High Response Rates to Neoadjuvant Chemotherapy in High-Grade Upper Tract Urothelial Carcinoma

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OBJECTIVE To evaluate the impact of cisplatin-based neoadjuvant chemotherapy (NAC) in patients who underwent nephroureterectomy for high-grade (HG) upper tract urothelial carcinoma (UTUC).

METHODS Retrospective review was conducted of patients with HG UTUC from 2011 to 2017 who underwent nephroureterectomy at 2 institutions. Patients with eGFR >50 mL/min/1.73 m^2 were considered eligible for NAC and were referred for evaluation of NAC prior to nephroureterectomy. Patient demographics, kidney function, clinical and pathologic response rates, and outcomes were analyzed.

RESULTS Of 95 patients with HG UTUC meeting inclusion criteria (mean age 72.3 years, mean preop eGFR 57.0 mL/min/1.73 m^2), 61 patients were considered eligible for NAC with eGFR >50 mL/min/1.73 m^2, of which 25 (41%) received NAC. Of the patients who received NAC, 80% (20/25) of the patients had clinical response on imaging and 80% (20/25) had pathologic response (<pT2N0 disease) on nephroureterectomy. On final pathology, only 20% of the NAC group had ≥pT2 disease compared to 64% of patients who proceeded directly to surgery (P = .001). Patients who received NAC had significantly longer progression free survival (P = .051) and overall survival (P = .052) compared to patients who proceeded directly to surgery. No patients progressed or were deemed ineligible for surgery due to NAC.

CONCLUSION Cisplatin-based NAC demonstrated a high clinical and pathologic response rate in patients with HG UTUC without compromising definitive surgical treatment. Since nephroureterectomy significantly reduces kidney function and eligibility for cisplatin-based chemotherapy after surgery, patients with HG UTUC should be considered for NAC. UROLOGY 129: 146–152, 2019. © 2019 Elsevier Inc.

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease that comprises 10% of all renal tumors and 5% of urothelial carcinomas overall.[1] This is in contrast to bladder cancer (BC), which is the fourth most common cancer overall[2] and comprises 95% of all urothelial carcinomas.[3] Although UTUC shares histological features with BC, UTUC is frequently reported to be high-grade (HG) at the time of diagnosis[4] and is typically associated with poor outcomes[5] that have not improved over several decades[6] or even decreased in certain populations.[7] Moreover, UTUC is far more difficult to stage preoperatively compared to BC given the nature of upper tract anatomy and the limited accuracy of ureteroscopic biopsy.[8] Due to the aggressive nature of the disease and limitations in staging preoperatively, complete removal of the upper tract via radical nephroureterectomy (NU) has been established as the gold standard. However, patients with muscle-invasive disease, nonorgan confined UTUC and lymph node involvement after extirpative treatment have been associated with poor survival and increased risk for disease recurrence.[1,9,10]

Chemotherapy alongside surgical therapy has long been utilized to improve treatment outcomes in a variety of cancers. Although cisplatin-based adjuvant chemotherapy (AC) has been shown to improve survival,[11] patients are often precluded from receiving chemotherapy due to poor renal function after NU. Thus, cisplatin-based neo AC (NAC) has been thought to be particularly useful in this population, as these patients are more likely to tolerate cisplatin-based therapy with 2 kidneys. While Level 1 evidence exists demonstrating improved outcomes with NAC prior to treatment of muscle invasive BC,[12] there is less data supporting the utilization of NAC in HG UTUC, which is primarily composed of single center studies,[13-16] although recently presented results of the phase II Eastern Cooperative Oncology Group – American Collect of Radiology Imaging Network

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8141 trial at American Urological Association (AUA) 2018 annual meeting AUA demonstrated improvements in pathologic complete response rates with NAC.[17] However, given the limited utilization of NAC currently (1.8% of patients in SEER-medicare database),[18] we seek to contribute to the limited existing body of evidence by reporting on the outcomes and adverse events of patients who received NAC prior to NU for pathologically proven HG UTUC at our 2 institutions; and to promote the concept that all eligible patients should be offered NAC prior to definitive surgery.

METHODS

We performed a retrospective chart review of patients at 2 institutions who were diagnosed with HG UTUC and underwent NU between 2011 and 2017. HG UTUC was determined either by HG disease or carcinoma in situ on ureteroscopic biopsy or positive urine cytology with visualized mass on imaging. Patient demographic data, medical history, renal function, surgical parameters, and pathological characteristics were recorded in our database and approved by the local institutional review board. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Patients with eGFR <50 mL/min/1.73 m^2 or had clinically positive nodal disease were considered ineligible for NAC and were excluded from further analysis. At 1 institution, any patient planned for NU for HG UTUC with eGFR >50 mL/min/1.73 m^2 were considered eligible for NAC and referred to medical oncology for NAC evaluation. Patients with eGFR >50 mL/min/1.73 m^2 but had medical conditions including peripheral neuropathy, hearing loss, poor Eastern Cooperative Oncology Group performance status, or heart failure were not given NAC based on the clinical judgment of the medical oncologist. At the second institution, patients were not routinely offered NAC. Patients who had eGFR >50 mL/min/1.73 m^2 at either institution who did not receive NAC were used as the control cohort.

Patients who received NAC were treated with a cisplatin-based multidrug regimen (methotrexate − vinblastine − doxorubicin − cisplatin (MVAC) or gemcitabine/cisplatin) prior to surgery. Patients underwent cross-sectional imaging before and after NAC administration and largest tumor diameter were recorded. Clinical response (CR) was defined as any reduction of tumor size seen on post-treatment imaging. Complete CR was defined as no visible tumor on post-treatment imaging. Pathological response was defined as <pT2N0 disease on final pathology and complete pathologic response is defined as pT0N0 disease. The decision to perform a lymph node dissection and extent of the lymph node dissection during time of NU was left to the discretion of the surgeon.

Progression free survival (PFS), defined as no evidence of systemic disease, and overall survival (OS) were estimated using the Kaplan-Meier method and Log-Rank test. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 generated by the National Cancer Institute. Univariable categorical variable comparisons were performed using the chi-square test and continuous variables were evaluated with the Student *t* test. For each test result, a corresponding 2-tailed *P* value < .05 was considered a statistically significant finding. All analysis was carried out in Excel (Microsoft, Redmond, WA) with XLSTAT (Addinsoft, Long Island, NY) and SPSS statistics (IBM, Armonk, NY).

RESULTS

From 2011 to 2017, a total of 95 patients at 2 institutions (mean age 72.3 years, mean preop GFR 57.0 mL/min/1.73 m^2) presented with HG UTUC and were considered for NAC prior to surgery. Of this group, 61 patients were deemed eligible for NAC based on renal function with a mean eGFR of 69.9 mL/min/1.73 m^2. Thirty-four patients were ineligible for NAC with a mean eGFR of 34.7 mL/min/1.73 m^2. Of the 61 potential patients who were eligible for NAC based on renal function, 25 patients received NAC prior to undergoing NU. The control group consisted of the 36 patients who did not receive NAC prior to extirpative surgery. Baseline, surgical and tumor characteristics for both groups are listed in Table 1. Patients who received NAC were significantly younger compared to the control group (63.6 vs 74.3 years of age, P <.001).

OUTCOMES OF NAC

Of the patients who received NAC, 24% (6/25) received 3 cycles whereas the remaining patients received at least

Table 1. Patient characteristics

Characteristic	NAC (*n* = 25) Mean (SD)	No NAC (*n* = 36) Mean (SD)	P
Age	63.6 (12.0)	74.3 (9.3)	<.001
GFR (mL/min/1.73 m^2)			
Preop	70.2 (16.3)	68.9 (14)	.737
Postop	43.2 (15.8)	47.3 (15.0)	.338
	***n* (%)**	***n* (%)**	
Race			.957
Nonwhite	5 (20.0)	7 (19.4%)	
White	20 (80.0)	29 (80.6%)	
Sex			.690
Male	14 (56.0)	22 (61.1)	
Female	11 (44.0)	14 (38.9)	
Laterality			.351
Left	6 (24.0)	20 (55.6)	
Right	19 (76.0)	16 (44.4)	
Location			.029
Renal pelvis	20 (80.0)	18 (50)	
Ureter	4 (16.0)	8 (22.2)	
Both	1 (4.0)	10 (27.8)	
History of bladder cancer			.086
Yes	7 (28.0)	18 (50.0)	
No	18 (72.0)	18 (50.0)	
Lymphadenectomy			.012
Yes	22 (88.0)	21 (58.3)	
No	3 (12.0)	15 (41.7)	
Adjuvant chemotherapy			.324
Yes	2 (8.0)	6 (16.7)	
No	23 (92.0)	30 (83.3)	
Lymphovascular invasion			.011
Yes	2 (8.0)	14 (38.9)	
No	23 (92.0)	22 (61.1)	
Carcinoma in situ			.399
Yes	10 (40.0)	19 (52.8)	
No	15 (60.0)	17 (47.2)	
Multifocality			.164
Yes	7 (28.0)	16 (44.4)	
No	18 (72.0)	20 (55.6)	
Positive margin			.057
Yes	0 (0)	5 (13.9)	
No	25 (100)	31 (86.1)	

4 cycles of NAC, with 1 patient stopping after 3 cycles due to complete CR. Fifty-two percent (13/25) of patients had adverse events due to NAC, although the majority were grades 1 and 2 (Table 2). Of note, 0/25 patients progressed while receiving NAC, failed to proceed to NU, or were delayed from surgery due to adverse effects of NAC. The median time to surgery after initiation of NAC was 4.2 months (range 2.4-5.6 months), and time to surgery after completion of NAC was 1.6 months (range 0.8-2.3 months).

Of the 25 patients who received NAC, 80% (20/25) of patients experienced a CR prior to surgery. Within this group, 60% (12/20) of patients experienced a partial CR with average decrease of 57% in maximum tumor length and 40% (8/20) of patients had a complete CR with no visible tumor noted on imaging prior to NU. Eighty percent (20/25) of patients had pathologic response with <pT2N0 disease on final pathology, with 2 patients experiencing complete pathological response (pT0N0/pT0Nx). Of the 8 patients with complete CR, 2 patients had pTaN0, 1 patient had pTisN0, and 2 patients had pT0N0/pT0Nx on final pathology. Of the remaining 3 patients with complete CR, 1 patient had pT2N0 and 2 patients had pT1N0 disease.

EFFECTS OF NAC ON DISEASE STAGING AND RECURRENCE

Significant differences in disease staging were observed between the NAC and control group (No NAC) on final pathology, with 64% of patients in the control having ≥pT2 disease compared to 20% in the NAC group (P = .001) (Table 3). Patients in the NAC group also had significantly lower rates of nonorgan confined disease (P = .001).

On comparison of progression-free survival between patients who underwent NAC versus the control group over a median follow-up time of 21 months and mean follow-up time of 24 months (range 1-73 months), there was significantly longer PFS in the NAC group (P = .051) (Fig. 1A) and OS among patients who received NAC (P = .052) (Fig. 1B).

DISCUSSION

NAC for UTUC has the potential to significantly improve outcomes in patients with high-grade UTUC. Multiple prior studies[1,9,10] have demonstrated that patients with muscle-invasive, node positive, or nonorgan confined UTUC have poor outcomes and decreased survival. In our present study, we demonstrate that patients who received NAC prior to NU with HG UTUC have significantly decreased rates of muscle invasive disease and nonorgan confined disease compared to patients who proceeded directly to surgery during the same period. Our data supports the prior findings from single center studies demonstrating pathologic downstaging with the utilization of NAC prior to NU.[13-16] However, despite these encouraging results, including a 5 year OS benefit of 80% versus 58% in the Porten et al study,[14] and 5 year OS benefit of 65% versus 50% with NAC in the Hosogoe et al study,[19] the utilization of NAC is still quite low. A recent analysis using the SEER-Medicare database over a 9-year period found only 1.8% of patients received NAC, compared to 11.8% of patients who received AC after NU.[18] In this SEER-Medicare analysis, use of NAC did not reach statistical significance for survival, likely due to underutilization of NAC and small sample sizes.

Utilization of NAC for UTUC can vary widely between academic centers. While a few academic centers have adopted routine utilization of NAC prior to NU for UTUC,[14,20] the SEER-Medicare data demonstrates that this is the exception and not the rule. In addition, in our own collaborative UTUC database among 2 urban, tertiary referral academic medical centers, the rates of

Table 2. Adverse events due to neoadjuvant chemotherapy

AE Grade	n (%) pts	Adverse Events Experienced
1	4 (16)	Fatigue, dyspepsia, gross hematuria
2	7 (28)	Anemia, neutropenia, AKI, nausea, TIA
3	1 (4)	Anemia with Hgb <8 g/dL requiring transfusion
4	1 (4)	Febrile neutropenia/sepsis requiring ICU admission
5	0 (0)	Death

Table 3. Tumor staging for patients who underwent NAC versus No NAC and radical nephroureterectomy with eGFR >50 mL/min/1.73 m^2

T Stage	N Stage	NAC (n = 25)	No NAC (n = 36)	P
Noninvasive (<T1N0)		**13**	**8**	***.082***
T0	N0	1	1	
	Nx	1		
Ta	N0	7	2	
	Nx	1	2	
Tis	N0	3	3	
	Nx	-	-	
Invasive (≥T1N0)		**12**	**28**	***.002***
T1	N0	5	3	
	N1	-	-	
	N2	1	-	
	Nx	1	2	
Muscle invasive (≥T2N0)		**5**	**23**	***.001***
T2	N0	1	2	
	N1	-	1	
	Nx	-	1	
Nonorgan confined (≥T3N0)		**4**	**19**	.001
T3	N0	2	5	
	N1	1	1	
	N2	1	2	
	Nx	-	9	
T4	N0	-	1	
	Nx	-	1	

NAC, neoadjuvant chemotherapy; No NAC, no neoadjuvant chemotherapy.

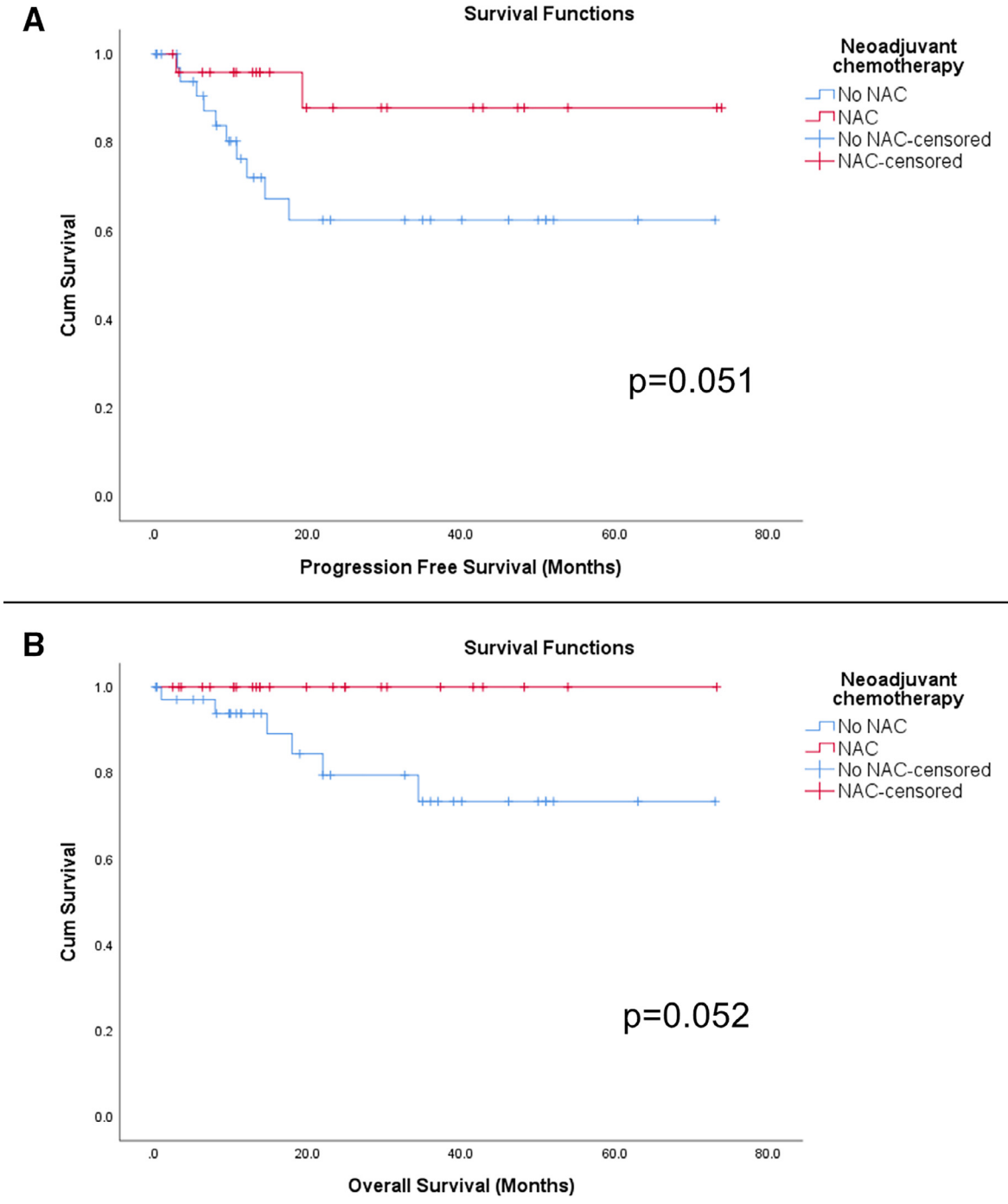

Figure 1. Effect of neoadjuvant chemotherapy on progression free survival and overall survival. Patients who received neoadjuvant chemotherapy prior to nephroureterectomy have significantly longer progression free survival compared to patients that proceeded directly to surgery, $P = .051$ (**A**) and increased overall survival, $P = .052$ (**B**).(Color version available online.)

utilization of NAC vary widely, likely due to multiple underlying factors. In addition, given the patient population, a high percentage of patients eligible for NAC based on renal function were also excluded due to other comorbidities, likely in part due to the older population of patients affected by UTUC compared to BC.

This study also confirms a few important points regarding NAC usage. None of the patients who underwent NAC in our cohort had progression of disease while receiving NAC or failed to proceed to NU in a timely fashion, with an average of 4.3 months from initiation of NAC to surgery. Although there are few studies examining the timing of NAC prior to surgery, our study shows that with proper patient selection, NAC can be implemented in a systematic fashion without affecting operative planning in these patients. While recent data has

demonstrated that AC improves PFS,[21] the renal function in this population of patients are severely affected after NU[22] and the ability to receive AC is often limited. In fact, in our cohort, the average eGFR after NU was only 46.0 mL/min/1.73 m^2, representing a drop in eGFR of around 30%, making the majority of our patients ineligible for cisplatin based AC.

The limitations of the current study include the inherent inaccuracies of initial clinical staging in UTUC secondary to less definitive biopsy methods, which impacts our ability to determine the true clinical stage of the disease prior to treatment and control for this factor in the analysis. Patients also did not undergo repeat endoscopic biopsy after NAC prior to NU, and evaluations of CR to NAC were based solely on cross-sectional imaging. In addition, 30% of the patients in the study did not undergo lymph node dissection and when lymph node dissection was performed, the extent and template used for the dissection were left to the discretion of the surgeon and likely affects the homogeneity of the lymph node dissection. Given the contemporary nature of our cohort, the median duration of follow-up is relatively short at less than 2 years, likely leading to the higher OS numbers seen in our study compared to prior reported 5-year OS survival data.[14,19] In addition, our control cohort contains patients who are eligible for NAC based on renal function but did not receive NAC secondary to medical comorbidities. The effect of these medical comorbidities on OS in the control cohort is likely difficulty to quantify, but also demonstrates the inherent difficulties of offering NAC to an older patient population and the necessity for selecting patients who receive NAC. Finally, our analysis is retrospective in nature and patients who received NAC were significantly younger compared to the control group, which partially affects our ability to accurately determine the effect of NAC on OS.

Despite multiple retrospective trials including ours demonstrating pathologic downstaging with NAC, further prospective and ideally randomized trials are necessary to further validate these findings and promote increasing adoption of NAC for HG UTUC prior to NU. Recently presented results from a single-arm phase II trial addressing this question [Eastern Cooperative Oncology Group − American Collect of Radiology Imaging Network 8141, NCT02412670] support the notion of NAC with 14% pathologic complete response in patients with HG UTUC with long-term results pending.[17] However, as NAC has been historically underutilized in the treatment of UTUC and given the relative rarity of UTUC compared to BC, these are significant limiting factor in patient accrual for prospective trials. Indeed, one prospective trial required 46.5 months to reach enrollment of 10 patients with HG UTUC,[23] another prospective trial required 40 months to enroll 16 patients with HG UTUC,[13] and other trials were terminated early secondary to low participant enrollment (NCT01663285). Given the existing issues with achieving sufficient patient numbers that are powered to detect differences in OS and PFS, we have joined an international multi-institutional collaboration to help address this question. In the meantime, we hope that the results of the current study add to the growing literature that patients with high-grade UTUC should be considered for NAC prior to NU. To that end, a more structured referral program where all patients with UTUC are subsequently referred to medical oncology for evaluation of NAC would likely increase rates of adoption of NAC for all eligible patients.

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EDITORIAL COMMENT

Despite improvements in cross-sectional imaging and endoscopy, survival rates for patients with high-grade upper tract urothelial carcinoma (UTUC) have not improved in 2 decades. Nearly half of all patients with high-risk features die within 5 years, and patients with locally-advanced disease have less than a 2-year median survival.[1,2] Given the persistently poor prognosis for patients with high-risk UTUC, a shift in treatment paradigm is needed.[3]

In this issue of *Urology*, the authors present retrospective data from 2 institutions regarding the use of neoadjuvant chemotherapy prior to radical nephroureterectomy for patients with high-risk UTUC. They found significant differences between the NAC and control group (No NAC) on final pathology, with 64% of patients in the control having ≥pT2 disease compared to 20% in the NAC group (P = .001). Notably, patients in the NAC group also had significantly lower rates of nonorgan confined disease (P = .001), although there was considerable variation in the use and extent of lymph node dissection during radical nephroureterectomy. Furthermore, while the median duration of follow-up was less than 2 years, there are promising survival benefits from use of NAC: patients in who received NAC had longer rates of progression free survival (P = .051) and overall survival (P = .052).

There are several unique challenges inherent to UTUC that make it difficult to determine the true benefit of neoadjuvant chemotherapy prior to extirpative surgery. UTUC is a rare (5%-8% of all urothelial cancers) and often fatal disease, which limits our ability to perform prospective, randomized studies. There are also significant limitations in the clinical staging of UTUC due to technical challenges in obtaining sufficient tissue endoscopically to diagnose muscle-invasive or locally advanced disease, and in limitations of cross-sectional imaging to accurately stage patients clinically, especially in those with pre-existing chronic kidney disease who cannot receive intravenous contrast.[3,4] For these reasons, it may be difficult to measure the true rate of pathologic downstaging through the use of NAC. As a result, we eagerly await the result of future randomized trials such as ECOG-ACRIN 8141 to help determine the benefits of NAC and to validate the current, limited number of retrospective studies on the topic.

In addition to future randomized clinical studies, growing research on the genomic characterization of UTUC will provide critical data on determining which patients would benefit most from NAC. Recent studies using targeted DNA sequencing have identified notable differences in somatic mutations between UTUC and urothelial carcinoma of the bladder and have also identified potential targets of therapy in the future.[5-7] Moss et al, for example, found that UTUC has a high prevalence of mutations of the gene FGFR3[5]; patients found to have high rates of microsatellite/genomic instability or FGFR3 mutations may consequently present a subset of patients who may benefit most from chemotherapy or immune checkpoint inhibitors that target the FGFR3 pathway in the future.

Thus, this well-written study by Huang et al provides a contribution to the important but limited body of evidence evaluating the use of NAC for patients with high-risk UTUC. Until prospective, randomized trials and molecular research clearly define a treatment paradigm for patients with this aggressive disease entity, it is essential we continue efforts to evaluate ways to improve the survival of patients with UTUC through multi-institutional data such as the one presented.

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AUTHOR REPLY

We agree wholeheartedly with the editorial comments regarding the significant unmet need in the management of upper tract urothelial carcinoma (UTUC). Despite therapeutic advances such as checkpoint inhibitors for urothelial carcinoma and advances in disease characterization on a genomic level, UTUC continues to pose a diagnostic and therapeutic challenge. Given the rarity of this disease, as

mentioned by the reviewer, we need to rely on multi-institutional collaborations and retrospective studies to help us establish standards of care and protocols for the administration of systemic therapy and extirpative surgery.

While we await the results of randomized trials such as Eastern Cooperative Oncology Group − American Collect of Radiology Imaging Network 8141,[1] we believe it is important to critically and carefully incorporate the limited but growing body of evidence supporting the use of chemotherapeutic agents for the management of UTUC. Given the demonstrated efficacy of adjuvant chemotherapy (AC) as reported in the POUT trial,[2] and the significant number of patients *ineligible* for AC following nephroureterectomy, we strongly believe that NAC should be considered prior to nephroureterectomy in patients with high-grade UTUC. In addition to demonstrating efficacy of NAC in our study, we feel that it is important to highlight the fact that NAC was well-tolerated in our cohort of patients. In addition, none of the patients progressed while receiving NAC or were precluded from proceeding for extirpative surgery in a timely fashion.

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