REVIEW

Optimal Management of Upper Tract Urothelial Carcinoma: Current Perspectives

Jeffrey J Leow[1,2,*]
Zhenbang Liu[1–3,*]
Teck Wei Tan [ID][1,2]
Yee Mun Lee[1,2]
Eu Kiang Yeo[1,2]
Yew-Lam Chong[1,2]

[1]Department of Urology, Tan Tock Seng Hospital, Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [3]Department of Surgery, Woodlands Health Campus, Singapore

*These authors contributed equally to this work

Introduction: Upper tract urothelial carcinoma (UTUC) is a relatively uncommon urologic malignancy for which there has not been significant improvement in survival over the past few decades, highlighting the need for optimal multi-modality management.

Methods: A non-systematic review of the latest literature was performed to include relevant articles up to June 2019. It summarizes the epidemiologic risk factors associated with UTUC, including smoking, carcinogenic aromatic amines, arsenic, aristolochic acid, and Lynch syndrome. Molecular pathways underlying UTUC and potential druggable targets are outlined.

Results: Surgical management for UTUC includes kidney-sparing surgery (KSS) for low-risk disease and radical nephroureterectomy (RNU) for high-risk disease. Endoscopic management of UTUC may include ureteroscopic or percutaneous resection. Topical instillation therapy post-KSS aims to reduce recurrence, progression and to treat carcinoma-in-situ; this may be achieved retrogradely (via ureteric catheterization), antegradely (via percutaneous nephrostomy) or via reflux through double-J stent. RNU, which may be performed via open, laparoscopic or robot-assisted approaches, is the gold standard treatment for high-risk UTUC. The distal cuff may be dealt with extravesical, transvesical or endoscopic techniques. Peri-operative chemotherapy and immunotherapy are increasingly utilized; level 1 evidence exists for adjuvant chemotherapy, but neoadjuvant chemotherapy is favored as kidney function is better prior to RNU. Immunotherapy is primarily reserved for metastatic UTUC but is currently being investigated in the perioperative setting.

Conclusion: The optimal management of UTUC includes a firm understanding of the epidemiological factors and molecular pathways. Surgical management includes KSS for low-risk disease and RNU for high-risk disease. Peri-operative immunotherapy and chemotherapy may be considered as evidence mounts.

Keywords: carcinoma, transitional cell, chemotherapy, upper tract urothelial carcinoma, immunotherapy, nephroureterectomy, ureteral neoplasms, ureteral neoplasms

Introduction

Urothelial carcinoma is the fourth most common solid malignancy.[1] The majority (90–95%) of cases occur in the lower urinary tract (urinary bladder and urethra) and the rest in the upper urinary tract (renal calyces, renal pelvis, and ureter).[2] Upper tract urothelial carcinomas (UTUC) are of the same histological type as lower tract urothelial carcinomas but they have been found to have various phenotypical and genotypical (genetic and epigenetic) differences, which have led clinicians to label them as disparate twins.[3] Stage for stage, UTUC follows a different natural history from UCB (urinary carcinoma of the bladder) and often at point of diagnosis, UTUC demonstrates a higher incidence of local invasion at diagnosis.[4] However,

Correspondence: Yew-Lam Chong
Department of Urology, Tan Tock Seng Hospital, Singapore
Tel +65 6357 7678/7808
Fax +65 6357 3198
Email Yew_Lam_Chong@ttsh.com.sg

the management of lower tract urothelial carcinoma remains more extensively studied in the literature by far compared to UTUC, which therefore informs the optimal management strategies for UTUC more by inference than by direct evidence especially for systemic therapies;[5] yet we know they should be really be considered "distinct entities in terms of management".[6]

A retrospective review of the MD Anderson Cancer Center's experience in the United States from 1986 to 2004 found that there had been no appreciable improvement in disease-specific survival of UTUC over two decades and called for a change in the treatment paradigm.[7] With improving knowledge of the molecular tapestry of UTUC[8,9] and with more options in the therapeutic arsenal, the future holds greater promise for the optimal management of UTUC. This review paper aims to focus on the epidemiological factors and molecular pathways for UTUC, optimizing surgical management in both low- and high-risk disease, role of perioperative chemotherapy in UTUC and the recent implementation of immune checkpoint therapy in the management of UTUC.

Methods

We performed a non-systematic review of the latest literature including relevant articles up to June 2019. We included only English articles available in the MEDLINE/ Pubmed database. Search terms included "nephroureterectomy", "upper tract urothelial carcinoma", "chemotherapy", "immunotherapy", and associated search terms. Additionally, references of key articles were reviewed. Finally, abstracts from the past 5 years of the Annual Meeting of American Urological Association (AUA) and American Society of Clinical Oncology (ASCO) were searched online to include any relevant late-breaking abstracts which have not been fully published yet.

Epidemiological Factors

The estimated annual incidence in Western countries is about 2 per 100,000 inhabitants.[2] UTUC is three times more common in men than women and has a peak incidence in the age 70–90 yr.[1,10] In a Swedish series of 963 patients by Holmang et al, 1.6% of UTUC were bilateral and were associated with bladder cancer diagnosis either before or after UTUC diagnosis in 80% of the cases.[11] Renal pelvis UTUCs are twice as common as those found in the ureter.[12] In terms of staging, 60% of UTUCs are invasive (≥pT2) at diagnosis in contrast to the 15–25% for

bladder cancers.[13] About 7% of patients present with metastatic disease.[14]

Risk factors associated with UTUC are similar to urothelial bladder cancers such as cigarette smoking and various occupational exposures to carcinogenic aromatic amines including benzidine and beta-naphthalene.[2,15] However, there are other risk factors specific to UTUC which the clinician should be aware of.

Arsenic
Unusually high incidences of upper urinary tract tumors have been reported in Blackfoot disease-endemic areas in the southwest coastal region of Taiwan, and the arsenic-contaminated water has been postulated to be the cause of this prevalence.[16,17] This region has a 1:2 male-to-female ratio for UTUC in contrast to the male predominance found globally. This could be related to the higher exposure of women to arsenic fumes during cooking from the steam generated from boiling water and suggest both inhalation and ingestion risks.[18]

Balkan Endemic and Chinese Herb Nephropathy
Balkan endemic nephropathy and Chinese herb nephropathy are similar diseases related to UTUC.[19] Balkan endemic nephropathy is found in people living in Balkan countries (Bulgaria, Croatia, Greece, Romania, and Serbia) and in this region, urothelial tumors account for almost 50% of all renal tumors.[20] It is familial but not obviously inherited suggesting an environmental cause and it is believed to be due to dietary exposure to aristolochic acid (AA). AA is derived from Aristolochic plants (*fangchi* and *clematis*) and is a potent carcinogen which causes codon 139 of p53 gene to be mutated leading to UTUC. Aristolactam-DNA adducts are deposited in the renal cortex which may explain why AA-related nephropathy increases the incidence of UTUC and not bladder cancer. AA-related UTUC are more commonly low grade, multiple and bilateral compared to non-AA-related UTUC.[21] In Taiwan, the incidence of UTUC is estimated to be 20–25% of all urothelial cancers, the highest worldwide and this has been attributed to the use of aristolochic plants.[22] Chinese herb nephropathy causes a progressive renal fibrosis leading to UTUC. UTUC patients with prior AA exposure have been found to have poorer cancer-specific survival.[23]

Hereditary Nonpolyposis Colorectal Cancer (HNPCC, Lynch Syndrome)
Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant genetic

mutation that impairs DNA mismatch repair that is associated with a high risk of colon cancer as well as other cancers such as endometrial, ovarian, gastric and also urothelial cancers especially that of the upper tract. According to Koornstra et al, patients with this condition have an estimated 22-fold increased relative risk of developing UTUC.[24] This has led to experts and guidelines recommending that UTUC patients be screened with a short interview and patients identified as high risk for Lynch/HNPCC syndrome should undergo DNA sequencing for patient and family counseling.[2]

Molecular Pathways

The understanding of the molecular landscape of UTUC is sparse and often extrapolated from bladder urothelial cancer. However, there are distinct epidemiological and clinicopathological differences between the two suggesting different genetic phenotypes.[6] Insight into these molecular pathways is important as it holds the promise for potential targets for therapy.

Recently, Sfakianos et al used a custom next-generation sequencing assay to identify somatic mutations and copy number alterations in 300 cancer-associated genes in tumor and germline DNA from patients with UTUC (n=83) and bladder urothelial cancer (n=102).[8] The authors found that although the spectrum of genes mutated was similar, the frequency of alteration in several recurrently mutated genes such as FGFR3, HRAS, TP53, and RB1 was different. In high-grade UTUC, there were more frequent mutations in FGFR3 and HRAS and less TP53 and RB1 as compared to high-grade bladder urothelial cancer.

This molecular tapestry of UTUC was further characterized by Moss et al who carried out whole-exome sequencing on DNA and RNA from UTUC tumor specimens and protein analysis.[9] They found 2784 somatic mutations with FGFR3 being the most commonly mutated gene (74%) in both low grade (92%) and high-grade UTUC (60%). High-grade UTUC as compared to low-grade UTUC had higher frequency of mutations in p53 and related interacting pathways with greater genomic instability, copy number alterations, and disruption of cell cycle and apoptotic pathways. The authors were also able to subdivide UTUC into 4 subtypes based on their RNA expression and their unique clinical presentations. Cluster 1 had no PIK3CA mutations, was more common in non-smokers, had higher frequency of high-grade non-muscle invasive tumors and high recurrence rates but favorable survival. Cluster 2 had 100% FGFR3 mutations, had more

low-grade non-muscle invasive disease and no bladder recurrences. Cluster 3 also had 100% FGFR3 mutations; 71% PIK3CA and no TP53 mutations; and had high number of smokers and bladder recurrences. All the tumors were non-muscle invasive. Cluster 4 had KMT2D (62.5%), FGFR3 (50%) and TP53 (50%) mutations but no PIK3CA mutations; and had higher numbers of high grade, muscle invasive disease, smokers, carcinoma in situ and shorter survival. Interestingly, CTLA4, CD274 (PDL1) and PDCD1 (PD1) mRNA expression levels were all upregulated in the majority of Cluster 4 cases which represent the most aggressive clinical disease. These three immune checkpoint genes have recently been shown to be effective targets for immunotherapy for various cancers. These data support specific genes as rational therapeutic targets along with immune checkpoint therapies, especially for the most aggressive disease states.

Multiple agents targeting FGFR3 in urothelial cancer are already undergoing studies. Erdafinitib, a pan-FGFR tyrosine kinase inhibitor was shown in a Phase I dose-escalation study to have acceptable toxicity and a substantial signal of activity in patients with advanced urothelial cancer pre-treated with chemotherapy.[25] An open-label Phase II trial (BLC2001) recruited 99 patients who had locally advanced and unresectable or metastatic urothelial carcinoma with FGFR alterations and had a history of disease progression during or after at least 1 course of chemotherapy/immunotherapy. This landmark trial, recently published in New England Journal of Medicine, revealed that after receiving a median of 5 cycles of erdafitinib, 40% of patients had an objective tumor response.[26]

Surgical Management - Kidney-Sparing Surgery for Low-Risk Disease

Traditionally, the gold standard of management of UTUC has been radical nephroureterectomy (RNU) and excision of the bladder cuff.[2,27] Although the reported 5-year recurrence-free and cancer-specific survival for 1363 patients at multiple academic centers treated with RNU is reasonable (69% and 73%, respectively),[7] RNU reduces the nephron mass by 50% or more depending on split renal function predisposing to chronic kidney disease (CKD) or even end-stage renal failure (ESRF) requiring dialysis. CKD/ESRF is associated with cardiovascular events and increased mortality[28,29] and ESRF carries the increased financial burden of lifelong hemodialysis. These problems become more apparent as patients live longer and

remaining nephrons shoulder the burden of chronic medical diseases such as hypertension, diabetes, and obesity.

With improvement in current endourological techniques and equipment, kidney-sparing surgery (KSS) allows preservation of the ipsilateral kidney without compromising oncological outcomes[2] and survival after KSS has been shown to be similar to RNU in low-risk disease[30] hence prompting current guidelines such as EAU[2] and NCCN[31] to recommend KSS for all low-risk disease and to be considered in select patients with serious CKD or solitary kidney. Low-risk disease is defined as having all of the following features: unifocal disease, tumor size less than 2 cm, low-grade cytology, low-grade URS biopsy and no invasive aspect on CT urogram. An important point to note when offering KSS is that the patient must be willing to undergo repeated and stringent surveillance follow-up including upper tract imaging, flexible cystoscopy, ureteroscopy, and urine cytology.

Endoscopic Management

The retrograde approach with ureteroscopy is more commonly used with new flexible scopes having good distal-tip deflection.[32] However, the antegrade approach is still useful for tumors that are in the lower caliceal system that are inaccessible via flexible ureteroscopy. Moreover, antegrade approach allows for lower intrapelvic irrigation pressures due to the large working channel (up to 30Fr diameter) and ability to clear larger tumor volumes. However, this carries the risk of tumor seeding.[33,34] With endoscopic management, a risk of understaging and undergrading remains. Novel optical technologies such as confocal laser endomicroscopy are promising adjuncts to provide real-time histologic characterization of UTUC lesions to identify potential candidates for kidney-sparing management.[35,36]

Segmental Ureteric Resection

Segmental ureteric resection with wide margins allows for ipsilateral kidney preservation and adequate pathological staging and lymphadenectomy can also be performed at the time of surgery.[30] Guidelines recommend complete distal ureterectomy with ureteroneocystostomy for low-risk tumors in the distal ureter that cannot be removed completely with endoscopic management and for high-risk tumors when KSS is necessary (e.g., in a solitary kidney).[2,31] Segmental resection of the mid and upper ureter is associated with higher failure rates than for the distal ureter.[2] Partial pyelectomy or partial nephrectomy is extremely rarely indicated.[2]

Topical Instillation Therapies for Upper Urinary Tract

The role of topical instillation therapies in UTUC is to reduce risk of recurrence and progression after KSS and to treat carcinoma-in-situ (CIS). Similar to bladder cancer, common agents instilled include bacillus Calmette–Guerin (BCG) and mitomycin C (MMC). However, unlike its bladder counterpart, there is insufficient evidence for current EAU guidelines to make it a recommended treatment.[2] The controversial areas are its modality of administration and its clinical effectiveness.

There are currently three methods of instillation of topical therapies into the upper urinary tract described in the literature – antegrade perfusion via a percutaneous nephrostomy tube,[37] retrograde perfusion via an open-ended ureteric catheter[38] or intravesical administration with vesicoureteral reflux via an indwelling ureteric stent.[39] Antegrade perfusion is feasible but carries the potential risks of tumor seeding with the insertion of the nephrostomy tube and the possibility of missing calyxes if the therapy solution flows straight down into the ureter. Retrograde instillation with a ureteric catheter has been described but it has a risk of ureteric obstruction and pyelovenous influx during instillation.[2] The main problem with vesicoureteral reflux via indwelling ureteric stent is that reflux is not guaranteed and the therapy solution often does not reach the renal pelvis. Indeed, Yossepowitch et al showed that only 59% of patients had reflux with ureteric stents,[40] making this an unreliable method to instill topical agents into the upper urinary tract. There have been an ex-vivo and in-vivo animal comparison study to evaluate the staining intensity of the urinary collecting system at predefined points. In an ex-vivo indigo carmine porcine model study,[41] the mean percent of kidney collecting system surface area stained for the nephrostomy tube, double-pigtail stent, and open-ended ureteral catheter groups was 65.2%, 66.2%, and 83.6%, respectively (p=0.002). The authors concluded that retrograde infusion with an open-ended ureteral catheter is the most efficient method. In an attempt to reduce potential confounding factors of a lack of natural ureteral peristalsis and continuous urine production, and the absence of intra-abdominal pressure found in this ex-vivo study,[41] Liu et al investigated the staining intensity of the three methods in the collecting system at 6 pre-defined points (upper pole, mid pole, lower pole, renal pelvis, mid ureter, distal ureter) in an in-vivo porcine model.[42] Retrograde approach via an open-ended ureteric

catheter resulted in the highest mean fluorescence detected at all the 6 pre-defined points compared to the other 2 methods and this was significant on statistical analysis.[42] More clinical studies are needed to determine which is the best method among the three.

Instillation of topical therapy to the upper urinary tract has better clinical response for treating CIS than adjuvant therapy for Ta/T1 disease post-KSS. In the large series by Giannarini et al, 42 renal units were treated with antegrade BCG perfusion of the upper urinary tract for curative intent for CIS and 22 renal units for adjuvant intent after ablation of Ta/T1 tumors.[43] Recurrence in the CIS group was 40% and progression was 5% while in the Ta/T1 tumors group, recurrence was 59% and progression was 41%. Patients treated with curative intent for CIS significantly better progression-free survival (p<0.01). These results were also similar to a 2009 review by Rastinehad and Smith.[44] However, a more recent study showed more promising intermediate-term data.[45] Twenty-seven patients and 28 renal units with Ta/T1 UTUC that had complete endoscopic resection underwent induction MMC followed by a maintenance course with median follow-up of 19 months; the 3-year recurrence-free survival, progression-free, and RNU-free survival rates were 60%, 80%, and 76%, respectively. The future of instillation of topical therapy to the upper urinary tract may lie with novel agents to prolong the contact between drug and urothelium such as drug-eluting stents[46] and thermosensitive polymers.[47]

Surgical Management - Surgery for High-Risk Disease

High-risk disease is defined as having any of the following: hydronephrosis, tumor size more than 2 cm, high-grade cytology, high-grade biopsy, multifocal disease, previous radical cystectomy for bladder cancer and variant histology.[2] The gold standard for the treatment of high-risk disease is RNU with bladder cuff excision. This may be approached via an open, laparoscopic or robot-assisted laparoscopic approach. A recent review of 42 studies including 7554 patients who underwent open vs laparoscopic nephroureterectomy found no significant differences in oncologic outcomes in most series; however, 3 studies including the only randomized trial reported significantly poorer oncological outcomes among those who underwent laparoscopic RNU particularly in the subgroup of locally advanced (pT3/4) or high-grade UTUC patients.[48] Robot-assisted RNU has been described, is

increasingly utilized, and reportedly facilitates the bladder cuff excision and reconstruction.[49–51]

Distal Ureter and Bladder Cuff Excision

In a systemic review and meta-analysis of clinicopathologic factors associated with intravesical recurrence after RNU by Seisen et al,[52] it was shown that there is significant risk of tumor recurrence in the distal ureter and its orifice and this area is difficult to survey with imaging or endoscopy. Hence, excision of the bladder cuff/intramural ureter is recommended at the time of RNU.

Three different methods have been used to excise the intramural ureter and a cuff of bladder around the ureteric orifice – extravesical, transvesical and endoscopic techniques.[53] The extravesical approach involves dissecting the entire intramural ureter and with gentle traction on the ureter, the distal ureter is resected with its bladder cuff. The transvesical approach involves creating an anterior cystostomy in the bladder, confirming the contralateral ureteral orifice and circumferentially incising the ipsilateral ureteral orifice through the full thickness of the bladder. The anterior cystostomy is then closed in two layers. Endoscopic approach involves placing the patient in the lithotomy position and then using a resectoscope to incise a circumferential 10 mm cuff of bladder mucosa around the ureteral orifice. The incision is then deepened to perivesical fat and the intramural ureter detached. The specimen with the distal ureter cuff is removed en bloc during the RNU.

It has been shown in a large retrospective study of 2681 patients who underwent RNU with various methods for the bladder cuff excision in 24 international institutions to have no differences in cancer-specific or overall survival among the three methods but the endoscopic technique has a higher risk of intravesical recurrence.[54] Current EAU guidelines do not recommend a method over the other but ureteral stripping (a dated procedure) is not advised.[2]

Lymph Node Dissection

The prognostic and potentially curative role of lymph node dissection (LND) at the time of radical cystectomy for bladder cancer has been extensively studied and supported by evidence.[55–57] The anatomical templates have also been well established. However, LND at the time of RNU for UTUC has not gained the same oncological role. The lymphatic drainage from UTUC is variable and there is a lack of consensus on anatomical boundaries and selection criteria.[58] A detailed description of primary lymph node

metastasis sites was first reported by Kondo et al in 2007.[59] In a retrospective multi-institutional study from three National Cancer Institute designated comprehensive cancer centers, the authors investigated the patterns of lymph node metastasis in 73 patients undergoing RNU with LND and proposed a dissection template according to the laterality and location of the tumor.[60] In a systemic review of anatomical templates of LND for UTUC in 2017,[61] the authors found that LND is not routinely performed at the time of RNU and there was a lot of variation in templates among surgeons from different institutions. That said, a LND typically included: the renal hilar, paracaval, precaval, and retrocaval nodes for right-sided tumors of the renal pelvis, upper and middle third of the ureter; while for left-sided tumors, the renal hilar, paraaortic and preaortic nodes. For tumors of the lower ureter, an extended pelvic LND was performed in most cases and the paracaval, paraaortic or presacral nodes in selected series. The therapeutic benefits of LND at the time of RNU still remain controversial but there is a growing body of evidence that shows staging and therapeutic benefits of LND at the time of RNU especially for muscle invasive or locally advanced disease.[62,63] Current EAU guidelines recommend LND for invasive disease (pT2 and above).[2]

Single Post-Operative Bladder Instillation

Intravesical recurrences are common after RNU, with rates up to 22–47%,[2] potentially because of implantation from the primary UTUC. In the ODMIT-C trial by O'Brien et al, 144 patients were randomized to receive mitomycin C (MMC) and 140 patients to receive standard care.[64] These patients did not have any previous or concurrent history of bladder tumor and all underwent RNU for UTUC. In this trial, a single post-operative dose of MMC given at the time of catheter removal resulted in an absolute reduction in risk of intravesical recurrence in the first year by 11%; the relative reduction in risk was 40% and the number needed to treat to prevent one bladder tumor was 9. Another randomized controlled trial by Ito et al where a single intravesical dose of pirarubicin was given post-RNU within 48 hrs also showed a reduction in the risk for intravesical recurrence.[65] A 2019 Cochrane review concluded that single-dose intravesical chemotherapy post-RNU reduces the risk of bladder cancer recurrence over time compared to no instillation (hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.32 to 0.82, low-certainty evidence) and that after 12 months follow-up, this would result in 127 fewer bladder cancer recurrences (95% CI:

182 to 44 fewer bladder cancer recurrences) per 1000 participants.[66] Current EAU guidelines give it a Grade B recommendation to offer post-operative bladder instillation of chemotherapy to lower the bladder recurrence rate.[2]

Based on the SWOG S0337 trial by Messing et al for low-grade non-muscle invasive bladder cancer, intravesical instillation of gemcitabine has been shown to significantly reduce recurrence. Given its cheaper price and favorable toxicity profile compared to mitomycin-C, it is also a possible option in the context of UTUC as mentioned in the latest NCCN guidelines.[31]

Clinical Nomograms and Predictive Tools

There have been numerous pre-operative and post-operative prognostic markers that have been shown to be associated with survival in UTUC. These are mostly based upon retrospective cohort studies. There have been efforts to use these collectively as predictive tools to aid in clinical management.

Preoperatively, there are 2 models that have been developed. The first nomogram is aimed to predict lymph node involvement in locally advanced UTUC, in order to guide clinicians on whether to perform a lymph node dissection or not. Three variables, namely tumor grade, architecture, and location of tumor were found to be independently associated with non-organ-confined disease. Together these 3 variables achieved 76.6% accuracy in prediction of non-organ confined UTUC.[67] The second model combines imaging and ureteroscopy variables to help select non-organ-confined UTUC which is likely to benefit from RNU.[68] Lastly, a multi-center database was used to develop a preoperative nomogram to help predict disease recurrence to better select patients who can most benefit from RNU.[69]

There exist 5 different postoperative nomograms. They can help to predict survival rates based on standard pathological features,[70–74] which can be helpful for postoperative follow-up and counseling. Another prognostic nomogram based on 2926 patients which are based on 4 variables (namely age, pT stage, pN stage, and architecture) has good prognostic accuracy and risk stratification for patients with high-grade UTUC.[75]

Medical Management - Peri-Operative Systemic Therapy

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy for UTUC prior to definitive RNU makes sense because of the availability of 2 renal units during receipt of systemic therapy. Particularly in

patients with chronic kidney disease, the surgical-induced loss of 1 kidney (via definitive surgical therapy with RNU) may render a patient ineligible for further systemic therapy. Attaining pathologic down-staging provides important prognostic information as well and has been shown in retrospective studies to accurately predict survival.[76] Most studies evaluated platinum-based (cisplatin or carboplatin) regimens,[77] although some believe that carboplatin-based regimens are inferior oncologically for UTUC and adds to the delay to surgical therapy. A 2014 meta-analysis revealed 2 trials.[78] An update in 2019 revealed 4 retrospective cohort studies[76,79–81] found that the pooled odds ratio for the effect of neoadjuvant chemotherapy on down-staging was 0.21 (95% CI, 0.09–0.60; p = 0.004), indicating that those who received neoadjuvant chemotherapy had a 4.76-fold higher probability of having pathologic N stage 0 than the control group which underwent surgery alone.[82]

Prospective data for neoadjuvant chemotherapy are scarce (Table 1).[83] One using neoadjuvant gemcitabine/cisplatin was terminated due to poor accrual (Clinicaltrials.gov identifier: NCT01663285). Another phase 2 trial - the ECOG-ACRIN Research Group 8141 (Clinicaltrials.gov identifier: NCT02412670) - was presented at the Annual Meeting of American Urological Association (AUA) 2018 and showed a pathologic complete response rate of 14% (4/29).[84,85] Finally, a phase 2 multi-center prospective single-arm trial (Clinicaltrials.gov identifier: NCT01261728) from Memorial Sloan Kettering Cancer Center was reported at the AUA meeting in May 2019;[86] all 53 patients had high-risk UTUC (defined by 1) high-grade histology on biopsy, and/or 2) imaging (cT2-4a) and positive selective cytology) with no metastases, good kidney function (CrCl≥55 mL/min using CKD-EPI), and good performance status (Karnofsky performance status ≥70%). These patients received 12 weeks of neoadjuvant gemcitabine/cisplatin combination chemotherapy administered every 21 days x 4 cycles, prior to definitive surgery (RNU or distal ureterectomy). Notably, all patients underwent ipsilateral RPLND using standardized template as proposed by Matin et al.[60] The primary endpoint of pathologic response rate, defined as ≤pT1N0, was 60% (n=32; 95% CI: 47–75%). Of the 21 patients (40%) who did not respond, 5 had pT2 disease, 9 pT3 disease, and 7 had pTany N+ disease. No patients progressed prior to surgery (0%), allaying concerns that "delay" to definitive surgical treatment may predispose to progression. It would not be unreasonable to presume that

"progression" was simply determined by the final pathological and nodal staging after RNU; however, this is subject to pre-operative understaging bias known in UTUC.[2,32] At a median follow-up for survivors at 2.6 years, the 2-year progression-free survival rate was 76% (95% CI: 64–90%) and 2-year overall survival rate was 89% (95% CI: 80–100%). This is remarkable considering the 2-year survival of high-grade UTUC of ~68% of patients who underwent surgery alone in another series.[87]

Peri-Operative Systemic Therapy – Adjuvant Chemotherapy

Adjuvant chemotherapy has the advantage of accurate pathological staging from the radical nephroureterectomy specimen, and hence preventing over-treatment in non-invasive disease. Leow et al performed meta-analysis of retrospective studies in 2014 which found an overall survival (HR 0.43, 95% CI 0.21–0.89, p=0.023) and disease-free survival benefit (HR 0.49, 95% CI 0.24–0.99, p=0.048) among patients who received adjuvant cisplatin-based chemotherapy compared to those who underwent RNU alone.[78] Seisen et al followed on with a large observational study (n=3253) using the National Cancer Data Base in the United States, confirming an overall survival benefit for patients with pT3/T4 and/or pN+ UTUC in the real-world setting,[88] with an HR 0.77 (95% CI 0.68–0.88, p<0.001).

Subsequently, results of the POUT trial, a multi-center RCT from the UK found that adjuvant chemotherapy after RNU provided a disease-free survival benefit of 51% (HR 0.49, 95% CI 0.30–0.79, p= 0.003) as compared to surgery alone, with a favorable toxicity profile.[89] These results firmly etched and supported the role of adjuvant chemotherapy in the armament of a urologic oncologist in treating patients with high-risk and/or locally advanced UTUC. Publication in a peer-reviewed journal is pending and may be due to immature overall survival data at this time.

Looking to the future, several ongoing trials may shed light on how we can optimize peri-operative therapy for UTUC patients. The European Uro-Oncology Group is currently recruiting patients into their URANUS trial which aims to explore the feasibility of treatment options based on real-world data in various European countries. The URANUS investigators aim to determine the true proportion of patients that fit to receive complete cisplatin-based neoadjuvant or adjuvant chemotherapy, and the proportion and clinical outcome of patients with poor prognostic factors (PS and renal function) who receive only standard treatment of RNU. Secondary outcomes

Table 1 Ongoing Phase II and III Trials Evaluating the Efficacy of Neoadjuvant Chemotherapy for Upper Tract Urothelial Carcinoma

ClinicalTrials. gov Identifier	Phase	Country	Population	Outcomes	Neoadjuvant Chemotherapy Regimens	Surgery	Interim Results
NCT02876861	III	China	• Histologically confirmed high-grade upper tract transitional cell carcinoma, and/or • Radiographically visible tumor stage T2-T4a N0/X M0 disease,	DFS ORR OS Toxicities	Gemcitabine and Cisplatin	RNU with ipsilateral cuff excision or distal ureterectomy	Nil (estimated completion Aug 2020)
NCT02412670	II	USA	• Positive selective urinary cytology or high-grade concomitant bladder tumor. • Hydronephrosis associated with tumor on biopsy will be considered invasive by	pCR rate RFS CSS Bladder cancer free survival	MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) Gemcitabine and Cisplatin	RNU and lymph node dissection	Presented at AUA 2018 • pCR rate was 4/29 (14%)
NCT01261728	II	USA	definition.	• Absence of high-grade carcinoma (<pT2 disease) • Absence of microscopic lymph node metastases (N0) on the final RNU specimen. • PFS • OS	Gemcitabine and Cisplatin	Nil	Presented at AUA 2019 at Chicago, IL[86] As of January 2019 • Majority of patients (40/48; 85%) tolerated all 4 cycles of GC. • 90-day grade≥3 surgical complication rate: 6.2%. • Median follow-up 2.6y • 6 patients died of disease. • Two-year overall survival was 89% (95% CI 79%, >99%). • Patients with pathologic response had improved survival compared to those who did not respond (2-year survival 100% vs 74%, log-rank p = 0.02).

Table 2 US FDA Approved PD1/PDL1 Drugs for Urothelial Carcinoma

Generic Name (Brand)	Manufacturer	FDA Approval for Urothelial Carcinoma Indication	Mechanism of Action	FDA-Labeled Dose and Frequency
Pembrolizumab (Keytruda)	Merck Sharp and Dohme	May 2017	PD-1/IgG4	IV 200 mg every 3 weeks
Nivolumab (Opdivo)	Merck Sharp and Dohme Bristol-Myers Squibb New	Feb 2017	PD-1/IgG4	IV 3 mg/kg every 2 weeks
Atezolizumab (Tecentriq)	Genentech	May 2016	PD-L1/IgG1	IV 1200 mg every 3 weeks
Avelumab (Bavencio)	eMD Serono	May 2017	PD-L1/IgG1	IV 10 mg/kg every 2 weeks
Durvalumab (Imfinzi)	AstraZeneca	May 2017	PD-L1/IgG kappa	IV 10 mg/kg every 2 weeks

include DFS, OS, and CSS (ClinicalTrials.gov Identifier: NCT02969083).

Peri-Operative Systemic Therapy – Immunotherapy

Checkpoint inhibitors have been extensively investigated in recent years, in part due to favorable objective response rates compared to standard of care chemotherapy.[90,91] Approved immunotherapeutic agents for urothelial carcinomas include the following 5 checkpoint inhibitors: pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab.[92] Table 2 outlines these 5 US FDA-approved PD1/PDL1 drugs for urothelial carcinoma, their mechanisms of actions, dose, and frequency.

Most of the patients included in these trials had urothelial carcinomas of bladder. Only Pembrolizumab[93,94] and Atezolizumab[95] have Phase III randomized data published (KEYNOTE 045 and IMVigor 211, respectively). Other checkpoint inhibitors have been evaluated with Phase II single-arm trials (Table 3) with favorable objective response rates and toxicities profile.[96–99] Within KEYNOTE 045 and IMVigor 211, it is important to note that up to 27% of the included trial population were diagnosed with UTUCs; however, no further published data exist for this sub-group yet.[93–95]

As these immunotherapeutic agents are increasingly utilized, it is important to be familiar with associated toxicities associated. A systematic review and meta-analysis of treatment-related adverse events of PD-1 and PD-L1 inhibitors used in 125 clinical trials involving 20,128 patients[100] found that the most common all-grade adverse events were fatigue

(18.26%; 95% CI, 16.49–20.11%), pruritus (10.61%; 95% CI, 9.46–11.83%), and diarrhea (9.47%; 95% CI, 8.43–10.58%), while the most common grade 3 or higher adverse events were fatigue (0.89%; 95% CI, 0.69–1.14%), anemia (0.78%; 95% CI, 0.59–1.02%), and aspartate aminotransferase increase (0.75%; 95% CI, 0.56–0.99%)

Physicians are encouraged to refer to local or international clinical practice guidelines on how best to diagnose, treat and follow-up on toxicities arising from immunotherapy, such as this 2017 guideline from European Society of Medical Oncology.[101]

Systemic Therapy for Advanced or Metastatic UTUC

In terms of systemic treatments for advanced UTUC, virtually all of what is practiced had been derived from the experience in lower tract urothelial cancers. For metastatic UTUC, extrapolating from metastatic UCB, platinum-based combination chemotherapy, particularly cisplatin-based regimens, forms the mainstay of therapy traditionally. This extrapolation is further backed up by a recent retrospective analysis of prospectively collected data from 3 European Organization for the Research and Treatment of Cancer (EORTC) advanced urothelial carcinoma studies, including 30,924 (methotrexate, vinblastine, doxorubicin and cisplatin vs high dose methotrexate, vinblastine, doxorubicin, and cisplatin), 30,986 (methotrexate, carboplatin, and vinblastine vs gemcitabine and cisplatin in patients who were not candidates for cisplatin) and 30,987 (gemcitabine and cisplatin-paclitaxel vs gemcitabine and cisplatin in candidates for cisplatin). Moschini et al found that the primary tumor

Table 3 Landmark Trials for US FDA Approved PD1/PDL1 Drugs for Urothelial Carcinoma

Generic Name (Brand Name)	Pembrolizumab (Keytruda)	Atezolizumab (Tecentriq)	Nivolumab (Opdivo)	Avelumab (Bavencio)	Durvalumab (Imfinzi)
Phase II trials	KEYNOTE-052[107]	IMVigor 210 cohorts 1 and2[93,108]	CHECKMATE 275[96] and 032[97]	JAVELIN[99]	Study 1108[98]
Phase III trials	KEYNOTE-045[93,94]	IMVigor 211 cohort3[95]	Nil	Nil	Nil
Main features of study population	Cisplatin-ineligible patients and no prior chemotherapy	Metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy	Locally advanced or metastatic urothelial carcinoma whose disease progressed after previous platinum-based chemotherapy	Locally advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy	Locally advanced/ metastatic UC whose disease had progressed on, were ineligible for, or refused prior chemotherapy
Comparator	Paclitaxel, docetaxel, vinflunine	Physician's choice: IV vinflunine 320 mg/m,^{2} paclitaxel 175 mg/m^2, or 75 mg/m^2 docetaxel	Nil	Nil	Nil
Efficacy outcome	Overall survival 10.3 vs 7.4 months (HR 0.73, 95% CI: 0.39–0.91, p=0.002)	Overall survival 11.1 vs 10.6 months (HR 0.87, 95% CI: 0.63–1.21, p=0.41)	CHECKMATE 275 Confirmed objective response was achieved in 52 (19·6%, 95% CI 15·0-24·9) of 265 patients	In 161 post-platinum patients with at least 6 months of follow-up, a best overall response of complete or partial response was recorded in 27 patients (17%; 95% CI 11-24), including nine (6%) complete responses and 18 (11%) partial responses	ORR 17.8% (34 of 191; 95% CI, 12.7%-24.0%), including 7 complete responses
	Progression-free survival 2.1 vs 3.3 months (HR 0.98 95% CI: 0.81–1.19 p=0.42)	Progression-free survival 2.1 vs 4.0 months (HR 1.01 95% CI: 0.75–1.34, p=NS)	CHECKMATE 032 Confirmed objective response was achieved in 19 (24·4%, 95% CI 15·3-35·4) of 78 patients.		
Safety outcome (treatment-related adverse events)	Any grade 62.0% vs 90.6% Grade≥3 16.5% vs 50.2%	Grade≥3 20% vs 43% Adverse events leading to treatment discontinuation 7% vs 18%	Grade≥3 18% (CHECKMATE 275); 22% (CHECKMATE 032)	Grade≥3 8%	
UTUC specific information					
Proportion of population with UTUC	38 (14.1%) in treatment arm 37 (13.6%) in comparator arm	126 (27%) in treatment arm 110 (24%) in comparator arm	–	–	
Subgroup of results available for UTUC	Not published	Not published	N/A	N/A	N/A

location (i.e., bladder vs upper tract) did not significantly affect progress-free or overall survival in patients with locally advanced or metastatic urothelial carcinoma treated with platinum-based combination chemotherapy.[102]

Ongoing randomized trials in 1st line metastatic urothelial carcinoma include IMvigor 130, DANUBE, KEYNOTE 361, CHECKMATE 901, and JAVELIN.[99]

Radiotherapy
Adjuvant radiotherapy after RNU had been explored to determine efficacy in improving disease-free survival in pT3 disease; however, 2 retrospective studies have been negative showing no benefit.[103,104] A small study (n=31) showed that adding concurrent cisplatin with adjuvant radiotherapy improved overall and disease-free survival compared to adjuvant radiotherapy alone in pT3/4 and/or N+ UTUC; however, this was limited by small numbers and lack of multivariable analysis.[105]

In the metastatic setting, radiotherapy may be considered for palliative purposes to arrest bleeding that has not responded to conservative measures.

Surgery for Metastatic Disease
Indications for RNU for metastatic UTUC are limited to that of palliative intent, aimed to control symptomatic disease. Moreover, advances in palliative specialist care have diminished the role of RNU, since most pain associated with metastatic disease can be addressed in a multi-disciplinary approach with adequate medical therapy. Possible clinical scenarios necessitating surgical therapy may include (a) very locally advanced disease-causing bowel obstruction that has failed conservative management; (b) refractory bleeding which has failed to respond to conservative measures, super-selective angioembolization and palliative radiotherapy.

Observational studies have found that RNU may be associated with cancer-specific and overall survival in selected patients, particularly in those fit enough to receive cisplatin-based chemotherapy.[106] Although the National Cancer Data Base cohort study was well conducted statistically, it is still subject to biases related to observational study design and should be considered hypothesis generating for a future randomized trial addressing this question.

Conclusion
The optimal management of UTUC includes a firm understanding of the epidemiological factors and molecular pathways. Surgical management includes kidney-sparing surgery for low-risk disease and radical nephroureterectomy

for high-risk disease. Peri-operative immunotherapy and chemotherapy may be considered as evidence mounts.

Disclosure
The authors report no conflicts of interest in this work.

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