Chemotherapy increases survival and downstaging of upper tract urothelial cancer

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Introduction: *To evaluate the overall survival and pathologic downstaging effect of neoadjuvant chemotherapy for upper tract urothelial cell carcinoma.*
Materials and methods: *The National Cancer Database (NCDB) was queried for patients with stage II-IV upper tract urothelial cell carcinoma undergoing definitive surgical resection (nephroureterectomy) from 2004-2015. Patients with metastatic disease were excluded. Cohorts were stratified by receipt of neoadjuvant chemotherapy (NAC). Kaplan-Meier analysis and Cox regression were used to evaluate overall survival. Logistic regression was used to predict the odds of pathologic downstaging to non-invasive disease (< pT2). Propensity score matched analysis was performed between groups.*
Results: *A total of 3634 patients were identified with non-metastatic stage II-IV disease undergoing surgical resection; 3364 received no chemotherapy and 270 received NAC. Patients undergoing NAC had a 10.9% rate of downstaging to non-invasive disease (OR 6.35, $p < 0.001$). Moreover, on Kaplan-Meier analysis, median survival was 27.3 months and 44.8 months for no chemotherapy versus NAC, respectively (log-rank, $p = 0.001$). Cox regression for death also revealed benefits for receiving NAC (HR 0.67, $p < 0.001$). Findings were confirmed on propensity score matching (532 matched patients). After matching, Cox regression for death noted improvement with neoadjuvant as compared to no chemotherapy (HR 0.61, $p < 0.001$).*
Conclusion: *Neoadjuvant chemotherapy increases likelihood of downstaging to non-invasive disease in patients with upper tract urothelial cell carcinoma. Chemotherapy also provides an overall survival benefit in patients undergoing nephroureterectomy.*

Key Words: transitional cell carcinoma, neoadjuvant therapy, survival

Introduction

Upper tract urothelial cancer (UTUC) is an uncommon malignancy, comprising only 5%-10% of all urothelial tumors.[1] Due to this low incidence of disease, randomized clinical trials to guide specific treatment modalities for UTUC are lacking. Currently for non-metastatic UTUC, histologic grade, tumor location, and clinical stage guide therapeutic interventions; however, all curative treatment pathways involve surgical resection of some nature.[2] For patients with invasive disease (≥ pT2), radical nephroureterectomy is typically the standard surgical procedure, while the incorporation and timing of chemotherapy is still a topic of research and debate.

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The National Comprehensive Cancer Network recommends consideration of adjuvant chemotherapy (AC) for ≥ pT2 disease, while reserving the discussion of neoadjuvant chemotherapy (NAC) for those with higher grade or stage.[2] These recommendations are, in part, extrapolated from treatment of urothelial cancer of the bladder.[1] In the setting of urothelial cancer of the bladder, meta-analysis of randomized trial data shows an overall survival (OS) benefit associated with NAC, as well as significant odds of downstaging disease to a non-invasive status.[3] On the other hand, studies investigating chemotherapy in the setting of UTUC are derived from small retrospective reviews or institutional series.[1] Goldberg et al has suggested that patients receiving perioperative chemotherapy have increased cancer specific mortality.[4] Ultimately, the value of perioperative chemotherapy in UTUC remains undetermined.

We interrogated the National Cancer Database for patients with invasive, non-metastatic UTUC treated by radical nephroureterectomy to elucidate the survival effects of chemotherapy. We postulated that the use of NAC would improve OS outcomes and increase the chance of downstaging after surgical resection.

Materials and methods

Data source

Data for this analysis was derived from the Commission on Cancer's National Cancer Data Base (NCDB) Participant User File for kidney cancer from 2004 to 2015. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB is a national cancer outcomes dataset that includes input from over 1500 Commission on Cancer-accredited centers in the United States. This data includes all cancer patients treated at participating Commission on Cancer-accredited institutions and is estimated to capture over 70% of new cancer cases in the United States. Standardized coding definitions are utilized, and the data is freely available to participating institutions after application for projects are accepted by the NCDB. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Study population

The NCDB was queried for patients with UTUC, including site specific histology codes, between 2004 and 2015. Patients were included with non-metastatic, invasive disease (cT2-4 and M0) that underwent definitive nephroureterectomy. Node positive disease was allowed. Patients undergoing endoscopic management or segmental ureterectomy were not included. Patients were further selected according to the receipt of chemotherapy (no chemotherapy or neoadjuvant chemotherapy). Patients had no previously malignancy diagnosis and were diagnosed with renal pelvis or ureteral tumor location, although the location of the tumor is not specified within the NCDB. We identified 3634 patients age ≥ 18 years old meeting inclusion criteria.

Patient demographic variables included age, race, sex, Charlson comorbidity index, income status, treatment facility volume, and insurance status. Treatment facility type was categorized as low volume or high volume. Treatment facilities that accumulated 500 or more newly diagnosed cancer cases per year were considered to be high volume, while facilities with less than 500 were labeled low volume. Disease and operative outcomes included histologic nuclear grade, days from diagnosis to surgery, clinical stage, pathologic stage, length of hospital stay, length of follow up, and all-cause mortality. Pathologic downstaging was categorized as < pT2.

Statistical analysis and outcomes measures

Our primary outcomes were pathologic downstaging of disease after surgery and overall survival, stratified by receipt of neoadjuvant chemotherapy. One-way ANOVA was performed for continuous variables, while Fischer's exact or Pearson chi-square test was used for categorical variables. Multivariable analysis was performed using logistic regression to identify risk factors associated with pathologic downstaging. Cox regression analysis was performed for overall survival. Kaplan-Meier analysis was performed for survival outcome by receipt of chemotherapy.

To provide further balance between two groups, we performed propensity score matching (PSM) on a subset of patients. For a binary treatment indicator of chemotherapy receipt (neoadjuvant versus none), covariates included age, race, Charlson score, clinical stage, treatment facility volume, and nuclear grade. Matching was performed 1:1 between groups with logistic regression estimation and a nearest neighbor matching algorithm. Matching was achieved for 532 patients (266 per cohort) in this subset. Analysis was performed with SPSS, version 23 (SPSS Inc., Chicago, IL, USA), and R, version 23 extension (Vienna, Austria) with $p < 0.05$ denoting statistical significance.

Results

Patient demographics and tumor characteristics

Patient demographics and tumor characteristics of the 3634 patients with UTUC undergoing radical nephroureterectomy can be found in Table 1. A total of 3364 did not receive perioperative chemotherapy, while 270 received NAC. The average age of the cohort was 73.4 ± 10.6 years. The mean age of those undergoing no chemotherapy was 73.9 ± 10.6 while those choosing NAC on average were over six years younger ($p < 0.001$). Those forgoing chemotherapeutic treatment were more likely to have comorbidities as evidenced by higher Charlson scores in comparison to those undergoing NAC. Variables such as race, gender, and income status were not significantly different between the treatment groups. Meanwhile, those receiving neoadjuvant chemotherapy were more likely to be privately insured and less likely to be Medicare patients, relative to those choosing only surgical therapy. Notably those choosing no chemotherapy were more likely to receive treatment at low volume centers ($p < 0.001$).

Histology and survival outcomes

Table 2 lists values pertaining to the histology and survival outcomes of patients evaluated. There was a significant difference in time from diagnosis to surgery date, with those receiving NAC waiting an average of 139 days from diagnosis (None 30.5, NAC 139.9, $p < 0.001$). NAC patient had a higher rate of preoperative cT4 disease (58.9% for NAC versus 16.7% for none; $p < 0.001$). The rate of pathologic downstaging to non-invasive disease was higher for those receiving NAC (10.7%, versus 1.7%, $p < 0.001$). Additionally, patients receiving NAC had a decreased rate of mortality compared to no chemotherapy (40.0% versus 55.1%, respectively, $p < 0.001$).

Logistic regression and downstaging

Logistical regression for downstaging was performed including age, Charlson score, clinical stage, receipt of neoadjuvant chemotherapy, and nuclear grade, Table 3. Increasing age was associated with decreased odds of downstaging disease after surgery (OR 0.98, $p = 0.03$). Using clinical stage cT4 as reference, cT2 disease was associated with increased likelihood of downstaging (OR 2.06, $p = 0.021$) while cT3 disease had no effect.

					Propensity Score Matched Analysis			
Variable	**All (n = 3634)**	**None (n = 3364)**	**NAC (n = 270)**	**p value**	**All (n = 532)**	**None (n = 266)**	**NAC (n = 266)**	**p value**
Mean age	73.4 ± 10.6	73.9 ± 10.6	67.2 ± 9.4	< 0.001	67.6 ± 9.9	68.0 ± 10.5	67.2 ± 9.3	0.390
Race				0.938				0.646
White	3345 (92.0%)	3095 (92.0%)	250 (92.6%)		490 (92.1%)	244 (91.7%)	246 (92.5%)	
Black	162 (4.5%)	151 (4.5%)	11 (4.1%)		26 (4.9%)	15 (5.6%)	11 (4.1%)	
Other	127 (3.5%)	118 (3.5%)	34 (3.3%)		16 (3.0%)	7 (2.6%)	9 (3.4%)	
Male	2117 (58.3%)	1960 (58.3%)	157 (58.1%)	0.970	310 (58.3%)	156 (58.6%)	154 (57.9%)	0.930
Charlson				0.006				0.318
0	2486 (68.4%)	2278 (67.7%)	208 (77.0%)		412 (77.4%)	207 (77.8%)	205 (77.1%)	
1	833 (22.9%)	782 (23.2%)	51 (18.9%)		105 (19.7%)	55 (20.7%)	50 (18.8%)	
2	233 (6.4%)	225 (6.7%)	8 (3.0%)		11 (2.1%)	3 (1.1%)	8 (3.0%)	
3+	82 (2.3%)	79 (2.3%)	3 (1.1%)		4 (0.8%)	1 (0.4%)	3 (1.1%)	
Income status				0.141				0.582
< $38,000	534 (14.9%)	501 (15.1%)	33 (12.4%)		65 (12.2%)	32 (12.0%)	33 (12.4%)	
$38,000-47,999	846 (23.7%)	787 (23.8%)	59 (22.2%)		111 (20.9%)	52 (19.5%)	59 (22.2%)	
$48,000-62,999	982 (27.5%)	915 (27.7%)	67 (25.2%)		148 (27.8%)	81 (30.5%)	67 (25.2%)	
$63,000+	1211 (33.9%)	1104 (33.4%)	107 (40.2%)		208 (39.1%)	101 (38.0%)	107 (40.2%)	
Insurance status				< 0.001				0.374
Uninsured	63 (1.7%)	59 (1.8%)	4 (1.5%)		11 (2.1%)	8 (3.0%)	3 (1.1%)	
Private	795 (21.9%)	703 (20.9%)	92 (34.1%)		174 (32.7%)	83 (31.2%)	91 (34.2%)	
Medicaid	97 (2.7%)	91 (2.7%)	6 (2.2%)		15 (2.8%)	9 (3.4%)	6 (2.3%)	
Medicare	2585 (71.1%)	2432 (72.3%)	153 (56.7%)		305 (57.3%)	154 (57.9%)	151 (56.8%)	
Other Govt	24 (0.7%)	23 (0.7%)	1 (0.4%)		4 (0.8%)	3 (1.1%)	1 (0.4%)	
Unknown	70 (1.9%)	56 (1.7%)	14 (5.2%)		23 (4.3%)	9 (3.4%)	14 (5.3%)	
Facility type				< 0.001				1.000
Low volume	695 (19.1%)	666 (19.8%)	29 (10.7%)		58 (10.9%)	29 (10.9%)	29 (10.9%)	

Table 1. Patient demographics and clinical tumor characteristics.

					Propensity Score Matched Analysis			
Variable	**All (n = 3634)**	**None (n = 3364)**	**NAC (n = 270)**	**p value**	**All (n = 532)**	**None (n = 266)**	**NAC (n = 266)**	**p value**
High grade	2744 (75.5%)	2552 (75.9%)	192 (71.1%)	0.090	406 (76.3%)	216 (81.2%)	190 (71.4%)	0.011
Days to surgery	41.2 ± 59.3	30.5 ± 45.5	139.9 ± 82.3	< 0.001	94.0 ± 87.3	30.3 ± 41.4	156.8 ± 74.1	< 0.001
Clinical stage				< 0.001				0.251
cT2	839 (23.1%)	813 (24.2%)	26 (9.6%)		46 (8.6%)	20 (7.5%)	26 (9.8%)	
cT3	2073 (57.0%)	1988 (59.1%)	85 (31.3%)		183 (34.4%)	100 (37.6%)	83 (31.2%)	
cT4	722 (19.9%)	563 (16.7%)	159 (58.9%)		303 (57.0%)	146 (54.9%)	157 (59.0%)	
cN+	517 (14.2%)	364 (10.8%)	153 (56.7%)	< 0.001	301 (56.6%)	150 (56.4%)	151 (56.8%)	0.930
Pathologic stage				< 0.001				< 0.001
< pT2	87 (2.4%)	58 (1.7%)	29 (10.7%)	< 0.001	39 (7.3%)	10 (3.8%)	29 (10.9%)	
pT2	392 (10.8%)	375 (11.1%)	17 (6.3%)		24 (4.5%)	7 (2.6%)	17 (6.4%)	
pT3	1407 (38.7%)	1358 (40.4%)	49 (18.1%)		132 (24.8%)	83 (31.2%)	49 (18.4%)	
pT4	606 (16.7%)	493 (14.7%)	113 (41.9%)		219 (41.2%)	109 (41.0%)	110 (41.4%)	
pTx	1142 (31.4%)	1080 (32.1%)	62 (23.0%)		118 (22.2%)	57 (21.4%)	61 (22.9%)	
pN+	399 (11.0%)	308 (9.2%)	91 (33.7%)	< 0.001	189 (35.5%)	100 (37.6%)	89 (33.5%)	0.365
Length of stay	5.9 ± 7.3	5.9 ± 7.1	6.1 ± 9.9	0.611	5.7 ± 7.9	5.4 ± 5.3	6.1 ± 10.0	0.305
Readmission within 30 days	156 (4.3%)	144 (4.3%)	12 (4.4%)	0.876	26 (4.9%)	15 (5.6%)	11 (4.1%)	0.547
Length of follow up (months)	33.1 ± 28.4	33.2 ± 28.8	32.0 ± 22.8	0.557	31.2 ± 25.8	30.1 ± 28.1	32.5 ± 22.8	0.339
Mortality	1963 (54.0%)	1855 (55.1%)	108 (40.0%)	< 0.001	262 (49.2%)	158 (59.4%)	104 (39.1%)	< 0.001
Within 30 days	101 (3.1%)	98 (3.2%)	3 (1.4%)	0.085	12 (2.7%)	10 (4.1%)	2 (1.0%)	0.036
Within 90 days	278 (8.4%)	271 (8.8%)	7 (3.3%)	< 0.001	42 (9.3%)	37 (15.4%)	5 (2.4%)	< 0.001

Table 2. Histology and survival outcomes.

					Propensity Score Matched Analysis			
Variable	OR	95% CI low	95% CI high	P value	OR	95% CI low	95% CI high	p value
Age	**.978**	**.959**	**.998**	**.030**	.976	.944	1.010	.350
Charlson score (0 ref)					1.483	.672	3.274	.329
1	.813	.461	1.435	.476	1.029	.120	8.799	.979
2	1.120	.437	2.872	.813	6.813	.653	71.043	.109
3+	1.304	.307	5.546	.719				.850
Clinical stage (cT4 ref)					1.401	.438	4.481	.570
cT2	**2.063**	**1.117**	**3.811**	**.021**	1.039	.496	2.176	.919
cT3	.597	.323	1.104	.100	.976	.944	1.010	.350
Neoadjuvant chemo	**6.350**	**3.617**	**11.149**	**< 0.001**	**2.694**	**1.261**	**5.754**	**.010**
Low nuclear grade	**2.595**	**1.672**	**4.026**	**< 0.001**	**3.605**	**1.810**	**7.180**	**< 0.001**

Table 3. Logistic regression for pathologic downstaging.

					Propensity Score Matched Analysis			
Variable	HR	95% CI low	95% CI high	p value	HR	95% CI low	95% CI high	p value
Age	**1.042**	**1.037**	**1.047**	**< 0.001**	1.029	1.015	1.043	.941
Race (white ref)								
Black	1.188	.961	1.468	.111	1.124	.627	2.017	.694
Other	.835	.651	1.070	.155	.724	.356	1.473	.374
Charlson score (0 ref)								
1	1.084	.975	1.205	.136	1.076	.795	1.457	.634
2	**1.499**	**1.266**	**1.776**	**< 0.001**	1.037	.382	2.820	.942
3+	**1.805**	**1.386**	**2.350**	**< 0.001**	1.294	.408	4.109	.662
Clinical stage (cT2 ref)								
cT3	**1.394**	**1.239**	**1.569**	**< 0.001**	1.313	.764	2.257	.324
cT4	**3.167**	**2.755**	**3.641**	**< 0.001**	**2.548**	**1.520**	**4.271**	**< 0.001**
Neoadjuvant chemo	**.668**	**.544**	**.820**	**< 0.001**	**.609**	**.472**	**.784**	**< 0.001**
High nuclear grade	**1.236**	**1.107**	**1.381**	**< 0.001**	1.136	.833	1.550	.420

Table 4. Cox regression for death.

Low nuclear grade, on the other hand, was associated with downstaging (OR 2.59, p < 0.001). Furthermore, NAC was the single greatest predictor of downstaging disease (OR 6.35, p < 0.001).

Cox Regression and death

Table 4 lists values of our Cox regression analysis for death. Increasing age was associated with increased risk of death. Charlson scores of 2 and 3 had increased mortality (p < 0.001) whereas Charlson score of 1 and race were non-contributory. Similarly, increasing clinical stage (relative to cT2) and high nuclear grade were found to be statistically significant detriments to survival. Receipt of neoadjuvant chemotherapy was the only factor that decreased the hazard of death (HR 0.66, p < 0.001).

Kaplan-Meier survival analysis

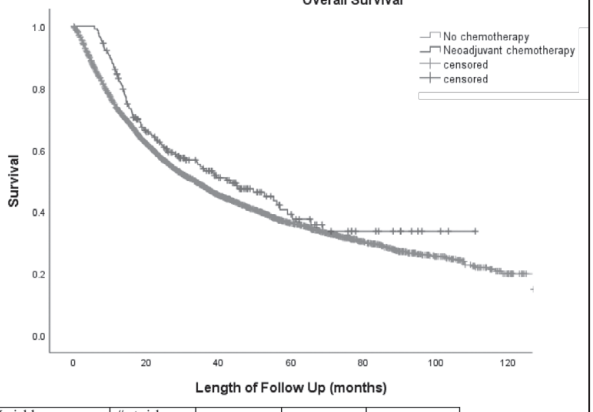
Figure 1 depicts the Kaplan-Meier survival analysis stratified by chemotherapy status (log-rank p < 0.001). Time zero represents the date of diagnosis. Median OS in months was 33.35 for no perioperative chemotherapy and 43.3 months for NAC. The 2 and 5 year OS for patients undergoing no chemotherapy and NAC were 57.5% and 36.3%, and 61.9% and 39.1% respectively.

Propensity score matching

Propensity score matched cohort descriptors are noted in table one and two. NAC and no chemotherapy cohorts were well balanced with no difference in age, race, gender, Charlson score, income level, insurance status, facility volume, nuclear grade, or clinical stage.

Variable	Median OS	95% CI Low	95% CI High	2 year OS	5 year OS
No chemotherapy	33.35 months	30.80	35.90	57.5% ± 0.9	36.3% ± 1.0
Neoadjuvant	43.30 months	30.05	56.55	61.9% ± 3.4	39.1% ± 4.4

Log rank p=0.041

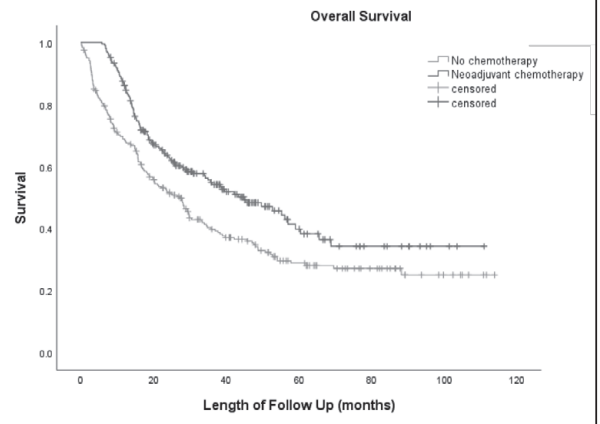


Variable	# at risk			
No chemotherapy	3081	1561	568	20
Neoadjuvant	214	112	26	0
Time	0 months	24 months	60 months	120 months

Figure 1. Kaplan Meier overall survival analysis.

Variable	Median OS	95% CI Low	95% CI High	2 year OS	5 year OS
No chemotherapy	27.3 months	21.5	33.1	51.7% ± 3.3	28.9% ± 3.3
Neoadjuvant	44.8 months	31.2	58.4	63.1% ± 3.4	39.9% ± 4.5

Log rank p=0.001



Variable	# at risk			
No chemotherapy	241	113	38	0
Neoadjuvant	210	112	26	0
Time	0 months	24 months	60 months	120 months

Figure 2. Kaplan Meier overall survival analysis.

Of note, the unadjusted rate of downstaging disease was highest for NAC (10.9% versus 3.8%, p < 0.001) and the rate of mortality was lower for NAC (39.1% versus 59.4%, p < 0.001).

On multivariate analysis, improvements were again seen with NAC, Table 3 and 4. The logistic regression for downstaging showed a significant effect associated with low nuclear grade (OR 3.61, p < 0.001) and NAC (OR 2.69, p = 0.01). Additionally, the Cox regression for death was repeated after PSM, noting that cT4 disease (HR 2.55, p < 0.001) significantly increased the risk of mortality. Notably, the only risk factor for decreased mortality was NAC (HR 0.61, p < 0.001). On KM analysis in Figure 2, median OS was improved for NAC (44.8 versus 27.3 months, log-rank p = 0.001; Figure 2).

Discussion

For invasive, non-metastatic UTUC we demonstrate an overall survival benefit and increased odds of tumor downstaging when treated with NAC. This was in spite of an expected delay in surgical intervention, associated with NAC. After propensity score matching, the downstaging and survival benefits of NAC were maintained. This evidence provides further credence to existing data regarding the increasing use of perioperative chemotherapy, particularly for NAC, and should encourage clinicians to pursue NAC when clinically feasible.[3]

Despite the encouraging results associated with perioperative systemic treatment and data reporting

the increased utilization of NAC, it is estimated that only 16% of patients with non-metastatic disease are receiving chemotherapy of any nature.[4,5] The current data landscape of perioperative chemotherapy in the setting of UTUC is dominated by small, single institution retrospective studies or extrapolated data from urothelial bladder cancer. Existing guidelines admit as much when providing recommendations for treatment.[1,2] Generalization of the existing urothelial bladder cancer evidence to UTUC may be perilous, as the two disease processes are anatomically, biologically and molecularly distinct diseases.[6] However, although strong evidence is lacking, these retrospective studies and our own analysis provide promising oncological outcomes.

A recent systematic review and meta-analysis performed by Leow and associates reviewed the current evidence for NAC in the setting of UTUC.[7] Compiling five retrospective and three prospective studies, they substantiated an increased tendency to downstage (14%) disease after surgical resection and 5 year overall survival of 13%-80% when using NAC.[8-10] When combined, these studies examined 154 patient outcomes, and only 89 of those patients are evaluated for overall survival data. Liao et al added to these results by examining 240 patients with UTUC, of which 32 had NAC and 208 had no chemotherapy. Pathologic T stage was significantly lower for those receiving NAC with a complete remission rate of 9.4%.[11] Our NCDB analysis reviewed 5 year overall survival for nearly twice as many patients and notes a similar rate of pathologic downstaging (10.7% for NAC before PSM and 10.9% after PSM). Our analysis reveals median overall survival of 43.3 and 33.3 months for patients receiving NAC and no chemotherapy, respectively. The larger cohort and analysis of a national registry increases the generalizability of our results. Taken together, our study and the results of previous analyses add to the ongoing discussion regarding benefits of chemotherapy for UTUC. While NAC may not be feasible or warranted for all patients with UTUC, the current data available suggests well selected patients may be downstaged to non-invasive disease and can derive associated long term survival benefits.

More recent retrospective studies have been focusing on specific chemotherapy regimens. Kubota et al preformed a multi-center, retrospective review and exhibited improved cancer specific survival and a predisposition for downstaging locally advanced UTUC (cT3-T4, N+ disease) in those receiving platinum-based NAC.[12] The NAC cohort predominantly received two cycles of either gemcitabine + carboplatin therapy (75%) or gemcitabine + cisplatin (21%) therapy. Within this analysis of 234 patients, recurrence-free and cancer-specific survival was improved for NAC; however, the OS benefit was not statistically significant. Similarly, Hosogoe and associates corroborated improved cancer specific survival (HR 0.37, 95% CI 0.15–0.92; $p = 0.031$) for those receiving platinum based NAC, however they also noted a non-significant OS benefit on multivariable analysis.[13] Our results echo these conclusions by showing similar findings with regards to downstaging of disease for NAC (HR 7.98, $p < 0.001$) and noting statistically significant improvements in OS; however, the NCDB does not allow for stratification of chemotherapy agents or cancer-specific survival outcomes. Additionally, our analysis did identify significant OS benefits, in contrast to these previous retrospective reviews. This likely reflects selection bias associated with a retrospective tumor registry. These differing results and lack of knowledge regarding chemotherapy regimen with the NCDB increase the need for a randomized clinical trial to further evaluate specific platinum-based regimens.

Lack of prospective and randomized data for treatment of UTUC is linked to the rarity of the disease and difficulties with enrollment; however, future studies are ongoing. Recently the POUT trial (Peri-Operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer), a randomized control trial examining the effects of AC in ≥ T2M0 UTUC, terminated enrollment early due to improved outcomes favoring AC. After four cycles of gemcitabine-cisplatin, patients were found to have 2 year disease-free survival of 70% compared to 51% for those undergoing surveillance after nephroureterectomy.[14] Studies investigating the effects of AC on oncological outcomes are difficult to perform due to decreased renal function post-operatively. Moreover, postoperative complications requiring a prolonged treatment course may significantly delay or even completely exclude a patient from AC. For that reason, exploring the benefits of NAC is paramount. Similar studies evaluating disease free survival after platinum based chemotherapy in the preoperative setting are ongoing.[15] These encouraging results foreshadow the possibility of trial-based UTUC guidelines, including recommendations for perioperative chemotherapy, with associated better oncological outcomes. Our findings provide further support to the use of perioperative chemotherapy with invasive disease, as we noted an improved OS associated with NAC on Cox regression. Ultimately, the use of NAC appears to carry survival benefit in well selected patients who are appropriate candidates.

Retrospective reviews of large databases, such as ours, carry with them inherent limitations. First and foremost, its retrospective nature allows only proof of association and is limited by selection bias. Future

prospective and randomized control trials will be needed to validate our data for real world application. Furthermore, there is a wide range of providers and clinical settings within the NCDB registry; thus, surgery and chemotherapy treatment plans are not standardized. We also noted that on average the patient sub-population receiving NAC were younger with less comorbidity (Charlson Score 0) than in the other groups. These differing patient characteristics could play a part in the improved survival outcomes seen in NAC; however, multivariable analysis and PSM was used, in an attempt to mitigate these effects. There is also a lack of data regarding how many patients receiving NAC where unable to complete the number of planned cycles or never were able to receive definitive surgery. Finally, as discussed, recent publications have been attempting to discern the best chemotherapeutic regimen. Unfortunately, the NCDB does not identify specific agents utilized. Still, as one of the largest retrospective review to date examining oncologic outcomes, our study is able to affirm the need for additional research in NAC use in the setting of non-metastatic UTUC.

Conclusion

There is a modest overall survival benefit in patients being treated with NAC when combined with surgical extirpation for non-metastatic UTUC. Furthermore, treatment with NAC, along with lower grade or clinical stage disease, increases the likelihood of downstaging of disease after surgical intervention. Thus, chemotherapy should be considered part of multi-modal treatment for those diagnosed with non-metastatic UTUC when clinically feasible. □

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