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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 \geq 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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