Curr. Treat. Options in Oncol. (2019) 20: 40
DOI 10.1007/s11864-019-0637-2

Genitourinary Cancers (S Gupta, Section Editor)

Optimal Management of Upper Tract Urothelial Carcinoma: an Unmet Need

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Published online: 1 April 2019

This article is part of the Topical Collection on *Genitourinary Cancers*

Keywords Upper tract urothelial carcinoma · Kidney-sparing surgery · Radical nephroureterectomy · Minimally invasive surgery · Adjuvant chemo-immunotherapy · Systemic therapy

Opinion statement

Upper tract urothelial carcinoma (UTUC) is a rare genitourinary entity of the renal pelvis and the ureter characterized by a more aggressive disease phenotype when compared with urothelial carcinoma of the bladder (UCB) with more than half of UTUC cases presenting with invasive disease at diagnosis compared to 20% for bladder tumors. There is growing evidence suggesting that its distinct natural history from that of bladder cancer can be related to several genetic and epigenetic differences. Treatment of low-risk disease consists of kidney-sparing surgeries such as ureteroscopic and percutaneous treatments, segmental ureterectomy, and adjuvant topical and intracavitary chemo-immunotherapies. The standard of care for high-risk non-metastatic disease remains radical nephroureterectomy and bladder cuff excision with increasing utilization rates of minimally invasive approaches leading to reduced morbidity without compromising outcomes while the role of lymphadenectomy is still being investigated. The prognosis of UTUC has been stagnant over the past decade highlighting the need for further studies on the role

of multimodal therapy (neoadjuvant/adjuvant chemotherapy, immunotherapy, targeted therapy) to optimize management and improve outcomes.

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare subset of urothelial carcinomas that can arise along the upper urinary tract lined with urothelium (renal pelvis, ureter). The estimated incidence of UTUC in the USA is not well-defined due to the categorization of renal pelvis cancer and ureter cancer with "kidney" and "other urinary organs," respectively [1]. UTUC represents approximately 5–10% of all urothelial cancers with a ratio of renal pelvis to ureter tumor origin of 2:1 and is twice more common in men compared with women [2]. There is increasing evidence that UTUC may be a distinct disease entity from urothelial carcinoma of the bladder although both share a urothelial origin [3]. Several genetic and epigenetic variances may in part explain their differences in terms of natural history, disease phenotype, and response to systemic therapy [4••, 5]. Thus, optimal management of UTUC requires improved clinical risk stratification in order to better tailor surgical management, surveillance strategies, and systemic therapy [6•].

The aim of this manuscript is to review the current literature on the controversies and developments in the contemporary management of UTUC. Epidemiology, diagnosis, and imaging of UTUC are beyond the scope of the current review article.

Surgical management of localized disease

Accurate clinical staging for upper tract tumors can be more challenging when compared with bladder cancer. Pre-intervention risk stratification has been suggested to guide decision-making regarding definitive therapy and improve outcomes. The European Association of Urology (EAU) guidelines stratify UTUC patients into low-risk vs. high-risk based on clinical, endoscopic, radiographic, and histopathologic factors [7•]:

Low-risk: unifocal disease, tumor < 2 cm, low-grade cytology and/or URS biopsy and noninvasive disease on imaging.

High-risk: hydronephrosis, multifocal disease, tumor > 2 cm, high-grade cytology and/or URS biopsy, invasive disease on imaging and prior radical cystectomy.

Low-risk disease

Kidney-sparing surgery

In recent years, advances in diagnostic imaging and refinements in endoscopic armamentarium contributed to the increasing utilization of KSS including segmental ureterectomy (SU), ureteroscopic (URS), and percutaneous (PC) management for upper tract disease. Moreover, there is growing evidence to support the use of KSS as a primary treatment option for low-risk disease while avoiding the morbidity of radical surgery and preserving kidney function [8]. A recent systematic review by the EAU Non-muscle Invasive Bladder Cancer Guidelines Panel found that oncological outcomes associated with KSS including URS and PC treatments were similar to radical surgery in cases of low-grade

and noninvasive tumors despite an increased risk of local recurrence [9•]. Similarly, the authors demonstrated that SU can be considered in selected patients (e.g., solitary kidney, renal insufficiency, bilateral disease) with high-grade and invasive tumors without compromising survival. When offering KSS, patients need to be willing to undergo meticulous and stringent surveillance follow-up with repeat cystoscopy, ureteroscopy, upper urinary tract imaging, and urine cytology [7•].

High-risk disease

Open radical nephroureterectomy (ORNU) with bladder cuff excision (BCE) remains the standard of care for high-risk UTUC [10].

Open vs. minimally invasive surgery

Up until this past decade, the majority of RNU surgeries were performed through an open approach [11]. Since then, there has been a rapid dissemination of laparoscopic and robotic utilization for abdominal and pelvis surgeries in the urologic community with current data suggesting comparable oncological outcomes [12–14]. A recent systematic review and meta-analysis by Liu et al. demonstrated that laparoscopic RNU (LRNU) was a safe and effective alternative to ORNU for UTUC [15]. When compared with open surgery, minimally invasive surgery for UTUC has been associated with improved perioperative outcomes such as shorter length of stay, decreased blood loss, and fewer intraoperative complications [11, 12].

Distal ureter and bladder cuff management

Several techniques have been described for the management of the distal ureter and bladder cuff including extravesical, transvesical, and endoscopic "pluck" approaches [16, 17]. A large international retrospective study by Xylinas et al. compared the oncologic outcomes following RNU using these three methods of BCE and found no difference in terms of overall (OS), cancer-specific (CSS), and recurrence-free (RFS) survival although the endoscopic approach was associated with higher intravesical recurrence rates [18]. A recent report using the Surveillance, Epidemiology, and End Results database demonstrated increased rates of bladder cuff excision (BCE) at the time of RNU for renal pelvis (T1-3N0M0) from 63.0% in 2004 to 74.5% in 2014 ($P < 0.001$), confirming improved adherence to guidelines [19].

Regional lymphadenectomy

Similarly to UCB, metastatic dissemination of UTUC can follow lymphatic channels to regional nodes and is a well-known prognosticator of poor oncological outcomes. Yet, data regarding the patterns of nodal spread as well the potential benefit of regional lymphadenectomy (LAD) remains sparse [20]. Mapping studies to establish dissection templates for UTUC are complicated by the relative rarity of the disease and the anatomic extent of the upper urinary tract with possible tumor involvement arising from the renal pelvis to the ureterovesical junction [21]. Matin et al. reviewed patterns of lymph node metastases (LNM) in 73 patients with node-positive disease undergoing RNU or SU with template LAD from three National Cancer Institute designated

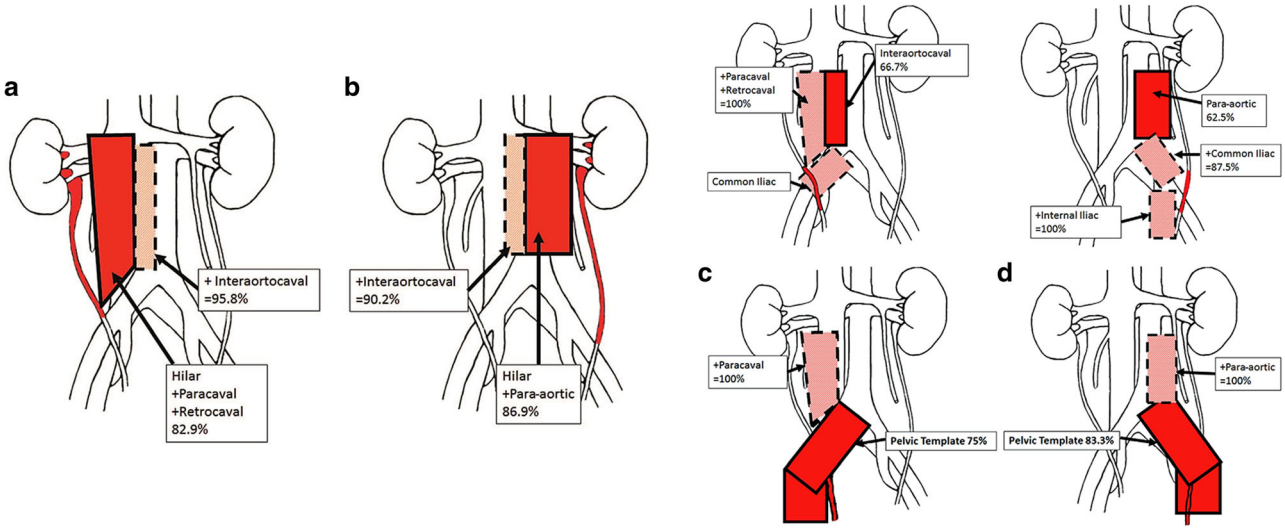

Fig. 1. Lymph node dissection templates for renal pelvis and proximal ureter tumors (**a**, **b**) and mid- and distal ureter tumors (**c**, **d**). Reproduced from [22•] with permission from Wolters Kluwer.

Comprehensive Cancer Centers and proposed dissection templates according to laterality and location of tumor within the upper urinary tract [22•]. Figure 1 describes the consolidated LAD templates (percentages represent proportions of LNM captured):

Renal pelvis/proximal ureter:

Right-sided tumors: hilar, paracaval, precaval and retrocaval ± interaortocaval
Left-sided tumors: hilar, para-aortic and preaortic ± interaortocaval

Mid ureter:

Right-sided tumors: paracaval +interaortocaval + right common iliac
Left-sided tumors: para-aortic + interaortocaval + left common iliac

Distal ureter:

Right-sided tumors: right pelvic nodes ± paracaval
Left-sided tumors: left pelvic nodes ± para-aortic

The therapeutic benefits of LAD at time of RNU remain controversial [20, 23]. In 2017, the EAU Guidelines Panel on Non-muscle Invasive Bladder Cancer published a systematic review and found a survival benefit in patients who underwent LAD for muscle-invasive tumors (≥pT2) of the renal pelvis with a node-positive rate ranging from 14.3 to 40% [24•]. However, there was a potential publication bias favoring the LAD group while the benefit of LAD in ureteral tumors remained uncertain. Conversely, a recent meta-analysis from China including 11 eligible studies concluded that although LAD allowed for more accurate staging and prediction of outcomes, it remained uncertain whether LAD independently improved survival in UTUC patients [25].

Postoperative surveillance

Bladder and contralateral upper tract recurrences occur in 27–47% and 0.8–5.8% of patients with UTUC, respectively [26–28]. Per NCCN and EAU clinical

practice guidelines, surveillance regimens post RNU are based on cystoscopy and urine cytology at 3 months then annually and computed tomography (CT) urography every year for > 5 years for noninvasive tumors [7•, 29••]. For invasive tumors CT urography is to be performed every 6 months for 2 years then annually. After KSS, the follow-up is more stringent with urine cytology and CT urography at 3 and 6 months then annually, while cystoscopy, ureteroscopy, and in situ cytology are performed at 3, 6 months then every 6 months for 2 years and the annually.

Topical/intracavitary therapy

The use of adjuvant topical and intracavitary chemo-immunotherapy agents plays a growing role in the management of UTUC after KSS and RNU.

After kidney-sparing surgery

Despite advances in endoscopic technology, reported ipsilateral recurrence rates after kidney-sparing treatment remain high, ranging from 30 to 70% [30–32]. Therefore, there is interest in the use of adjuvant topical therapies to reduce the risk of recurrence and progression. Though the literature remains sparse, the most commonly investigated agents include bacillus Calmette-Guerin (BCG) and mitomycin C (MMC). For carcinoma in situ (CIS) of the upper tract, BCG has shown some success [31, 33]. However, the use of BCG in Ta or T1 disease is less promising, with one series showing a recurrence-free survival of 41% and progression-free survival of 59%, with 23% of patients subsequently undergoing nephroureterectomy [33]. Different series also utilize different instillation techniques, with no accepted standardized procedure. A study by Pollard et al. evaluated the degree of urothelial exposure using three different techniques (antegrade infusion via nephrostomy, reflux via double-pigtail stent, and retrograde infusion via 5Fr open-ended ureteral catheter) by utilizing an ex vivo porcine model and estimating total percentage staining with indigo carmine after 1 h of dwell time. Mean percent staining was 65.2% (nephrostomy), 66.2% (stent), and 83.6% (ureteral catheter) ($P = 0.002$). The most recent recommendations by the National Comprehensive Cancer Network (NCCN) on upper urinary tract tumors include postsurgical intracavitary or topical therapy with chemotherapy or BCG as an option, but do not comment on regimen or method of instillation [29••]. The EAU also recommends the use of adjuvant BCG and mitomycin C for treatment of CIS (LE, 3), but not for Ta or T1 disease [7•].

Another concern for intracavitary therapies is the lack of dwell time with upper tract disease. In order to address this concern, a more recent agent being investigated is a novel formulation of mitomycin C combined with a reverse-thermal gelation hydrogel called Mitogel©. This formulation exists as a liquid in cold temperatures but solidifies to a gel state at body temperatures. The contact with urine results in a slow dissolution of the gel leading to a sustained release of MMC. Preclinical studies in animals have shown that Mitogel© remains visible in pelvicalyceal system for 4–6 h with no evidence of urinary obstruction, acute kidney injury, or myelosuppression [34]. Currently, the OLYMPUS

study (Optimized Delivery of Mitomycin for primary UTUC study; NCT02793128) is prospectively studying Mitogel© for patients with low-grade, noninvasive UTUC of the pyelocalyceal system with an expected study completion date of February 2020.

Post radical nephroureterectomy

The rationale for administering topical agents after RNU is to reduce risk of recurrence in the bladder. Several series have shown that the risk of urothelial recurrence within the bladder following RNU can range from 20 to 40% [35–38]. Two recent clinical trials have examined the benefit of single postoperative dose of intravesical chemotherapy after surgery. The ODMIT-C trial utilized a single dose of mitomycin C instilled at the time of catheter removal and found an 11% absolute risk reduction of bladder recurrence [39]. The THP Monotherapy study group trial used intravesical pirarubicin instilled 48 h postop and found a reduction of 25% [40]. A meta-analysis by Deng X et al. also demonstrated a benefit for postoperative instillation of chemotherapy, with an OR of 0.45 of intravesical recurrence (95% CI 0.34–0.61; $P < 0.0001$) [41]. Based on these two prospective randomized clinical trials, the NCCN guidelines now recommend the use of a single dose of intravesical chemotherapy after RNU for UTUC (LE, 2) [29••]. However, there is currently no consensus regarding the exact timing of instillation of postoperative chemotherapy and thus practice patterns amongst clinicians can differ. One study surveyed 158 urologic oncologists and found that only 49% of respondents used postoperative intravesical chemotherapy following RNU, and that timing of instillation varied with 7% at < 3 days, 37% in 4–7 days, 20% at 8–14 days, and 3% at > 14 days after surgery [42]. A meta-analysis by Wu et al. showed a non-statistically significant decrease in intravesical recurrences if a single dose is given within the first 24 h of surgery vs. 48 h or 2 weeks [43]. Table 1 shows the agents used with level I evidence, as well as details of the timing, dwell time, and duration of intravesical treatment.

Advanced disease

Systemic therapy

The literature for the use of neoadjuvant or adjuvant chemotherapy in UTUC is limited, with much of the data extrapolated from urothelial

Table 1. Randomized controlled trials of intravesical instillations after radical nephroureterectomy

Study (year)	Drug	Time of administration	Dwell time	Duration
Ito et al. (2013)	THP 30 mg	48 h postop	0.5 h	Once
O'Brien et al. (2011)	MMC 40 mg	Prior to catheter removal (median 7 days postop)	1 h	Once
Sakamoto et al. (2001)	MMC 20 mg + Ara-C 200 mg	1–2 week(s) postop	2 h	6 times

carcinoma of the bladder. Currently, there are no published prospective randomized data for either neoadjuvant or adjuvant chemotherapy in upper tract disease. Leow et al. published a thorough systemic review and meta-analysis on both adjuvant and neoadjuvant chemotherapy for upper tract disease [44•]. In examining retrospective studies on adjuvant chemotherapy (AC), the most commonly used regimens where methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) or gemcitabine + cisplatin (GC). Across 3 cisplatin-based studies, the pooled HR for overall survival was 0.43 (95% CI 0.24–0.99; $P = 0.048$), with no benefit seen in non-cisplatin-based regimens. There are fewer published data for neoadjuvant chemotherapy (NAC). However, smaller retrospective studies have shown potential benefit. A study from MD Anderson Cancer of 43 patients undergoing NAC prior to RNU (44.2% with MVAC, 11.6% with GC) demonstrated a 14% complete pathologic response rate [45]. The same meta-analysis reviewed 2 retrospective NAC studies demonstrating a disease-specific survival benefit with a pooled HR of 0.41 (95% CI 0.22–0.76; $P = 0.005$) [44•].

Potential benefits for neoadjuvant systemic therapy are the treatment of micro-metastases and the ability to administer full-dose cisplatin-based regimens prior to surgical removal of a renal unit. One study found that the median estimated glomerular filtration rate (eGFR) decreased by 18.2 after nephroureterectomy. Utilizing an eGFR threshold of 60 mL/min/1.73 m^2, only 37% of patients were eligible for neoadjuvant cisplatin-based chemotherapy compared with 16% for adjuvant therapy [46]. There are concerns for overtreatment with NAC due to the limitations in accurate clinical staging of primary tumors with cross-sectional imaging and inability to obtain full thickness of ureteral or renal pelvic wall for histopathological examination [47]. With limited evidence-based literature, NAC may be considered in selected patients (retroperitoneal lymphadenopathy and > 3 cm, high-grade, sessile and/or invasive primary tumors) according to the most recent NCCN guidelines [29••]. There are currently several active prospective trials looking to answer questions regarding the use systemic perioperative chemotherapy for upper tract disease (Table 2).

Radiation

Smaller, retrospective studies have shown no benefit for adjuvant radiotherapy and are not currently recommend by guidelines other than for locoregional and bladder control in selected patients [48, 49].

Emerging therapies/ future directions

A remarkable development for the treatment of all urothelial carcinomas has been the use of immunotherapy. In 2016, the FDA approved atezolizumab, a monoclonal antibody against programmed death-ligand 1 (PD-L1), for patients with urothelial carcinoma with progression during or after platinum-based chemotherapy [50]. Since then, four additional agents (nivolumab, durvalumab, avelumab, and pembrolizumab) have been approved and, in single-arm trials, have demonstrated objective response rates from 14 to 24% [51]. Though no study has directly evaluated the efficacy of immunotherapy in UTUC

Table 2. Active trials for adjuvant and neoadjuvant chemotherapy in upper tract urothelial carcinoma

NCT Trial No. (estimated completion date)	Phase	Estimated enrollment	Modality	Arms	Regimen	Primary outcome
NCT02969083 (October 2023)	2	210	NAC vs AC	A: RNU alone B: NAC C: AC	3 cycles GC or ddMVAC	Tolerability of 3 therapy courses
NCT02876861 (August 2020)	2	50	NAC vs RNU	A: RNU alone B: NAC	2–4 cycles GC	Disease-free survival
NCT01261728 (December 2019)	2	54	NAC	A: NAC	4 cycles GC	Pathologic response rate <pT2
NCT02412670 (February 2020)	2	36	NAC	A: NAC B: NAC	A: 4 cycles MVAC B: 4 cycles G-Carbo	Pathologic complete response
NCT01993979 (May 2022)	3	345	AC	A: RNU only B: AC	4 cycles GC (if GFR 30–49, substitute with Carbo)	Disease-free survival

patients, many of them were enrolled in these trials. Immune checkpoint inhibitors have shown promise in UTUC patients who are more likely to be cisplatin ineligible after extirpative therapy [52, 53].

Another promising area is targeting molecular alterations of UTUC [6•]. One group noted that in comparison with urothelial carcinoma arising in the bladder, UTUC had higher rates of microsatellite instability and fibroblast growth factor receptor 3 (FGFR3) mutations [4••]. Several trials are currently underway permitting the enrollment patients with UTUC, but no data has been published to date.

Conclusion

UTUC is a rare subset of urothelial carcinomas arising from the renal pelvis and the ureter and is believed to have a more aggressive disease phenotype compared with bladder cancer. Although many aspects of the current management strategies of UTUC have been extrapolated of data from bladder cancer, growing evidence suggest that UTUC may be a distinct disease entity. Conservative kidney-sparing techniques are to be reserved for low-risk disease, whereas extirpative radical surgery remains the standard of care for high-risk patients. The benefit of lymph node dissection at the time of nephroureterectomy and the role of perioperative systemic therapy are still being investigated. Outcomes of UTUC patients have not improved over the past decade and continued research is needed to optimize the management of UTUC.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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