RoNU HR 0.81 (0.55–1.19, $P=0.3$) LNU HR 0.93 (0.68–1.28, $P=0.6$) (ref. ONU)

CSS, cancer-specific survival; HR: hazard ratio; ONU, open nephroureterectomy; LOS, length of stay; LNU, laparoscopic nephroureterectomy; NA, not available; OS, overall survival; PSM, positive surgical margin; RoNU, robotic nephroureterectomy.

Another possible issue of LND in UTUC regards the extent of LND. Despite harvesting a greater number of lymph nodes decreases the likelihood of missing metastasis, this effect is not observed when harvesting >10 lymph nodes [44,45]. Furthermore, complications during or after RNU range between 15% and 45%, and some of them may be associated with LND (including chylous ascites, vascular and pancreas injuries) [46▪]. Thus, although two recent systematic reviews suggested no statistically significant differences in oncologic outcomes between patients who underwent LND compared to those who did not [47,48], a template-based and complete LND is currently recommended by the EAU and AUA guidelines as it improves recurrence and cancer-specific mortality in patients with ≥pT2 UTUC and reduces the risk of unnecessary postoperative morbidity [49–51]. In this regard, the AUA panel conducted a re-analysis of four studies included in previously published meta-analyses, in which HRs were all converted so the comparison was in the same direction (LND versus no LND), to pool data from all studies, indicating an improvement in RFS (HR 0.58) [3]. Recently, the ROBUUST group published data from a contemporary cohort of 877 patients treated with robotic RNU. Overall, 40% of patients received LND. Although high-grade tumors ($P = 0.015$) and increasing tumor size ($P = 0.001$) were confirmed to be predictive for N+ disease, LND in patients with positive lymph nodes provided only prognostic data but was not associated with improved OS [52]. Another argument that should be defined is the role of LND in patient selection for adjuvant therapies. For instance, in the POUT trial which compared adjuvant gemcitabine and platinum-based chemotherapy, subgroup analysis revealed no benefit of adjuvant chemotherapy compared to surveillance in patients with N+ disease in terms of disease-free and OS [53▪▪]. Similarly, in the CheckMate 274 trial, which compared adjuvant Nivolumab versus placebo for muscle-invasive urothelial carcinoma, the subgroup analysis of patients with UTUC did not show an added benefit with Nivolumab (HR 1.23) [54]. Thus, patient selection for LND is still needed to properly define its diagnostic, prognostic, and, potentially, therapeutic benefits.

CHEMOPROPHYLAXIS OF INTRAVESICAL RECURRENCE

Intravesical recurrence after RNU is a common event in patients with UTUC and can be as high as 47% [55]. A systematic review and meta-analysis of 18 studies published in 2015 identified several key risk factors for intravesical recurrence including male sex, previous BCa, positive preoperative urinary cytology, ureteral tumor site, multifocality, invasive pathologic T-stage, presence of necrosis, laparoscopic approach, extravesical BCE, and positive surgical margins [56]. While patient-specific factors may not apply to other patient groups, recent studies have confirmed that tumor-related factors, such as ureteral tumor location, multifocality and positive surgical margins are strong predictors of intravesical recurrence [57,58]. Furthermore, the probability of intravesical recurrence has been reported to be higher within 3 years from RNU, with most recurrences recorded within the first 2 years [59]. Thus, following the results achieved in non-muscle invasive BCa, several treatment strategies have been implemented to reduce early intravesical recurrence after RNU. To date, two prospective RCTs demonstrated that a single instillation of intravesical chemotherapy after RNU is effective in reducing subsequent intravesical recurrences. A phase III trial by O'Brien *et al.* randomized patients to either a single postoperative intravesical dose of mitomycin-C (MMC) or standard management. On the intention-to-treat analysis, 17% in the MMC arm experienced a bladder recurrence in the first year compared to 27% in the standard treatment arm ($P = 0.055$). By treatment as per protocol analysis, 16% vs. 27% developed recurrence in the MMC and standard treatment arms, respectively ($P = 0.03$) [60]. Similar results were achieved in a smaller phase II trial by Ito *et al.* that randomized 77 patients to a single intravesical instillation of pirarubicin or standard care within 48 h of RNU [61]. Recently, another trial randomized patients to receive single-dose or maintenance treatment with epirubicin, up to 1-year after RNU. Despite the low number of patients included, the maintenance regimen was not superior to single-dose instillation in reducing intravesical recurrence after RNU [62]. Therefore, the evidence strongly supports the use of a single dose of intravesical chemotherapy around the time of RNU to reduce the risk of subsequent bladder recurrence.

ONCOLOGIC SURVEILLANCE

The optimal oncologic surveillance strategy in patients treated with RNU for UTUC is still a matter of debate. Although both the EAU and AUA guidelines have been recently updated, they still provide weak recommendations on this topic as they are mainly based on expert opinion. The risk of recurrence during follow-up, such as bladder, local, or distant recurrence can be as high as 47%, 18%, and 17%, respectively [3,4]. Given these relatively high rates of recurrence, a stringent surveillance protocol based on cystoscopies and cross-sectional imaging is warranted to achieve timely detection of recurrence and treatment. However, despite several studies

Table 2. Surveillance regimens for patients with upper tract urothelial carcinoma treated with radical nephroureterectomy

	EAU					AUA				
Low-risk	**I**	**II**	**III**	**IV**	**V**	**I**	**II**	**III**	**IV**	**V**
Cystoscopy	3 and 12 mo	Yearly				3-6-12 mo	Every 6 mo	Yearly		
Imaging	–	–	–	–	–	Every 6 mo	Yearly			
High-risk										
Cystoscopy	Every 3 mo		Every 6 mo			3-6-12 mo	Every 6 mo		Yearly	
Imaging	Every 6 mo Y		Yearly			3-6-12 mo	Every 6 mo	Yearly		

AUA, American Urological Association; EAU, European Association of Urology; mo, months.
[a]Adapted from EAU and AUA guidelines on upper tract urothelial carcinoma.

recording an increased risk of tumor recurrence among UTUC patients with a prior history of BCa, multifocal, stage T3-4, LVI, and high-grade tumors, surveillance protocols are not currently stratified for these factors [63–66]; yet, considering both LR and HR UTUC patients as a homogeneous population with an equal risk of recurrence regardless previous risk factors and comorbid conditions may not be appropriate. Two recent studies tried to consider some of these factors. Shigeta *et al.* reported follow-up results of 714 patients treated with RNU in a multicenter study. The risks of cancer-specific mortality (CSM) and other cause mortality (OCM) over time were estimated using Weibull distributions. The Authors found that the HR of OCM gradually increased over time in all age groups regardless of the smoking status, whereas CSM decreased markedly according to the pT stage and was affected by the smoking status [67]. Similarly, Martini *et al.* suggested a novel surveillance regimen after RNU based on the results of 1378 HR patients. Among patients without a prior BCa history, individuals younger than 60 years should continue both cystoscopies and imaging beyond 10 years from RNU, 70–79-year-old patients should continue only imaging beyond 10 yr, while patients older than 80 yr might discontinue oncologic surveillance because of an increased risk of OCM [68▪].

Currently, both the EAU and AUA guidelines recommend a follow-up scheme adjusted to the pre-RNU disease risk category. However, recommendations are not uniform among guidelines (Table 2). Thus, further studies are needed to provide more accurate disease risk-adapted and patient-tailored surveillance regimens. In this regard, novel biomarkers may help in stratifying patient risk categories, guiding patient selection for perioperative treatment, and adapting regimens follow-up [69,70]. Finally, follow-up strategies should also consider RNU sequelae, as patients are at high risk of developing chronic kidney disease and metabolic disorders.

CONCLUSION

UTUC is a challenging to treat disease. Although available disease risk stratification models lack strong validity, RNU with BCE and LND is the gold standard treatment for high-risk patients. Robot-assisted is currently the most used approach worldwide, however, surgical approach should be chosen according to surgeon preferences and patient characteristics. BCE can be performed by either an intra- or extravesical approach, although extravesical is the most used in minimally invasive surgeries. Early intravesical chemotherapy instillation is the main tool to reduce bladder recurrence, despite the lack of recent trials on this topic. Current surveillance strategies should be refined and adapted to disease characteristics and patient morbidity.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Philippe E. Spiess is vice-chair of the NCCN bladder and penile cancer guidelines.
Andrea Necchi: Honoraria: Roche, MSD, AstraZeneca, Janssen, Foundation Medicine, BMS, Astellas. Consulting or Advisory role: MSD, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen, Incyte, Seattle Genetics/Astellas, Bristol-Myers Squibb, Rainier Therapeutics, Bycicle Therapeutics, GlaxoSmithKline, Basilea Pharmaceutica, Catalym. Research Funding (Institution): MSD, AstraZeneca, Ipsen, Gilead. Travel, Accommodations, Expenses: Roche, MSD, AstraZeneca, Janssen, Rainer Therapeutics, Pfizer. Employment and Stock Ownership (spouse): Bayer.
The other Authors declare no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73:17–48.
2. Soria F, Shariat SF, Lerner SP, *et al.* Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol 2017; 35:379–387.
3. Coleman JA, Clark PE, Bixler BR, *et al.* Diagnosis and management of non-metastatic upper tract urothelial carcinoma: AUA/SUO guideline. J Urol 2023; 209:1071–1081.
4. Rouprêt M, Seisen T, Birtle AJ, *et al.* European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2023 update. Eur Urol 2023; 84:49–64.
5. Catto JWF, Mandrik O, Quayle LA, *et al.* Diagnosis, treatment and survival from bladder, upper urinary tract, and urethral cancers: real-world findings from NHS England between 2013 and 2019. BJU Int 2023; 131:734–744.
6. Gallioli A, Basile G, Territo A, Breda A. New technologies for nephron-sparing surgery in upper urinary tract cancers. Curr Opin Urol 2023; 33:510–515.
7. Janisch F, Shariat SF, Baltzer P, *et al.* Diagnostic performance of multidetector computed tomographic (MDCTU) in upper tract urothelial carcinoma (UTUC): a systematic review and meta-analysis. World J Urol 2020; 38:1165–1175.
8. Breda A, Territo A, Sanguedolce F, *et al.* Comparison of biopsy devices in upper tract urothelial carcinoma. World J Urol 2019; 37:1899–1905.
9. Gallioli A, Territo A, Mercadé A, *et al.* The impact of ureteroscopy following computerized tomography urography in the management of upper tract urothelial carcinoma. J Urol 2021; 205:392–399.
10. Foerster B, Abufaraj M, Matin SF, *et al.* Pretreatment risk stratification for endoscopic kidney-sparing surgery in upper tract urothelial carcinoma: an international collaborative study. Eur Urol 2021; 80:507–515.
11. ■ Marcq G, Foerster B, Abufaraj M, *et al.* Novel classification for upper tract urothelial carcinoma to better risk-stratify patients eligible for kidney-sparing strategies: an international collaborative study. Eur Urol Focus 2022; 8:491–497.

A multicenter study identifying novel risk-classification for upper tract urothelial carcinoma

12. Ferro M, Chiujdea S, Vartolomei MD, *et al.* Advanced age impacts survival after radical nephroureterectomy for upper tract urothelial carcinoma. Clin Genitourin Cancer 2024; 22:27–37.
13. Teoh JYC, Ng CF, Eto M, *et al.* Radical nephroureterectomy for UTUC conferred survival benefits irrespective of age and comorbidities. World J Urol 2022; 40:2657–2665.
14. Koterazawa S, Kanno T, Kobori G, *et al.* Clinical outcomes following laparoscopic radical nephroureterectomy in octogenarians. Int J Clin Oncol 2023; 28:155–162.
15. Ni S, Tao W, Chen Q, *et al.* Laparoscopic versus open nephroureterectomy for the treatment of upper urinary tract urothelial carcinoma: a systematic review and cumulative analysis of comparative studies. Eur Urol 2012; 61:1142–1153.
16. O'Sullivan NJ, Naughton A, Temperley HC, Casey RG. Robotic-assisted versus laparoscopic nephroureterectomy; a systematic review and meta-analysis. BJUI Compass 2023; 4:246–255.
17. Peyronnet B, Seisen T, Dominguez-Escrig JL, *et al.* Oncological outcomes of laparoscopic nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: an European Association of Urology guidelines systematic review. Eur Urol Focus 2019; 5:205–223.
18. Ji R, He Z, Fang S, *et al.* Robot-assisted vs. laparoscopic nephroureterectomy for upper urinary tract urothelial carcinoma: a systematic review and meta-analysis based on comparative studies. Front Oncol 2022; 12:964256.
19. ■ Rajan K, Khalifa A, Geraghty R, *et al.* Oncological efficacy of robotic nephroureterectomy vs. open and laparoscopic nephroureterectomy for suspected non-metastatic UTUC-A systematic review and meta-analysis. Cancers (Basel) 2023; 15:4926.

The lastest published systematic review and meta-analysis on oncological outcomes after open vs laparoscopic vs robot-assisted radical nephroureterectomy

20. Veccia A, Carbonara U, Djaladat H, *et al.* Robotic vs laparoscopic nephroureterectomy for upper tract urothelial carcinoma: a multicenter propensity-score matched pair "tetrafecta" analysis (ROBUUST Collaborative Group). J Endourol 2022; 36:752–759.
21. ■ Grossmann NC, Soria F, Juvet T, *et al.* Comparing oncological and perioperative outcomes of open versus laparoscopic versus robotic radical nephroureterectomy for the treatment of upper tract urothelial carcinoma: a multicenter, multinational, propensity score-matched analysis. Cancers (Basel) 2023; 15:1409.

A multicenter study comparing oncological and perioperative outcomes of open versus laparoscopic versus robotic radical nephroureterectomy for the treatment of upper tract urothelial carcinoma

22. Pearce SM, Pariser JJ, Patel SG, *et al.* The effect of surgical approach on performance of lymphadenectomy and perioperative morbidity for radical nephroureterectomy. Urol Oncol 2016; 34:121; e15-121.e21.
23. Tinay I, Gelpi-Hammerschmidt F, Leow JJ, *et al.* Trends in utilisation, perioperative outcomes, and costs of nephroureterectomies in the management of upper tract urothelial carcinoma: a 10-year population-based analysis. BJU Int 2016; 117:954–960.
24. Lenis AT, Donin NM, Faiena I, *et al.* Role of surgical approach on lymph node dissection yield and survival in patients with upper tract urothelial carcinoma. Urol Oncol 2018; 36:9e1–9e9.
25. Rodriguez JF, Packiam VT, Boysen WR, *et al.* Utilization and outcomes of nephroureterectomy for upper tract urothelial carcinoma by surgical approach. J Endourol 2017; 31:661–665.
26. Lee H, Kim HJ, Lee SE, *et al.* Comparison of oncological and perioperative outcomes of open, laparoscopic, and robotic nephroureterectomy approaches in patients with nonmetastatic upper-tract urothelial carcinoma. PLoS One 2019; 14:e0210401.
27. Bae H, Chung JH, Song W, *et al.* Robotic radical nephroureterectomy with bladder cuff excision for upper tract urothelial carcinoma: a trend analysis of utilization and a comparative study. Cancers (Basel) 2022; 14:2497.
28. Zhu P, yu. Wang L, *et al.* Chen X bin Perioperative and oncologic outcomes of transperitoneal versus retroperitoneal laparoscopic nephroureterectomy for upper urinary tract urothelial carcinoma: a systematic review and pooled analysis of comparative outcomes. World J Surg Oncol 2023; 21:163.
29. Veccia A, Carbonara U, Der Weesh I, *et al.* Single-stage Xi® robotic radical nephroureterectomy for upper tract urothelial carcinoma: surgical technique and outcomes. Minerva Urol Nephrol 2022; 74:233–241.
30. Shi Y, Wang S, Liu W, *et al.* Single-position complete retroperitoneoscopic radical nephroureterectomy with bladder cuff excision for upper urinary tract urothelial carcinoma. J Endourol 2023; 37:768–774.
31. Pellegrino AA, Chen G, Morgantini L, *et al.* Simplifying retroperitoneal robotic single-port surgery: novel supine anterior retroperitoneal access. Eur Urol 2023; 84:223–228.
32. Li ZUOW, Tang Z, Fan Q, *et al.* Robot-assisted radical nephroureterectomy using the KangDuo Surgical Robot-01 system: a prospective, single-center, single-arm clinical study. J Endourol 2024; 38:661–667.
33. Motoyama D, Matsushita Y, Watanabe H, *et al.* Robot-assisted radical nephroureterectomy for upper urinary tract tumor: initial experience with the use of novel surgical robot system, Hinotori. Transl Cancer Res 2023; 12:3522–3529.
34. Sui W, Wallis CJD, Luckenbaugh AN, *et al.* The impact of hospital volume on short-term and long-term outcomes for patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma. Urology 2021; 147:135–142.
35. Morriss S, Zargar H, Dias BH. Management of the distal ureter during nephroureterectomy for upper tract urothelial carcinoma: a comprehensive review of literature. Urol J 2021; 18:585–599.
36. Joseph JP, O'Malley P, Su LM. Robot-assisted radical nephroureterectomy. J Endourol 2021; 35:S122–S131.
37. ■ Lai S, Guo R, Seery S, *et al.* Assessing the impact of different distal ureter management techniques during radical nephroureterectomy for primary upper urinary tract urothelial carcinoma on oncological outcomes: a systematic review and meta-analysis. Int J Surg 2020; 75:165–173.

The latest systematic review and meta-analysis on perioperative and oncological outcomes of different techniques for distal ureter management during nephroureterectomy for upper urinary tract urothelial carcinoma.

38. Gallioli A, Baboudjian M, Diana P, *et al.* Perioperative and oncological outcomes of distal ureter management during nephroureterectomy for upper urinary tract urothelial carcinoma: a systematic review and meta-analysis. Minerva Urol Nephrol 2023; 75:672–682.
39. Myers AA, Briganti A, Leibovich B, *et al.* Contemporary role of lymph node dissection in genitourinary cancers: where are we in 2023? Eur Urol Oncol 2024;7:412–20.
40. Moschini M, Foerster B, Abufaraj M, *et al.* Trends of lymphadenectomy in upper tract urothelial carcinoma (UTUC) patients treated with radical nephroureterectomy. World J Urol 2017; 35:1541–1547.
41. ■ Pallauf M, D'Andrea D, König F, *et al.* Diagnostic accuracy of clinical lymph node staging for upper tract urothelial cancer patients: a multicenter, retrospective. Observational Study J Urol 2023; 209:515–524.

A multicenter, retrospective, observational study assessing the diagnostic accuracy of clinical lymph node staging for upper tract urothelial cancer patients.

42. Lughezzani G, Jeldres C, Isbarn H, *et al.* A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 2010; 75:118–124.
43. Venkat S, Khan AI, Lewicki PJ, *et al.* Novel nomograms to predict muscle invasion and lymph node metastasis in upper tract urothelial carcinoma. Urol Oncol 2022; 40:108; e11-108.e17.
44. Zareba P, Rosenzweig B, Winer AG, Coleman JA. Association between lymph node yield and survival among patients undergoing radical nephroureterectomy for urothelial carcinoma of the upper tract. Cancer 2017; 123:1741–1750.
45. Xylinas E, Kluth L, Rieken M, *et al.* External validation of the pathological nodal staging score in upper tract urothelial carcinoma: a population-based study. Urol Oncol 2017; 35:33; e21-33.e26.
46. ■ Peng L, Mehmud I, Meng C, *et al.* Comparison of perioperative outcomes and complications of laparoscopic and robotic nephroureterectomy approaches in patients with upper-tract urothelial carcinoma. Ann Surg Oncol 2023; 30:3805–3816.

A retrospective study reporting perioperative outcomes and complications of laparoscopic and robotic nephroureterectomy approaches in patients with upper-tract urothelial carcinoma.

47. Guo R, Zhu Y, Xiong G, *et al.* Role of lymph node dissection in the management of upper tract urothelial carcinomas: a meta-analysis. BMC Urol 2018; 18:24.
48. Chan VWS, Wong CHM, Yuan Y, Teoh JYC. Lymph node dissection for upper tract urothelial carcinoma: a systematic review. Arab J Urol 2020; 19:37–45.
49. Yanagisawa T, Kawada T, Von Deimling M, *et al.* Need for and extent of lymph node dissection for upper tract urothelial carcinoma: an updated review in 2023. Curr Opin Urol 2023;33:258–68.
50. Kondo T, Hashimoto Y, Kobayashi H, *et al.* Template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract: impact on patient survival. Int J Urol 2010; 17:848–854.
51. Dominguez-Escrig JL, Peyronnet B, Seisen T, *et al.* Potential benefit of lymph node dissection during radical nephroureterectomy for upper tract urothelial carcinoma: a systematic review by the european association of urology guidelines panel on nonmuscle-invasive bladder cancer. Eur Urol Focus 2019; 5:224–241.
52. Hakimi K, Carbonara U, Djaladat H, *et al.* Outcomes of lymph node dissection in nephroureterectomy in the treatment of upper tract urothelial carcinoma: analysis of the ROBUUST Registry. J Urol 2022; 208:268–276.
53. ■■ Birtle A, Johnson M, Chester J, *et al.* Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet 2020; 395:1268–1277.

A phase 3, open-label, randomised controlled trial assessing the role of adjuvant chemotherapy in upper tract urothelial carcinoma

54. Bajorin DF, Witjes JA, Gschwend JE, *et al.* Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021; 384:2102–2114.
55. Xylinas E, Kluth L, Passoni N, *et al.* Prediction of intravesical recurrence after radical nephroureterectomy: development of a clinical decision-making tool. Eur Urol 2014; 65:650–658.
56. Seisen T, Granger B, Colin P, *et al.* A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. Eur Urol 2015; 67:1122–1133.
57. Chen CY, Chang CH, Yang CR, *et al.* Prognostic factors of intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 2024; 42:22.
58. Katims AB, Say R, Derweesh I, *et al.* Risk factors for intravesical recurrence after minimally invasive nephroureterectomy for upper tract urothelial cancer (ROBUUST Collaboration). J Urol 2021; 206:568–576.
59. Locke JA, Hamidizadeh R, Kassouf W, *et al.* Surveillance guidelines based on recurrence patterns for upper tract urothelial carcinoma. Can Urol Assoc J 2018; 12:243–251.
60. O'Brien T, Ray E, Singh R, *et al.* Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol 2011; 60:703–710.
61. Ito A, Shintaku I, Satoh M, *et al.* Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group Trial. J Clin Oncol 2013; 31:1422–1427.
62. Harraz AM, El-Shabrawy M, El-Nahas AR, *et al.* Single versus maintenance intravesical chemotherapy for the prevention of bladder recurrence after radical nephroureterectomy for upper tract urothelial carcinoma: a randomized clinical trial. Clin Genitourin Cancer 2019; 17:e1108–e1115.
63. Stangl-Kremser J, Muto G, Grosso AA, *et al.* The impact of lymphovascular invasion in patients treated with radical nephroureterectomy for upper tract urothelial carcinoma: an extensive updated systematic review and meta-analysis. Urol Oncol 2022; 40:243–261.
64. Nogueira LM, Yip W, Assel MJ, *et al.* Survival impact of variant histology diagnosis in upper tract urothelial carcinoma. J Urol 2022; 208:813–820.
65. Cirulli GO, Corsi N, Rakic I, *et al.* Impact of lymphovascular invasion on survival in surgically treated upper tract urothelial carcinoma: a nationwide analysis. BJU Int 2024; 133:555–563.
66. Martini A, Lonati C, Montorsi F, *et al.* The role of prior bladder cancer on recurrence in patients treated with radical nephroureterectomy. Clin Genitourin Cancer 2022; 20:e190–e198.
67. Shigeta K, Kikuchi E, Abe T, *et al.* A novel risk-based approach simulating oncological surveillance after radical nephroureterectomy in patients with upper tract urothelial carcinoma. Eur Urol Oncol 2020; 3:756–763.
68. ■ Martini A, Lonati C, Nocera L, *et al.* Oncologic surveillance after radical nephroureterectomy for high-risk upper tract urothelial carcinoma. Eur Urol Oncol 2022; 5:451–459.

A multicenter study proposing a novel oncologic surveillance scheme after radical nephroureterectomy for high-risk upper tract urothelial carcinoma.

69. Padullés B, Carrasco R, Ingelmo-Torres M, *et al.* Prognostic value of liquid-biopsy-based biomarkers in upper tract urothelial carcinoma. Int J Mol Sci 2024; 25:3695.
70. Huelster HL, Gould B, Schiftan EA, *et al.* Novel use of circulating tumor DNA to identify muscle-invasive and nonorgan-confined upper tract urothelial carcinoma. Eur Urol 2024; 85:283–292.