Review Article on Upper-Tract Urothelial Carcinoma: Current State and Future Directions

Perioperative chemotherapy in the management of high risk upper tract urothelial cancers

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Abstract: Radical nephroureterectomy (RNU) remains the gold-standard in the treatment of invasive urothelial cancers of the upper tract (>pT2). However, there are stage-related, postoperative recurrence and cancer-specific death rates that are unacceptably high. Multimodality treatment regimens including neoadjuvant and adjuvant cisplatin-based systemic chemotherapy have been studied. While there is a paucity of Level 1 evidence to support either regimen, both have advantages and disadvantages. The provision of chemotherapy in the neoadjuvant setting is supported by extensive bladder cancer literature, but randomized controlled trials in the upper tract have not been completed. Neoadjuvant chemotherapy also risks overtreatment of patients due to the lack of accurate pre-operative staging modalities. On the other hand, adjuvant chemotherapy is supported by the findings of one prospective randomized trial, and eliminates the need for patient selection based on imperfect pre-operative modalities. However, the rigors of surgery and the renal function loss related to nephrectomy, may preclude the provision of adjuvant chemotherapy in a significant subset of patients. One may conclude that multimodal therapy is desirable for oncologic control, but the best means of providing such therapy requires further study.

Keywords: Chemotherapy; urothelial carcinoma

Submitted Dec 31, 2019. Accepted for publication Jan 15, 2020.
doi: 10.21037/tau.2020.03.48
View this article at: http://dx.doi.org/10.21037/tau.2020.03.48

Introduction

Upper tract urothelial cancer (UTUC) is a rare malignancy arising from the epithelial lining of the renal pelvis and ureters. While there are 60,000 new cases of urothelial cancer in the United states each year, only 5% of these arise in the upper tracts, giving UTUC an incidence of 1.8 cases per 100,000 person-years (1-3). UTUC afflicts primarily elderly men. The median age at diagnosis is approximately 70, and the male to female ratio is 2:1 (2).

Most patients initially present with either gross or microscopic hematuria, which prompts a workup appropriately consisting of cystoscopy, retrograde pyelography and/or CT urography, and if indicated, ureteroscopic biopsy and/or selective upper tract cytology (4). Rarely, UTUC may be diagnosed due to flank pain, palpable mass, or as an incidental finding on imaging.

While much more rare than urothelial cancer of the bladder, UTUC tends to present at a more advanced stage and progresses more rapidly than bladder cancer. Organ sparing local management is complicated by the difficulties of accessing the upper tract for endoscopic resection and intraluminal delivery of topical therapy. Nevertheless, nephron sparing modalities are becoming more widely accepted. Non-invasive disease, in particular low-grade, low volume disease is more frequently managed via ureteroscopic or percutaneous resection, with or without instillation of topical agents like BCG. However, the gold standard in the management of high-grade, bulky, or invasive disease remains radical nephroureterectomy (RNU) with lymph node dissection (4).

Despite aggressive surgical intervention, many patients still experience disease recurrence, and prognosis for these patients is poor. In one study 80% of patients who

developed recurrence of their UTUC after RNU were dead of disease at 2 years (5). Patients with locally or regionally advanced disease (≥T3 and/or positive lymph nodes) at RNU are known to have poor prognosis, and for two decades outcomes in this patient population remained fairly static (6-8).

The frequency of disease recurrence after RNU and the poor outcomes experienced by these patients have prompted the adoption of multimodal therapy in the management of select high-risk UTUC patients. Over the last decade there have been multiple studies addressing the timing and tolerability of chemotherapy in the perioperative setting. While there are known barriers associated with both neoadjuvant and adjuvant chemotherapy around the time of RNU, and a unanimous consensus on the role and timing of perioperative chemotherapy has not been reached, several published guidelines now discuss its consideration (9,10).

This manuscript will examine the data addressing the expanded incorporation of perioperative chemotherapy (NAC) in the treatment of high risk UTUC, as well as the barriers to its utilization. The rationale for and tolerability of neoadjuvant and adjuvant chemotherapy will be discussed.

Current guideline recommendations

There are current guidelines addressing the management of UTUC published by the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN). In recent updates both organizations have begun to include suggestions regarding the role of NAC in the management of UTUC. The EAU guidelines on UTUC states that the efficacy of platinum-based chemotherapy is expected to mirror that seen in bladder cancer, but cautions that the risk of diminished glomerular filtration rate (GFR) after RNU may limit the patient's ability to receive chemotherapy (10). NAC is considered a safe option in select patients. The 2019 NCCN Guidelines on bladder cancer similarly state: "Neoadjuvant chemotherapy may be considered for select patients with UTUC, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy" (9). The 2019 NCCN management flowcharts for renal pelvic tumors and ureteral tumors both mention NAC as therapy to be 'considered' in the treatment of high grade UTUC in select patients.

The natural history of UTUC

While RNU is the gold standard therapy for high grade or large volume UTUC, survival rates following surgery remain consistently disappointing. Published survival data from the end of the last decade demonstrates 5-year disease-specific survival ranging from 61–76% (8,11). Cancer specific mortality is closely associated with advanced stage at the time of surgery. In one study evaluating 1363 patients undergoing RNU at twelve different institutions, greater than 50% of patients were pT2 or higher at RNU. The 5-year disease-specific survival rates for patients with pT2, pT3, and pT4 were 75%, 54% and 12% respectively. 23% of patients undergoing lymph node dissection were pN+, with an associated 5-year disease specific survival of 35%. This mirrors data from 1998 when the UT Southwestern group reported a 30% 5-year disease-specific survival rate for their cohort of high risk (≥pT3 and/or N+M+) patients (12). The importance of advanced disease at the time of RNU cannot be overemphasized.

More contemporary data collected on 414 patients undergoing RNU without NAC at seven academic medical centers between 2003 and 2012 revealed that 55% of patients were stage ≥pT2, 6% had a positive soft tissue margin, and of the 249 patients undergoing pathologic evaluation of lymph nodes, 11% had nodal disease (13). Adjuvant chemotherapy was used in the post-operative management of 31% of the patients in this cohort, and a small but statistically significant 5-year cancer-specific survival benefit was seen in those patients receiving chemotherapy (39% *vs.* 32%, P=0.04). However, the 5-year cancer-specific survival for the total cohort remained only 34%.

In summary, pathology reports following RNU for UTUC are likely to report ≥pT2 or N+ in over half of patients, putting a significant portion of the population at high risk of recurrence. As recently as 2012, Rink *et al.* reported that 80% of patients experiencing recurrence after RNU will die of their cancer within 2 years (5). Thus, despite aggressive surgical management our ability to achieve acceptable cancer-specific survival for these patients is limited with a single modality approach, providing an impetus for clinicians to evaluate ways in which we might deliver multimodal therapy to the majority of patients with high risk UTUC.

Neoadjuvant chemotherapy in muscle invasive bladder cancer

Initial recommendations to include NAC in the treatment of UTUC were almost exclusively based on literature demonstrating the efficacy of platinum-based NAC in

patients with muscle invasive bladder cancer. UTUC is a rare malignancy, and historically multimodal treatment selection has been hindered by shortcomings in staging which complicate patient selection for aggressive therapy. With minimal data specifically in the upper tract realm, the clinical community has extrapolated the findings in the bladder cancer literature to guide the utilization of perioperative chemotherapy in the upper tract.

NAC has proven efficacy in muscle invasive bladder cancer and has become, in combination with radical cystectomy and pelvic lymph node dissection, part of the standard of care. In 2003 the Southwest Oncology Group published their randomized controlled trial of radical cystectomy with or without cisplatin-based pre-operative chemotherapy (methotrexate, vinblastine, adriamycin, and cisplatin: MVAC) (14). Data from this trial demonstrated a 14% increase in disease-free 5-year survival with improved median survival (77 months NAC plus cystectomy *vs.* 46 months cystectomy alone). The evidence from other early NAC trials in MIBC was somewhat inconsistent, but in 2005 the Advanced Bladder Cancer Meta-analysis Collaboration published updated data on 11 trials encompassing 3,005 patients (15). They demonstrated a 5% improvement in overall survival and a 9% improvement in disease-free survival at 5 years in patients receiving NAC prior to cystectomy versus cystectomy alone.

Unfortunately, adoption of cisplatin-based NAC prior to cystectomy was slow (16,17). Investigation of the National Cancer Database showed that from 2004 to 2013, the utilization of NAC in patients undergoing RNU increased from 0.7% to 2.1% (18). Potential barriers to utilization were thought to be delayed time to cystectomy, and the possibility that chemotherapy-related complications might render patients ineligible for cystectomy altogether (19). However, in 2000 data was published demonstrating the efficacy of gemcitabine and cisplatin in the treatment of metastatic bladder cancer, with an improved side effect profile over standard MVAC (20). This regimen was subsequently accepted as a more tolerable NAC alternative to MVAC. More recently a dose-dense MVAC regimen was shown in a prospective phase II trial to have similar or improved toxicity profiles compared with standard MVAC in the neoadjuvant setting, with the added benefit of a shorter time to cystectomy (median 9.7 weeks) compared to both standard MVAC and standard gemcitabine/cisplatin dosing (21). The rate of complete pathologic response (38%; 95% CI, 23% to 53%) in the bladder at cystectomy (pT0), a presumed surrogate for disease specific survival, compared favorably with earlier regimens.

The data from early randomized controlled trials which confirmed a survival advantage associated with NAC, combined with more recent studies identifying more tolerable regimens, has made NAC prior to cystectomy part of the standard of care in muscle invasive bladder cancer. Given the urothelial origins of upper tract cancer, it seems reasonable to expect a similar benefit associated with NAC prior to RNU for UTUC.

Evidence for the efficacy of neoadjuvant chemotherapy in upper tract cancer

The theoretical goal of NAC in urothelial cancer is the eradication of micro-metastasis, the driver of disease recurrence and cancer-specific mortality after successful extirpative surgery in the clinical N0, M0 setting. Difficulties in measuring this benchmark, have led to the establishment of pathologic downstaging as a surrogate for response to NAC. Grossman *et al.* demonstrated that downstaging to <pT1 drives the survival advantage seen with neoadjuvant MVAC in their muscle invasive bladder cancer population (14). In a recent UTUC series, both pathologic complete response and pathologic downstaging by at least one stage (i.e., cT2 to pT1) were associated with improved overall survival (22).

Early multi-institutional data suggested efficacy for NAC in UTUC prior to RNU. In 2009, Margulis *et al.* published on 1,363 patients undergoing RNU at eleven centers (8). Only 3% of the combined cohort received NAC prior to RNU. The overall rate of downstaging to pT0 was <1% for the cohort, but was 12% in patients treated with NAC.

Matin *et al.* first published the M.D. Anderson experience with NAC in UTUC in 2010 (23). Forty-three patients received NAC between 2004 and 2008. These patients had biopsy proven, high-grade UTUC, and the cohort was enriched for high-risk features like sessile tumor architecture. The comparison group was a historical cohort, treated with RNU alone between 1993 and 2003. Patients in the group receiving NAC were significantly more likely to be downstaged at RNU (P=0.004). The rate of pathologic complete response (pT0) in the NAC cohort was 14% *vs.* none in the RNU alone group, and patients with locally advanced disease at RNU (≥pT2, any N) were significantly less common in the NAC treated group (46.5% *vs.* 65.4%, P=0.043). In a 2014 update of the original manuscript, survival data indicated improved overall and disease specific survival in patients treated with NAC prior

to RNU compared with a matched cohort undergoing initial RNU (24). The disease specific and overall survival at 5 years in the NAC treated group were 90% and 80% respectively, compared to 57.6% and 57.6% respectively for the RNU alone cohort.

More recently a retrospective study evaluated the outcomes of 95 patients undergoing RNU for UTUC at two institutions (25). Of the 95 patients undergoing surgery, 61 had renal function that permitted the use of cisplatin-based NAC, 25 of whom received NAC. 80% of patients receiving NAC had clinical response by imaging, and 80% had <pT2 disease at surgery *vs.* only 36% of the group not receiving NAC. These encouraging outcomes at surgery were reflected in improved progression free survival and overall survival in the NAC-treated cohort. A Japanese study published in 2017 compared two matched cohorts of patients undergoing RNU for locally advanced UTUC, one with NAC and one without NAC (26). Fifty-one matched pairs were selected from 233 patients undergoing RNU between 1995 and 2016. The NAC group demonstrated significantly better 5-year progression free survival (60% *vs.* 39%, P=0.018), cancer specific survival (71% *vs.* 54%, P=0.015) and overall survival (65% *vs.* 50%, P=0.032). NAC was an independent predictor of both progression-free and cancer-specific survival on multivariate analysis. Almassi *et al.* reviewed the National Cancer Database for patients undergoing RNU between 2006 and 2014 (27). The outcome of interest in this study was pT0 rate at RNU which was significantly higher in the NAC-treated population (6.1% *vs.* 0.4%; P<0.001), despite the fact that the NAC-treated patients were more likely to have clinically advanced disease (T2-4 in 47% *vs.* 29%; P<0.001). Receipt of NAC was an independent predictor of pT0 at RNU (OR 19.8, 95% CI, 11.8–33.5).

Most recently Margulis *et al.* presented the results of the prospective phase II ECOG-ACRIN 8141 trial (28). Thirty-six patients received neoadjuvant therapy in the form of ddMVAC (CrCl>50 mL/min, n=30) or gemcitabine/cisplatin (CrCl 30–50 mL/min, n=6). While the gemcitabine/cisplatin arm closed to accrual early, the ddMVAC arm demonstrated downstaging to ≤pT1 in 62% of patients. Grade 3–4 toxicities were reported in 23% of the ddMVAC patients, and the regimen was deemed acceptable for further study.

In summary, the existing data supports the efficacy of cisplatin-based NAC in patients with UTUC prior to RNU. However, prospective trials are lacking, making it difficult to advocate in favor of NAC over adjuvant therapy based on oncologic outcomes alone.

Work-up and patient selection for neoadjuvant chemotherapy in upper tract cancer

The existing data, while limited, suggests oncologic benefit for NAC in UTUC; however, utilization of NAC remains limited. Almassi's group identified 6,174 patients undergoing RNU in the United States between 2006 and 2014 (27). Only 4.2% received NAC prior to surgery, though utilization of chemotherapy increased from 1.9% to 7.1% over the study period. Lack of consistent clinical staging modalities limits clinicians' ability to preoperatively select patients who are at risk of harboring muscle invasive disease at RNU.

Preoperative urine cytology has been shown to predict both ≥pT3 and lymph node involvement at RNU (29,30), but is less consistent as a predictor of ≥pT2. Messer *et al.* evaluated 326 patients undergoing RNU and found that cytology was not a sensitive predictor of muscle invasion in UTUC (sensitivity 62%, PPV 44%) (31).

Similarly, hydronephrosis has been shown in a large multi-institutional study, to be an independent predictor of muscle invasive disease at RNU (HR 7.4, 95% CI, 4.6–11.8), non-organ confined disease (HR 5.5, 3.4–8.9), and high grade disease (HR 1.6, 1.0–2.6).(32) The association between pre-operative hydronephrosis and advanced disease has not been completely consistent across studies however. A large retrospective Japanese cohort, consisting of 722 patients undergoing RNU was reported in 2015 (30). While hydronephrosis was independently associated with lymphovascular invasion (OR 2.27, 95% CI, 1.17–4.54), there was no clear association between hydronephrosis and either advanced pathologic stage or high grade disease at RNU.

Ureteroscopic findings of sessile tumor architecture may also predict aggressive disease at the time of definitive resection (33,34). Remzi *et al.* reviewed the pathology slides of 1363 patients after RNU and categorized gross tumor architecture as papillary (72%) or sessile (28%) (34). Sessile tumor architecture was associated with advanced pathologic stage and lymph node involvement, and was an independent predictor of cancer recurrence and cancer-specific mortality. These findings were confirmed by a multi-institutional study of 754 patients using a similar protocol to evaluate RNU specimens as sessile or papillary (33). About 20% of the cohort had sessile tumors, of which 95% were associated with ≥pT2 and 98% were associated with high grade disease. On multivariable analysis, macroscopic

sessile architecture predicted recurrence free survival (HR 1.5, 95% CI, 1.03–2.1) and cancer-specific survival (HR 1.5, 95% CI, 1.03–2.2). Ureteroscopic biopsy findings are traditionally of limited utility in predicting pathologic stage. Brown *et al.* reported that ureteroscopic biopsy grade, not stage, correlated with pathologic stage at RNU (35). High grade biopsies (grade 3) correlated with ≥pT2: positive predictive value 66%; negative predictive value 72%.

Multiple attempts have been made to develop multivariable models with increased predictive power as a means of preoperatively identifying UTUC patients at high risk of progression after RNU. In 2010, the Upper Tract Urothelial Carcinoma Collaborative Group published a nomogram that included preoperative grade, architecture, and tumor location (36). The model achieved 77% accuracy in predicting pT3-4 and/or N+ disease at RNU. This was followed in 2012 by an effort from Memorial Sloan-Kettering their cohort of 274 patients (37). The MSKCC model included only local invasion on imaging and high grade tumor on ureteroscopy as independent predictors of nonorgan confined disease on multivariable analysis. The final model had an area under the curve (AUC) of 0.71 for predicting ≥pT2 and 0.70 for predicting pT3-4 and/or N+. More recently in 2019, Margulis *et al.* published a nomogram based on 245 patients. On multivariable analysis only sessile architecture was an independent predictor of recurrence (HR 2.52; 95% CI, 1.09–5.86). A nomogram predicting 2- and 5-year recurrence free survival was constructed including age, ECOG score, hydronephrosis, architecture, eGFR, clinical stage ≥T3, and hemoglobin. Patients with greater than three risk factors had 5-year recurrence free survival of 43% *vs.* those with three or less (78%). AUC for the model was 0.71.

Current NCCN recommendations guiding patient selection for NAC prior to RNU suggest that NAC should be "considered for select patients with UTUC, particularly for higher stage and/or grade tumors…" (9). At our institution we refer patients with high grade disease on biopsy, sessile appearing architecture, and/or radiographic findings suggestive of invasion (cT2-4 and/or cN+) to medical oncology for a discussion of cisplatin-based NAC.

Evidence for the efficacy of adjuvant chemotherapy in upper tract cancer

By selecting patients for systemic therapy based on their pathologic findings at RNU, adjuvant chemotherapy programs avoid the dilemma of patient selection based on imperfect pre-operative clinical staging modalities. However, as discussed later, the delivery of chemotherapy in the adjuvant setting may be limited by the patient's health following RNU. Postoperative complications may delay the provision of chemotherapy, and RNU-related decrements in renal function may preclude the use of nephrotoxic chemotherapy altogether.

Initial studies evaluating oncologic outcomes with adjuvant chemotherapy were retrospective in nature, and reported mixed results. Two early multi-institutional studies showed no oncologic advantage to adjuvant systemic therapy after RNU. Hellenthal *et al.* reported on 542 patients with high risk features at RNU (pT3-4 and/or positive LN), 121 of whom received adjuvant chemotherapy (38). There was no overall or cancer-specific survival advantage associated with adjuvant chemotherapy in this cohort. However, the group receiving adjuvant chemotherapy was enriched with higher risk patients based on pathologic features at surgery (lymph node positivity in adjuvant chemotherapy *vs.* no adjuvant chemotherapy, 43% *vs.* 18%). Vassilakopoulou *et al.* evaluated 627 patients who were ≥pT3, N+ or M+, of which 140 received postoperative chemotherapy (39). Adjuvant therapy did not confer better cancer-specific or overall survival. However, only 109 patients received therapy with adjuvant intent for regionally confined disease, the remainder had distant metastasis at RNU and were treated with palliative intent. It is not surprising that neither of these studies demonstrated an oncologic advantage associated with adjuvant therapy, given the enrichment of the adjuvant therapy groups with advanced, and in some cases distantly metastatic, disease.

In 2006 a Korean group published their initial experience with adjuvant chemotherapy in 19 patients who were ≥pT2, N any, M0 (40). Over a median follow-up period of 30.7 months (range, 4.7 to 98.8 months), 82% of the non-chemotherapy patients *vs.* 28% of the adjuvant chemotherapy patients expired. Adjuvant chemotherapy was associated with overall survival on multivariate analysis. The same group updated their data in 2015, reporting on 139 patients with pT3-4 or N+ (41). Of the 66 patients who received adjuvant chemotherapy, 60 received cisplatin-based regimens. The authors could show no oncologic advantage associated with adjuvant chemotherapy, but again the group receiving systemic adjuvant therapy was enriched for N+ patients (18% *vs.* 4%). A multi-institutional retrospective study was published by Huang *et al.* in 2015, comparing outcomes in 60 patients who received adjuvant chemotherapy after RNU *vs.* 111 who did not (42). Patients were specifically selected

pT3N0M0, and in this case, adjuvant chemotherapy was associated with both 5-year cancer-specific (80.5% *vs.* 57.6%, P=0.010) and recurrence-free survival (74.4% *vs.* 52.9%, P=0.026), as well as a trend toward improved overall survival. On multivariable analysis, adjuvant chemotherapy remained an independent predictor of cancer-specific survival.

More recently, Seisen *et al.* queried the NCDB for patients undergoing RNU between 2004 and 2012 for pT3-4 and/or pN+ (43). Of 3,253 patients, 762 received adjuvant chemotherapy. Over a median follow-up of almost 50 months, an overall survival advantage emerged for patients getting adjuvant chemotherapy (median (IQR) overall survival for adjuvant chemotherapy *vs.* no adjuvant chemotherapy: 47.4 months (19.9 to 112.4 months) *vs.* 34.8 months (14.1 to 99 months). This association between overall survival and adjuvant chemotherapy was maintained on multivariable analysis (HR 0.77, 95% CI, 0.68 to 0.88; P<0.001).

The first prospective randomized study of perioperative chemotherapy in UTUC (POUT), was completed recently and presented in February of 2018 (44). The authors accrued 345 patients undergoing RNU, between 2012 and 2017. Patients received either 4 cycles of gemcitabine/cisplatin within 90 days following surgery, or surveillance. The trial was closed when it met criteria for early termination. The primary endpoint was disease free survival at 2 years which was 0.70 (95% CI, 0.58 to 0.79) in patients receiving adjuvant therapy and 0.51 (95% CI, 0.39 to 0.61) in the surveillance group. Given the evidence presented above, it seems plausible that adjuvant chemotherapy after RNU, when provided to properly selected patients, may confer some oncologic advantage.

Barriers to adjuvant chemotherapy in UTUC

Adjuvant therapy after RNU is appealing in comparison to NAC because the ability to base clinical decision making on the pathology specimen avoids the uncertainty of pre-operative staging and potential for over-treatment associated with selecting patients for NAC. However, the act of undergoing RNU may preclude patients from therapy.

Raman *et al.* reported that while nearly half of their surgical cohort (177/414) had locally advanced disease, only 31% of locally advanced patients went on to adjuvant therapy (13). Factors preventing the delivery of adjuvant therapy were the 26% overall complication rate of which one quarter were grade III or IV, and the surgically induced decline in renal function. Receipt of adjuvant chemotherapy was directly related to Clavien grade of complications. 71% of patients with Clavien grade I or II complications received adjuvant therapy; however, only 17% of patients with grade III or IV complications eventually received chemotherapy post-RNU (P=0.004).

Several groups have evaluated the effect of RNU on eGFR in this patient population. In 2010 Lane *et al.* published on 336 patients undergoing RNU at the Cleveland Clinic (45). Using eGFR ≥60 mL/min/1.73 m^2 calculated by MDRD as a cutoff for chemotherapy eligibility, they demonstrated that only 48% of their patients were eligible for cisplatin-based therapy prior to RNU. Following RNU only 22% of patients still qualified for chemotherapy by eGFR criteria. In the same year, Kaag *et al.* reported on a multi-institutional retrospective effort that evaluated 388 patients (46). eGFR was calculated via the MDRD method prior to, and 3 months after RNU. eGFR cutoffs for chemotherapy eligibility were set at ≥60 mL/min/1.73 m^2 and ≥45 mL/min/1.73 m^2, with 45 mL/min/1.73 m^2 used as the cutoff for split dose cisplatin at the participating institutions. Prior to RNU 49% and 80% of patients were eligible for cisplatin using eGFR cutoffs of ≥60 mL/min/1.73 m^2 and ≥45 mL/min/1.73 m^2 respectively. After nephrectomy only 19% and 55% of patients remained eligible for adjuvant therapy using cutoffs of ≥60 mL/min/1.73 m^2 and ≥45 mL/min/1.73 m^2 respectively. The eGFR decrement was more pronounced in patients older than 70. An international, multi-institutional study published in 2013 confirmed these findings in 666 patients (47). The average loss of eGFR was 18% in this study. Using an eGFR cutoff of ≥60 mL/min/1.73 m^2, 37% of patients qualified for chemotherapy prior to RNU, only 16% qualified after surgery. Using an eGFR cutoff of ≥45 mL/min/1.73 m^2, 72% of patients were eligible for chemotherapy before RNU, falling to 52% after surgery.

Investigators have attempted to predict the degree of renal loss associated with RNU, and in so doing identify those patients for whom the provision of chemotherapy prior to nephrectomy is essential. Body mass index (48), contralateral kidney volume (48), Charlson index (49), and pre-operative hydronephrosis (50,51) have all been shown to be independent predictors of post-RNU renal function. However, age at surgery (49-51) and pre-operative eGFR (48-51) remain the most consistent predictors of post-operative renal function. Hashimoto *et al.* were able to use age, pre-operatieve eGFR, and pre-operative

hydronephrosis to develop a model predicting post-RNU renal function (51). The correlation coefficient for the model was 0.75. Thus, while the adjuvant setting may allow more accurate selection of patients for cisplatin-based chemotherapy based on pathologic criteria, the sequelae of RNU may prevent the administration of nephrotoxic chemotherapy in a fashion that we cannot reliably predict prior to surgery.

Molecular predictors of chemo-response in the perioperative setting

A significant amount of work has been done evaluating molecular markers of tumor response to cisplatin-based NAC in bladder cancer, which may potentially be extrapolated to predict tumor response in UTUC. Plimack *et al.* evaluated a panel of DNA repair genes including *ATM*, *RB*, and *FANCC* (52). Alterations in one or more of these genes correlated with pathologic response to NAC. 87% of patients achieving ≤pT1, N0 after MVAC had alterations in at least one of the three genes *vs.* none in the nonresponsive group. *BRCA1* is a known tumor suppressor which identifies damaged DNA for repair. Font *et al.* demonstrated that low and intermediate levels of *BRCA1* correlate with increased NAC response *vs.* high levels of *BRCA1* (66% *vs.* 22%, P=0.01) as judged by final pathologic stage ≤pT1N0 (53). *ERBB2* codes for a receptor tyrosine kinase that is upregulated in bladder cancer. In one study, *ERBB2* missense mutations were found in 24% of patients achieving pT0 after NAC, compared to 0/33 non-responders.

Furthermore, gene expression profiling and molecular subtyping in bladder cancer has led to the categorization of tumors into basal, luminal and p53-like subtypes (54). This molecular profiling may be used in bladder cancer to predict response to chemotherapy. For instance, while the basal subtype is associated with aggressive disease manifested as higher rates of metastatic disease at presentation and shorter cancer-specific survival, it has been demonstrated that an immune infiltrated subset of these tumors responds well to NAC. On the other hand, p53-like tumors were consistently resistant to cisplatin-based chemotherapy. These findings may or may not extrapolate to UTUC.

These molecular markers, among others, may add power to current preoperative models predicting pathologic stage at RNU. Further work is needed, specifically in the upper tract domain, to determine the utility of molecular markers as prognostic tools allowing the selection of patients for NAC prior to RNU.

Future directions

Currently, there is good evidence to support the use of adjuvant chemotherapy in patients with high-risk UTUC at the time of RNU. However, diminished renal function as a result of patient comorbidities combined with nephrectomy remains a very real barrier to the utilization of adjuvant cisplatin-based chemotherapy. At present, existing guidelines recommend consideration of NAC in patients with predictors of advanced disease at RNU, who have sufficient renal function to tolerate cisplatin-based regimens. Careful patient selection is based on the presence of preoperative characteristics, which are imperfect predictors of advanced disease at RNU. An improved understanding of the molecular predictors of advanced disease might allow the development of a preoperative nomogram that could accurately predict disease state at RNU. A review of the NIH trial listing at clinicaltrials.gov reveals 4 active trials involving neoadjuvant chemotherapy for UTUC. Two trials are evaluating gemcitabine/cisplatin, and two are comparing dose dense MVAC with gemcitabine/cisplatin in one, and gemcitabine/carboplatin in the other. The results from a well-designed clinical trial prospectively evaluating NAC in the UTUC population prior to RNU will clearly be beneficial.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (John J. Knoedler and Jay D. Raman) for the series "Upper-Tract Urothelial Carcinoma: Current State and Future Directions" published in *Translational Andrology and Urology*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau.2020.03.48). The series "Upper-Tract Urothelial Carcinoma: Current State and Future

Directions" was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kaag MG. Perioperative chemotherapy in the management of high risk upper tract urothelial cancers. Transl Androl Urol 2020;9(4):1881-1890. doi: 10.21037/tau.2020.03.48

