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Review

**Therapeutic strategies for upper tract urothelial carcinoma**

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Abstract

Introduction: Many controversies exist regarding the appropriate management of patients with upper tract urothelial carcinoma (UTUC), including staging, surgical management, use of systemic therapy and prevention of bladder recurrence. Due to the rarity of this condition, high level evidence is often lacking and in many cases guidelines are extrapolated from existing evidence on urothelial bladder cancer.

Areas covered: This review paper summarizes the evidence on proper diagnosis and staging, surgical techniques, prevention of bladder recurrences, the use of local or systemic treatments in both neoadjuvant and adjuvant settings as well as special consideration for hereditary UTUC.

Expert commentary: UTUC is a rare malignancy and slow progress is being made in the acquisition of high quality evidence in this field. Treatments that facilitate preservation of the kidney are being explored such as advanced endoscopic techniques or partial resection of ureteral disease with seemingly acceptable oncological results. Further prospective evidence is needed.

Keywords: upper tract urothelial carcinoma, urothelial carcinoma, transitional carcinoma, lynch syndrome, surgical management
1. Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon cancer accounting for about 5-10% of all urothelial carcinomas [1,2]. UTUC tumors are twice as often located in the renal pelvis than in the ureter and in about 20% of cases a concomitant bladder cancer is present [3]. Nearly 60% of UTUC tumors are invasive at time of diagnosis and nearly 25% have regional metastasis [4]. Reported 5-year cancer-specific survival is <50% for pT2/pT3 and <10% for pT4 disease [5].

Giving the rarity of this disease, there is a general lack of high level evidence guiding the management of these patients and, in many cases, decisions and treatment algorithms are based on existing high level evidence from urothelial bladder cancer (UBC), which may or may not be applicable in UTUC.

This review will summarize the existing data on UTUC focusing on controversial topics such as kidney sparing surgery, surgical approach, the use of lymph node dissection and chemotherapy.

2. Staging and risk stratification

Radical nephroureterectomy (RNU) with bladder-cuff removal remains the gold standard treatment for high risk UTUC, however, as in the management of parenchymal renal cancer, there is an increasing tendency towards kidney-sparing surgery (KSS) [1,6]. There is also growing evidence that those with high-risk disease might benefit from neoadjuvant chemotherapy [7-10]. Therefore, preoperative identification of those patients harboring low-risk UTUC versus individuals harboring a more aggressive disease is critical for patient counseling and shared decision making.

Diagnosis and staging of UTUC is currently achieved through a combination of cross-sectional imaging, endoscopic evaluation of the upper tract, urine cytology and tumor biopsy [1,6]. However, this process is challenging and in many cases, yields less than optimal results with many patients being eventually regraded or restaged at the time over extirpative surgery.
2.1 Diagnosis

CT urography (CTU) has become the imaging modality of choice for evaluation of UTUC [11-14]. Most commonly the abnormality suggesting the diagnosis is a filling defect on excretory phase of CTU. Sensitivity and specificity of CTU may vary according to indication, for example, in the workup of hematuria both sensitivity and specificity were >90% [15] but the sensitivity decreases as lesions decrease in size and often flat lesions are missed [12-14]. MRI has also been evaluated for detection of UTUC with reported 86% sensitivity and 99% specificity for lesions <2 cm [16]. In a review of literature comparing CTU, MRI, excretory urography and retrograde urography, sensitivity and specificity reported were 96% and 99%, 96% and 96%, 69% and 97%, 80% and 81%, respectively [14] which point to CTU as the preferred modality for evaluation of UTUC patients. Recently, a small prospective study directly comparing 3T MRI to CTU showed overall similar results, visualization of the renal cavity was slightly better by CTU while visualization of the ureter was slightly better with MRI [17]. Hydronephrosis, as a secondary finding has been shown to be associated with unfavorable outcomes [18].

Grahn et al. compared the performance of CTU to ureteroscopy in patients with suspected UTUC and showed superior performance for URS [12], and indeed, currently, axial imaging does not replace the recommended endoscopic visualization and biopsy of UTUC. Diagnostic ureteroscopy remains the cornerstone of UTUC diagnosis with a complete endoscopic evaluation of the bladder and upper urinary tracts [12, 19, 20], however concerns have been raised regarding bladder recurrences after URS with reports of URS almost doubling the risk compared to patients who had no diagnostic URS prior to RNU [21]. An initial cystoscopic evaluation is imperative, given nearly 20% of UTUC patients will have concomitant bladder tumors [3]. Technical strategies in imaging enhancement and optical diagnostic techniques will continue to improve our real-time knowledge regarding the clinical staging and detection of these tumors [22-24].

2.2 Pathological evaluation

Endoscopic biopsy is essential for pathologic diagnosis, grading and staging of UTUC. Unfortunately given the limited size of endoscopic instruments, biopsy is technically challenging
with often minute amounts of tissue procured [25] hence, biopsies hardly ever provide accurate staging information, further complicating decision making. Tumor grade assigned to biopsy specimens has been shown to be predictive of final stage at time of extirpative surgery and therefore has significant implications for management of UTUC [26], however, up to 25% of samples may eventually prove to be non-diagnostic [27]. Furthermore, despite technical improvements such as the BigOpsy® and use of ureteral access sheaths, the rate of grade reassignment from initial endoscopic biopsy results to final pathological report at time of definite surgery is substantial and can range from 36-96%, with almost 50% of cases being eventually reclassified from non-invasive or low grade disease to high risk – invasive HG disease[25,28]. Such findings may have detrimental effect on decision making process and oncological outcomes by placing patients at risk of under or overtreatment. Selective urine cytology provides yet further diagnostic information with high specificity of >90% but poor sensitivity of <50% [13,29].

2.3 Predictive models

It is clear that accurate preoperative UTUC staging and grading with current guidelines remains a challenge. With an increase in utilization of nephron-sparing procedures, clinical decision-making is hindered by the limited accuracy of preoperative evaluation. The combination of prognostic variables may improve predictions of oncologic outcomes through the use of nomograms. Multi-institutional collaborations have provided multiple nomograms and preoperative risk stratification to help determine which patients may have non-organ confined disease (Table 1) [30-33]. While these nomograms have demonstrated adequate discriminative accuracy with internal validation, a recent external validation in both a Chinese and US cohort demonstrate differences between the countries with regards to preoperative evaluation and therefore those nomograms may be of limited value [34].

The EAU guidelines have developed a summary for determining Low-risk UTUC and High-risk UTUC risk stratification [1]. To be considered low-risk, all of the following factors must be present: unifocal disease, tumor size <2cm, low-grade cytology, low-grade ureteroscopic biopsy and no invasion on CTU. High-risk requires just one of the following factors: hydrenephrosis,
tumor size >2cm, high-grade cytology, high-grade ureteroscopic biopsy, multifocal disease, previous radical cystectomy for bladder cancer, or variant histology.

Unfortunately, despite the extensive evaluation process the diagnostic accuracy of UTUC is far from perfect and much ambiguity and challenges still exist in this process. Hopefully future improvements will allow for more accurate diagnosis and risk stratification of patients.

3. Kidney sparing surgery

In many cases patients with UTUC are elderly with impaired baseline renal function[35], while RNU is the current standard of care for UTUC, performing RNU may have detrimental effect on these patients’ renal function. Furthermore, for patients with RCC performing KSS i.e partial nephrectomy has been shown to have a beneficial effect on both renal function and mortality[36,37]. According to the most recent EAU guidelines on the management of UTUC, a KSS approach is advocated for low risk tumors (as described in section 1.3) as the primary approach and for high risk tumor when there is an imperative indication (renal insufficiency or solitary functioning kidney) [1].

Possible KSS approaches include endoscopic ablation of tumors through URS or a percutaneous approach, segmental ureterectomy, and possible adjuvant treatment with either BCG or chemotherapeutic agents.

3.1 Endoscopic approach

Ablation of ureteral or renal pelvis tumors is becoming increasingly feasible with advances in endoscopic approaches. Urothelial tumor ablations have been described using both ureteroscopy (URS) and percutaneous (PCN) approach[38,39]. Nevertheless, the oncologic results of either have not been prospectively compared to that of RNU.

In a meta-analysis by Yakoubi et al. including 8 retrospective studies on endoscopic approach (no differentiation between URS and PCN), the authors found no evidence of increased risk for endoscopic approach in terms of OS – HR 1.47 (95% CI 0.7-3.08; p=0.31) and CSS HR 0.96 (95% CI 0.47-1.97; p=0.91) although with high heterogeneity (I² = 78% and 63% respectively), it is important to note that in this analysis patients were not grouped according to disease grade,
and that patients in the RNU group had generally higher stage disease which probably indicates selection bias. [40] Grasso found no difference in CSS for low grade disease between patients undergoing URS and RNU, but, reported 15% progression rate. [41] Local recurrence and DSS seems to be grade dependent for both PCN and URS, [39] and although CSS and OS may not be different between RNU and endoscopic approach for LG tumors, local recurrence is one of the obvious concerns when implementing an endoscopic approach. Hoffman described 44% vs 39% bladder recurrence rates for LG disease treated with URS and RNU respectively, and, 36% local recurrence rate for URS, nevertheless, all patients with local recurrence were successfully treated with subsequence ablations and with no evidence of disease progression. [42] Roupert reported no difference in bladder, contralateral or metastatic disease comparing RNU, URS and percutaneous approach for patients with variable disease characteristics including HG disease, he found no statistically significant difference in the rate of local recurrence between URS and PCN (14% and 6% respectively) although with small groups that may impair the results. [38] Pooled rates of salvage RNU after URS and PCN were 19% and 22% respectively in a review by Cutress. [39]

3.2 Segmental ureterectomy

Segmental (or distal) ureterectomy (SU), may preserve renal function by avoiding RNU, and at the same time provide sufficient oncological results. Unlike endoscopic treatment, during SU complete tumor excision and negative surgical margins may be verified, and lymph node dissection is also feasible. Unfortunately, much like in the case of endoscopic management, there is no prospective data on this subject.

In a review of literature, Seisen et al. have found no difference in 3-yr and 5-yr CSS for patients undergoing SU compared to RNU, OS, Metastatic free survival, local recurrence and bladder recurrence rates were also similar between those groups [43] Similarly, in a meta-analysis by Fang, there were no differences in the HR for CSS or OS between RNU and SU, although patients treated with SU were less likely to have non organ confined disease. [44] Reported rates of salvage RNU after SU range between 4 to 7% [43]
As for renal function after surgery, in spite of the assumption that SU may preserve renal function, in a recent study this point has not been proven and in fact more events of renal function worsening were observed in the SU group compared to RNU, the authors concluded that this difference might have been attributed to the higher rates of adjuvant chemotherapy used in the SU group[45]. However other studies show different results with better renal function for patients undergoing SU[46], and, in a meta-analysis Fang found a 9.32 ml/1.73m² decrease in mean eGFR for RNU compared to SU.[44]

There is scarce information directly comparing SU and endoscopic procedures, Seisen found higher risk for 5-yr local recurrence for endoscopic treatment HR 1.14 (95% CI 1.03-1.28; p=0.01) compared to SU for distal ureter lesions. [47].

### 3.3 Adjuvant instillations

The use of both Bacillus Calmette-Guerin (BCG) and chemotherapy instillations for UTUC has been described in small series. Such instillations have been used in the adjuvant setting after tumor ablation as well as for the treatment of UTUC CIS [48].

For the treatment of CIS, few small series have been published, the largest of which by Giannarini including 42 renal units and reporting 40% recurrence rate and 5% progression [49]. Other series reported recurrence rates ranging from 0-53% although it is important to note that the definition of UTUC CIS varies between the different studies [50]. In the setting of adjuvant instillation the largest study by Rastinhead, including 69 patients and 89 renal units after endoscopic ablation of papillary tumors, comparing those receiving antegrade BCG instillation via nephrostomy tube and those without adjuvant treatment. They reported similar recurrence (33-39%) and progression rates (15-26%) for low and HG tumors and for those receiving and not receiving instillations respectively, although the study probably lacked sufficient power. They have also reported 80% renal preservation rates [51]. In smaller series recurrence rates after BCG instillations range from 0-59% [50].

Fewer reports describe the use of Mitomycin C (MMC) in the adjuvant setting with a cumulative recurrence rate of 26%. [50]
Methods for instillation are either via a percutaneous nephrostomy tube [49], the insertion of a ureteral catheter or through intravesical instillation after the insertion of a double pigtailed ureteral stent to facilitate vesicoureteral reflux [52]. There are no comparative studies to prove the efficacy of one method over the other.

4. Radical surgery for UTUC

RNU remains the gold standard for the treatment and management of high risk UTUC. RNU includes the excision of the entire kidney and ureter including the ureteral orifice. Recurrence rates after RNU reported from a large multi-institutional cohort were 28%, with 3% local recurrence and a median OS and CSS of 24 and 18.5 months respectively. Both recurrence and CSS were stage and grade dependent. Sessile tumors, and LVI also inferred worse prognosis [53].

4.1 Surgical approach

Traditionally RNU was performed in open approach, however laparoscopically, and more recently robotic assisted approaches are becoming more common although controversy regarding the oncological results of these procedures still exist.

In the only RCT to date comparing laparoscopic and open RNU, Simone et al. found similar operating times for both groups, however blood loss and mean time to discharge were significantly lower for the laparoscopic group. 5-year CSS was 89.9% and 79.8% and 5-year MFS was 77.4% and 72.5% for the open and laparoscopic groups, respectively, although these differences were not statistically significant. In a subgroup analysis of patients with non-organ confined disease and high-grade disease, both CSS and MFS favored the open RNU group[54]. It is important to note that in this study distal ureteral management in the laparoscopic arm was performed laparoscopically, and that in both groups lymph node dissection was not performed – two factors that might affect their results. However, in a cumulative analysis Ni et al. found a 9% higher CSS rates for laparoscopic compared to open surgery although this group had a higher rate of Ta\Tis tumors and no stage or grade sub-analysis was performed. Overall and bladder recurrence rates were 15% and 17% respectively lower for the laparoscopic group[55].
Port site metastasis, which is a theoretical concern for laparoscopic RNU, is a rare occurrence and was only reported in 6 cases (0-2.8%). No cases of peritoneal carcinomatosis were reported[56]

4.2 Management of the distal ureter

For open RNU the management of the distal ureter may be performed through an intra vesicle bladder cuff (IVBC) or an extravesicle approach (EVBC), for laparoscopic RNU management of the distal ureter may be more complex and various methods have been described including an open approach, an intravesical laparoscopic approach[57], the use endoscopic staplers or LigaSure[58] during an extravesical pure laparoscopic approach, or, an endoscopic transurethral detachment of the ureteral orifice (the pluck technique[59].

Distal ureteral management is one of the concerns raised regarding the oncological results of laparoscopic RNU and improper management of the distal ureter might be a possible explanation for recurrences[56]. Krabbe et al. showed that non intravesical recurrence free survival (non IVR FS) and CSS were influenced by the management of the ureteral orifice. A HR of 3.2 and 3.4 for non IVR FS and CSS respectively was reported in those managed with EVBC vs IVBC [60]. However, Xylinas et al. found no difference in CSS, OS and RFS comparing EVBC, IVBC and endoscopic bladder cuff, but did show higher bladder recurrence rates for patients treated with an endoscopic approach (5-yr IVRFS-42%), with no difference between EVBC and IVBC [61]. In a similar single institution series Li et al. found no differences in terms of IVR, retroperitoneal recurrence, metastasis, RFS and CSS rates [62].

As evident, the proper management of the distal ureter remains controversial.

4.3 Role of lymph node dissection

Further complicating the surgical management is the potential advantage of lymph node dissection and the extent of dissection needed.
In the largest study to date based on a multi-institutional database Roscigno et al. described a significant difference in 5-year CSS for patients with pNx compared to pN0 (69% and 77% respectively) suggesting the possibility of a therapeutic benefit for lymph node dissection, such an effect may be explained due to micro-metastasis not identified in the routine pathological evaluation. In subgroup analysis, a similar difference was only found for patients with invasive disease and not for those with non-muscle invasive disease [63] – however this analysis is based on pathological tumor stage which is not available in the pre-operative setting, and as indicated above; due to the potential inaccuracy of clinical staging for UTUC lymph node dissection perhaps should be considered for all patients. In a different publication, the same group reported that the number of lymph nodes removed (≥8 vs <8) was independently associated with recurrence (HR 0.97) but not with CSM. Comparing renal pelvic and ureteral tumors Kondo et al. reported a significant risk reduction for renal pelvic tumors with template LND vs no LND (HR1.23) whereas such an advantage was not reported for ureteral tumors [64]. Overall 5-year CSS range from 40%-69% for noLND and from 50% - 79% for LND patient in a recent review of literature [65].

4.4 Techniques to prevent intravesical recurrence

Up to 40% of patients after RNU may develop bladder recurrence. Given the reported value of post-operative single MMC bladder irrigation after TURBT, endeavors have been taken to evaluate the effectiveness of chemotherapeutic bladder instillations after RNU. In a randomized prospective study (n=240) (ODMIT-C) O’Brien et. el. used one single post-operative bladder instillation of MMC following RNU. After 1 year of follow-up they reported 16% and 27% bladder recurrence rates for MMC and no MMC groups respectively (p=0.03, per protocol analysis), there was an absolute risk reduction of 11% and the number needed to treat calculated was 9. On subgroup analysis, recurrence rates for poorly diff. tumors were 26% and 18% and for moderately differentiated tumors 30% and 19% for no MMC and MMC, respectively. Although these differences were not statistically significant, the study was probably underpowered for this subgroup analysis[66]. It is important to note that surgical technique was not uniform in all cases included in this study. In another prospective study evaluating single instillation of Pirarubicin, recurrence rates at 1 and 2 years were 16.9% and
16.9% for the Pirarubicin group and 31.8% and 42.2% for the control arm with a relative risk reduction of 65%[67]. Based on this data the EAU guidelines recommend a single post-operative instillation after RNU, however, despite this recommendation being based on some of the only high level evidence available regarding UTUC management, the use of post-operative instillations seems to be low with only 51% of urologists reporting the use of such instillation in the US[68]. Additional measures to reduce bladder recurrence rates include early clipping of the ureter [69] and urine alkalization [70].

5. Systemic therapy for UTUC

Systemic therapies can be part of multimodal treatment approaches for patients with advanced or metastatic UTUC. However, the currently available body of evidence for UTUC specifically is rather limited with lack of prospective data and many principles are extrapolated from the management of UBC.

5.1 Pre-surgical therapies

For UBC, level I evidence exists towards the benefit of platinum-containing neoadjuvant chemotherapy for patients with muscle-invasive disease prior to cystectomy when compared to cystectomy alone.[71] In fact, subgroup analysis showed the largest benefit in patients with T3/4 and therefore, non-organ confined disease.[71] However as previously discussed, staging for UTUC is limited in accuracy, making it challenging to accurately determine advanced disease. Data from RNU series with minimal rates of pre-surgical therapies suggest that around 20% of patients harbor pT2 disease, around 35% of patients show pT3-4 disease and about 10% of patients have pathologically positive lymph nodes at time of surgery (with an additional large number possibly harboring undetected micrometastatic disease), indicating a large percentage of patients who may possibly benefit from neoadjuvant therapy [53]. Retrospective data (Table 2) indicate that as in urothelial carcinoma of the bladder (UCB), there are reasonable response rates with conversion to pT0 (13.8%) or non-invasive disease (34.5%) as well as indication of improved survival after neoadjuvant chemotherapy (DSS 90% with neoadjuvant chemotherapy vs. 57% in the matched historical control group).[72] While none of the patients in that study received regimens containing carboplatin, recent studies from Asia reveal that the utilization of
carboplatin containing regimens is much more common (up to 70%), however there are conflicting results with regards to its effectiveness and it is in general thought to be inferior to cisplatin in UTUC analogous to UCB.[73,74] Still, the question of agent is an important one as the accepted most efficacious systemic therapy for UTUC analogous to UCB is platinum-based chemotherapy, which requires adequate renal function, whereas carboplatin can be given at lower GFR levels. Unfortunately, as UTUC is a disease of the elderly, many patients already have impaired renal function at the time of diagnosis (eGFR >60 only in around 35% and eGFR >45 in around 70%), limiting their eligibility for platinum-based chemotherapy.[35] After RNU eligibility for platinum-based chemotherapy naturally decreases further to around 15% and 50% for a threshold of eGFR >60 and >45 respectively.[35] Ongoing trials prospectively evaluating the efficacy of neoadjuvant chemotherapy focus on cisplatin containing regimens and are underway and eagerly awaited to inform the field and guide treatment decisions.[75,76] Until then, neoadjuvant chemotherapy should be strongly considered in patients with high-grade, solid appearing lesions or advanced disease on imaging to maximize the number of treatment modalities available to the individual patient. The benefit of preoperative chemotherapy may be especially pronounced in the setting of locally advanced or unresectable disease as part of inductive or consolidative therapy. In patients with cT4 disease, the receipt of preoperative chemotherapy was an independent prognostic factor of freedom from recurrence and cancer-specific survival (HR 0.4 and 0.5 respectively) in a retrospective study of 70 patients.[77] Further, in patients with cN+ disease deemed unresectable, preoperative chemotherapy was found to achieve resectability in 85%, with pT0 status in 20% and pN0 status in 50% as well as significantly improved survival results.[78,79]

5.2 Post surgical therapies

Data supporting the utilization of adjuvant chemotherapy for UCB is not as robust as for neoadjuvant chemotherapy, mostly due to recruiting issues in prospective trials and the inherent shortcomings, mainly selection bias in retrospective studies.[80-82] In UTUC, due to the significant loss of renal function after removal of a renal unit during RNU, administration of adjuvant chemotherapy is challenging, and only a limited percentage of patients retain eligibility for such treatment, as discussed above.[35,83] There is recent large scale,
retrospective evidence from the National Cancer Database (NCDB) suggesting a survival benefit for adjuvant treatment in patients with locally advanced or node-positive disease (HR 0.77 overall with benefit across all subgroups).[84] However, it must be kept in mind that despite commendable efforts to adjust for available confounding variables, in such nationwide tumor registry studies there may very well be numerous other unknown and unadjusted confounders. Furthermore, contradictory evidence also exists, based on multicenter, propensity score matched retrospective analysis, Necchi et al. found no overall survival benefit when comparing adjuvant treatment to surveillance after RNU. In fact, according to this analysis adjuvant chemotherapy may have had a detrimental effect on OS, although unaccounted confounders may have influenced the results as well, stressing the need for high level evidence.[85]

5.3 Systemic therapy for metastatic disease.

First-line therapy for metastatic urothelial carcinoma of the bladder (mUCB) is cisplatin-based chemotherapy. There are different regimens available (methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) and gemcitabine cisplatin (GC), with overall similar efficacy, but a slightly more favorable toxicity profile for GC.[86] In metastatic UTUC (mUTUC), both regimens appear to be efficacious and even seem to reach slightly higher response rates than in mUCB.[87,88] A comparative multi-institutional Japanese study of 300 patients with metastatic urothelial carcinoma (50% mUTUC and 50% mUCB) showed no significant difference with regards to response rate to MVAC and GC.[88] In contrast, a Taiwanese group reported improved outcomes with MVAC as opposed to GC in patients with UTUC for recurrence-free and overall survival (7.3 vs. 4.0 months for RFS and HR 0.5 for OS).[87] As for now, the decision of regimen is left up to provider preference, the previously mentioned ongoing studies will inform the field with regard to efficacy of both regimens despite being set in the neoadjuvant and not metastatic setting primarily.[75,76] However, while the field is waiting for these results, compounds utilizing other methods of action have entered the arena. Immunotherapy in the form of checkpoint inhibitors has gained much interest in recent times and has led to a plethora of newly approved agents in various malignancies. The FDA has currently approved five agents for the treatment of advanced or metastatic urothelial carcinoma (atezolizumab, nivolumab, pembrolizumab, avelumab and durvalumab) in various settings (post-platinum or platinum-
ineligible.[89-94] Despite the relatively low overall response rates of between 15% to 23% for all comers and up to 28% of selected subpopulations of PD-L1 positive patients, these compounds can lead to dramatic and long lasting remissions, while harboring a favorable safety profile.[95] A multitude of reasons make checkpoint inhibitors attractive drugs for patients with mUTUC. First, they are applicable without necessity for dose reduction in patients with renal insufficiency, thereby addressing one of the largest problems to date with systemic therapies in the mUTUC patient population. Further, there is evidence that patients with mUTUC, seem to have higher response rates to checkpoint inhibition of up to almost 40% as compared to 17% in patients with mUCB in platinum-ineligible patients receiving atezolizumab.[92] This has not been uniformly reproduced in other studies, therefore warranting larger numbers of patients treated with these drugs to make definitive conclusions, however, there is a biologic rationale for this phenomenon. Patients with UTUC are more likely to harbor mutations in DNA-damage repair genes leading to microsatellite instability (MSI), (as further detailed below) There is evidence that patients with these alterations respond better to cisplatinum-based chemotherapy as well as to checkpoint inhibitors.[96,97] Many investigative efforts are currently undertaken and a plethora of new compounds are currently in the pipeline such that the therapeutic variety of mUTUC as well as locally advanced UTUC will hopefully grow further in the near future.

6. Hereditary UTUC

6.1 background

Due to the increased risk of associated malignancies and specific genetic alterations, special attention should be given to hereditary UTUC (H-UTUC). H-UTUC is related to hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. HNPCC is an autosomal dominant syndrome harboring an increased life time risk of colorectal malignancy with an earlier age of onset. Other cancer types such as endometrial, ovarian, stomach, pancreas, skin and brain are associated with HNPCC. UTUC is the 3rd most commonly (5%) associated HNPCC malignancy after colorectal and endometrial cancers[98] and It is estimated that as much as 21% of newly diagnosed UTUC patients may be HNPCC related. [99]. HNPCC
patients have a 6% lifetime risk of developing UTUC, which is 22 times higher compared to that of the general population[100], with the highest risk reported for those with MSH2 mutations [101]. H-UTUC is more common in the renal pelvis compared to non H-UTUC. [102]

6.2 Associated mutations and therapeutic implications

Microsatellites are short, repeating, non-coding nucleotide sequences found throughout the DNA, microsatellites alterations (MSI) may lead to frameshift mutations. The mismatch repair systems (MMR) is aimed at correcting DNA replication errors including MSI. In HNPCC, germline mutations of mismatch repair genes - MLH1(30%), MSH2(60%) or MSH6(5-8%) cause MMR loss of function and MSI leading to increased mutational load and eventually development of cancer. [100]

In a recent study across 12 tumor types with MSI treated with pembrolizumab, the overall response rate and complete remission rate were 53% and 21% respectively leading to the first agent approved by the FDA regardless of tumor type, but by mutational status.[97] The concept of higher response rates to checkpoint inhibition of patients with MSI due to lack of adequate DNA-damage repair, is backed by the association of higher mutational burden and neoantigen load, which are also found to be predictors of response to checkpoint inhibition.[89,90] Therefore, checkpoint inhibition as well as other systemic therapies like poly ADP ribose polymerase (PARP) inhibitors might be especially efficacious in patients with mUTUC in general and H-UTUC specifically.[103]

6.3 Diagnosis and screening

Correct and timely diagnosis of H-UTUC is of utmost importance and will lead to further screening for other HNPCC related malignancies in the index patient, as well as for familial genetic counseling. Furthermore, the diagnosis of H-UTUC may have implications regarding therapy selection especially for advanced disease as mentioned above. However, many urologist may be unaware of the prevalence of H-UTUC and the specific criteria that warrants further testing[100].
Initial screening and consideration for further diagnostic tests should be done based on the Bathesda [104] or Amsterdam [105] criteria for HNPCC however, these criteria offer relatively low sensitivity [106], and may prove to be cumbersome to the urologist. The EAU guidelines suggests that H-UTUC should be suspected in patients fulfilling one of the conditions described in table 3, those patients should further undergo genetic testing aimed at MSH2, MSH6 or MLH1 mutations to establish the final diagnosis [1]. Another suggested option is sending specimens of all newly diagnosed UTUC patients for MSI testing by polymerase chain reaction (PCR) or immunohistochemistry (IHC) evaluation of MMR proteins[106]. Metcalfe et al. compared different screening options including the Amsterdam criteria, IHC and MSI PCR, recognizing 13.9% of patients as at risk and eventually 5.2% with confirmed Lynch syndrome, all of which were recognized by a combination of Amsterdam criteria and IHC [107].

There is lack of evidence regarding the appropriate screening and follow-up strategies for patients already diagnosed with HNPCC syndrome in the absence of UTUC, such strategies should find the balance between the increased risk of UTUC, the importance of early detection and the harms associated with various diagnostic procedures. Routine urinary cytology or urinalysis for micro hematuria in different intervals has been suggested, however the sensitivity of these test is low [108]. More novel urinary markers for urothelial carcinoma may show better results in diagnosing UTUC however they were not tested in the specific scenario of HNPCC syndrome. As mentioned above, the risk of UTUC is higher in those harboring MSH2 mutations, hence, a risk stratification approach has been suggested by Acher et al. classifying patient into low (no history of urothelial carcinoma or MSH2 mutation) intermediate (family history of urothelial carcinoma or MSH2 mutation) and high (personal history of urothelial carcinoma) risk groups with specific screening test including annual urine cytology, dipstick and NMP22 for low risk, and the addition of ultrasound or contrast enhanced CT and cystoscopy for intermediate and high risk patients respectively [109], however, this strategy has not been tested or validated and other reports suggest that family history is not a strong predictor with 78% of H-UTUC tumors developed in those with no family history of UTUC [101].
Defining specific guidelines for the treatment of H-UTUC will probably remain a difficult task due to the relative rarity of this condition, nevertheless urologists should be aware of the increased risk of UTUC in those patients and use sound clinical judgment during follow-up.

7. Conclusions

UTUC is a relatively rare disease, many aspects in disease management are challenging with lack of level 1 evidence. Accurate diagnosis and staging may be difficult due to technical issues during URS biopsies and poor performance of local staging by imaging. KSS is becoming more accepted and is advocated by some societies, at least for the treatment of low risk disease with acceptable oncological results, nevertheless various aspects of the surgical management of UTUC such as surgical approach, distal ureter management and lymph node dissection are still controversial.

8. Expert commentary

As evident from the above review one of the main issues in the management of UTUC is the low level of evidence and the uncertainty in which the treating clinician must act. The major unresolved controversies are accurate diagnosis and local staging, the use of KSS, the performance and extent of lymph node dissection and the use of systemic therapy especially in the neoadjuvant setting before RNU and potential decline in renal function.

Hardships awaits beginning with the diagnostic phase with many technical issues evolving the acquisition of proper tissue samples, unfortunately even with the current advances in URS this issue is far from being resolved. Enhanced imaging and diagnostic techniques such as confocal laser microscopy or optical coherence tomography (NCT02326909) may provide further information in the future however are still far from practical clinical use.

Several prospective studies (such as NCT01261728) concerning the use of neoadjuvant chemotherapy are much expected and hopefully will shed additional light on this topic.
Prospective data regarding controversies in surgical technique mainly the use of KSS are not foreseeable in the near future due to the need of relatively high numbers of patients and large scale multi-institutional collaborations. Unfortunately, as appealing as it may be, retrospective studies based on national databases may not provide adequate answers to these questions due to various biases and the difficulty in controlling various confounders.

9. Five-year view

Within the next 5-10 years we would hopefully see an increase in the use of KSS as evidence, even if not level I, is accumulating regarding the oncological outcomes of these treatments and further advances are made in the development and implementation of endoscopic techniques.

Ongoing prospective trials, as mentioned above, will shed further light on the issue of neoadjuvant chemotherapy use. However, novel therapies such as checkpoint inhibitors, less affected by renal function, may very well revolutionize this field and may eventually prove neoadjuvant therapy to be redundant.

Finally, we should further strive for a wider use of post RNU intravesicle instillations based on the existing high level evidence and hopefully a change in national utilization trends will be evident.

Key Issues

- UTUC is a relatively rare disease, many topics remain controversial giving the paucity of high level evidence
- With the advancement of endoscopic techniques, and by proper selection of patients many tumors can be managed using kidney sparing surgery with overall good oncological results
- During RNU special attention should be given to complete resection of the distal ureter and ureteral orifice
- Methods for reducing bladder recurrence after RNU including the use of MMC bladder irrigation should be taken based on high level evidence
• Neoadjuvant chemotherapy for HG disease should be considered in many cases, especially in those with high risk of impaired renal function after RNU
• Special attention should be given to screening and detection of hereditary UTUC, as well as to proper follow-up and management of patients diagnosed with Lynch syndrome with no evidence of UTUC

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Declaration of interest
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References

Reference annotations

* Of interest
** Of considerable interest


*The most recent update of the European Urologic Association guidelines*

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**A recent review focusing on surgical management of UTUC**


60. Krabbe LM, Westerman ME, Bagrodia A et al. Surgical management of the distal ureter during radical nephroureterectomy is an independent predictor of oncological outcomes: results of a current series and a review of the literature. Urol Oncol. 2014;32: e19-26


*A systematic review focusing on lymph node dissection


67. 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


*A recent paper pointing to the prevalence and importance of early diagnosis of U-UTUTC

<table>
<thead>
<tr>
<th>Author</th>
<th>Model</th>
<th>Number of patients</th>
<th>Variables in final model</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Brien et al. (2010)33</td>
<td>Risk group stratification</td>
<td>172</td>
<td>Tumor grade, Positive cytology, Hydronephrosis</td>
<td>PPV: 73</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPV: 100</td>
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<tr>
<td>Margulis et al. (2010)30</td>
<td>Nomogram</td>
<td>659</td>
<td>Tumor location, Tumor grade, Tumor architecture</td>
<td>77%</td>
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<tr>
<td>Favaretto et al. (2012)32</td>
<td>Risk group stratification</td>
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<td>Tumor location, Tumor grade, Hydronephrosis, Invasion on imaging</td>
<td>70%</td>
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<tr>
<td>Chen et al. (2013)31</td>
<td>Nomogram</td>
<td>683</td>
<td>Gender, Tumor location, Tumor grade, Tumor architecture, Multifocality</td>
<td>79%</td>
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</tbody>
</table>

PPV-positive predictive value, NPV – negative predictive value
<table>
<thead>
<tr>
<th>Author</th>
<th>Disease status</th>
<th>Number of patients</th>
<th>Chemotherapy regimen</th>
<th>Pathological T0 Treatment\control</th>
<th>5 yr survival Treatment\control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youssef et al. (2011)(^{110})</td>
<td>cN+ for NAC pT2-4 N0 (1) or any T N+ (2) for no NAC</td>
<td>18 NAC 120 no NAC 175 no NAC 2</td>
<td>Gem+Cis MVAC</td>
<td>33%\NA</td>
<td>RFS – 49%\30%(1)\64%(2) CSS – 44%\36%(1)\64%(2)</td>
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<tr>
<td>Porten et al. (2014)(^{72})</td>
<td>cN0</td>
<td>31 NAC 81 no NAC</td>
<td>Cis containing or HD IDG or GPD</td>
<td>14\0\ p=0.001</td>
<td>CSS 90\57\ p=0.02 OS 80\57\ p=0.001</td>
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<tr>
<td>Kubota (2017)(^{74})</td>
<td>cT3-4 or N+</td>
<td>101 NAC 133 no NAC</td>
<td>Gem+Carbo\Cis</td>
<td>39\14\ p&lt;0.001</td>
<td>RFS – 53\50\ p=0.03 CSS – 74\62\ p=0.01 OS – 59\55\ p=0.08</td>
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<tr>
<td>Hosogoe (2017)(^{73})</td>
<td>cT2-4; N+\0</td>
<td>51 NAC 51 no NAC</td>
<td>Gem+Carbo\Cis</td>
<td>N\A</td>
<td>PFS – 60\39\ p=0.01 CSS – 71\54\ p=0.01 OS – 65\50\ p=0.03</td>
</tr>
</tbody>
</table>

Gem-gemcitabine, Cis-Cisplatinum, Carbo-Carboplatinum, HD IDG – High dose isofosfamid-doxorubicin gemcitabine, GPD- gemcitabine paclitaxel-doxorubicin, RFS – recurrence free survival, CSS – cancer specific survival, OS – overall survival, NA- not available
Table 3. Criteria for further diagnostic studies for hereditary UTUC based on EAU guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Age at diagnosis &lt;60 y.o</td>
</tr>
<tr>
<td>Personal history of HNPCC-spectrum cancer</td>
</tr>
<tr>
<td>1st degree relative &lt;50 y.o with HNPCC spectrum cancer</td>
</tr>
<tr>
<td>Two 1st degree relatives with HNPCC spectrum cancer</td>
</tr>
</tbody>
</table>

HNPCC – Hereditary Non Polyposis Colorectal Cance, Y.O-Year Old