The effect of tumor location on overall survival for pT2–4 bladder and upper tract urothelial carcinoma following radical surgery

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Abstract

Introduction: Historically, staging and treatment for upper tract urothelial carcinoma were extrapolated from bladder urothelial carcinoma literature. However, embryological, genetic, and anatomical differences exist between them. We sought to explore the relationship between location of urothelial cancer and overall survival (OS).
Methods: Data was culled from the National Cancer Database from 2004–2015. Patients with pT2–pT4 treated with definitive surgery were included; those with metastatic disease or who received neoadjuvant or adjuvant treatment were excluded. Patients were stratified by tumor location and pathological stage. The primary outcome was OS. Secondary outcomes were predictors of mortality in each pT stage stratum.
Results: A total of 11 330 patients with bladder, 954 patients with ureteral, and 1943 patients with renal pelvis urothelial carcinoma were analyzed. Mean followup was 43.3, 39.4, and 41.4 months for bladder, ureteral, and renal pelvis, respectively. On univariable analysis, ureteral pT2 was associated with worse OS compared to both bladder (61.3 vs. 80.4 months, p=0.007) and renal pelvis (61.3 vs. 80.5 months, p=0.014). Renal pelvis pT3 was associated with improved OS compared to both bladder (42.5 vs. 28.6 months, p=0.003) and ureteral (42.5 vs. 25.7 months, p<0.001). Renal pelvis pT4 had decreased survival compared to bladder (11.4 vs. 17.7 months, p<0.001). On multivariable Cox regression, only renal pelvis pT3 was associated with a 20% decreased risk of mortality compared to bladder pT3 (hazard ratio 0.80, 95% confidence interval 0.72–0.88, p<0.001).
Conclusions: Renal pelvis pT3 is associated with lower mortality. Mutational and embryological differences may play a role in this disparity.

Introduction

Carcinoma of the upper tract accounts for a small minority of urothelial carcinoma (UC) — the incidence is approximately 5–10% of newly diagnosed cases. Like other orphan diseases, there is a relative paucity of data on upper tract urothelial carcinoma (UTUC). As a result, clinical decision-making for UTUC has been largely extrapolated from the existing literature on UC of the bladder. This is reflected in the bundling of guidelines for bladder and upper tract UC by both the National Comprehensive Cancer Network and the American Urological Association. Presently, the European Association of Urology (EAU) is the only urological association with guideline statements tailored specifically to UTUC.[1]

Tumor stage and grade are widely accepted as predictors of oncological outcome, with contemporary studies suggesting that differences in UTUC outcomes are attributable to these factors.[1-3] Recently, several publications have disputed that location has an impact on prognosis.[4-10] Nevertheless, genetic analyses have shown differences in the mutational profile between UTUC and bladder cancer, suggesting differences in the nature of the urothelium between the upper tract and bladder.[11-13] In fact, the progenitors of bladder and upper tract urothelium are entirely different — bladder is derived from mesoderm whereas the upper tract is derived from endoderm.[1] We hypothesize that this foundational difference leads to heterogeneous urothelium. We thus used the National Cancer Database (NCDB) to determine the prognostic significance of UC location on survival.

Methods

Patient population

The NCDB is a nationwide database comprised of patient-related, tumor-related, and treatment outcomes information for patients treated at Commission on Cancer-accredited programs. It captures approximately 70% of all newly diagnosed cancers in the U.S. From 2004–2015, there were 59 642 patients with UTUC and 525 323 patients with bladder cancer. We included patients with American Joint Committee on Cancer (AJCC) pT2–pT4 bladder and UTUC who underwent open or minimally invasive radical cystectomy or radical nephroureterectomy (with bladder cuff

excision) with or without lymph node dissection. Patients with prior non-urothelial malignancy, more than two urothelial tumors, more than one recurrence, variant histology (i.e., non-urothelial cell), clinically or pathologically positive nodes, and clinical or pathological metastatic disease were excluded. To better study the impact of embryological and genetic differences between upper and lower tract disease, patients who received neoadjuvant or adjuvant chemotherapy, postoperative intravesical chemotherapy, radiotherapy, immunotherapy, or enrolled in a clinical trial were also excluded. The justification for this being that use of these therapies in UTUC is not standard of care. Data points with missing variables for staging and treatments received were excluded. This is summarized via CONSORT diagram in Fig. 1. The NCDB contains de-identified patient information and therefore is exempt from internal review board approval.

Study outcomes

The database includes demographics, tumor pathology, treatments received, length of followup, and living/death status. Patients were stratified according to tumor location as follows: renal pelvis, ureteral, or bladder. The primary outcome was overall survival (OS). We also sought to identify potential predictors of mortality in each pathological T stage stratum.

Statistical analysis

Univariable analysis of categorical data was completed with Chi-squared tests, whereas continuous, non-parametric data was evaluated with Kruskall-Wallis tests. Kaplan-Meier survival curves were used to depict OS and were stratified by pathological T stage. Log-rank testing was used to determine statistical significance. Predictors of OS were estimated with multivariable Cox proportional hazard regression. Covariates included in the regression were: age, gender, race, Hispanic origin, median income quartile (<$38 000, $38 000–47 999, $48 000–62 999, or ≥$63 000), Charlson/Deyo score (0, 1, or ≥2), era of diagnosis (2004–2006, 2007–2009, 2010–2012, or 2013–2015), facility type (community cancer program, comprehensive community cancer program, academic program, or integrated network cancer program), ICD-O-3 tumor grade, tumor size, location, nodes examined, margin status, days from diagnosis to definitive surgery, days from surgery to discharge, and re-admission within 30 days of surgery. Data
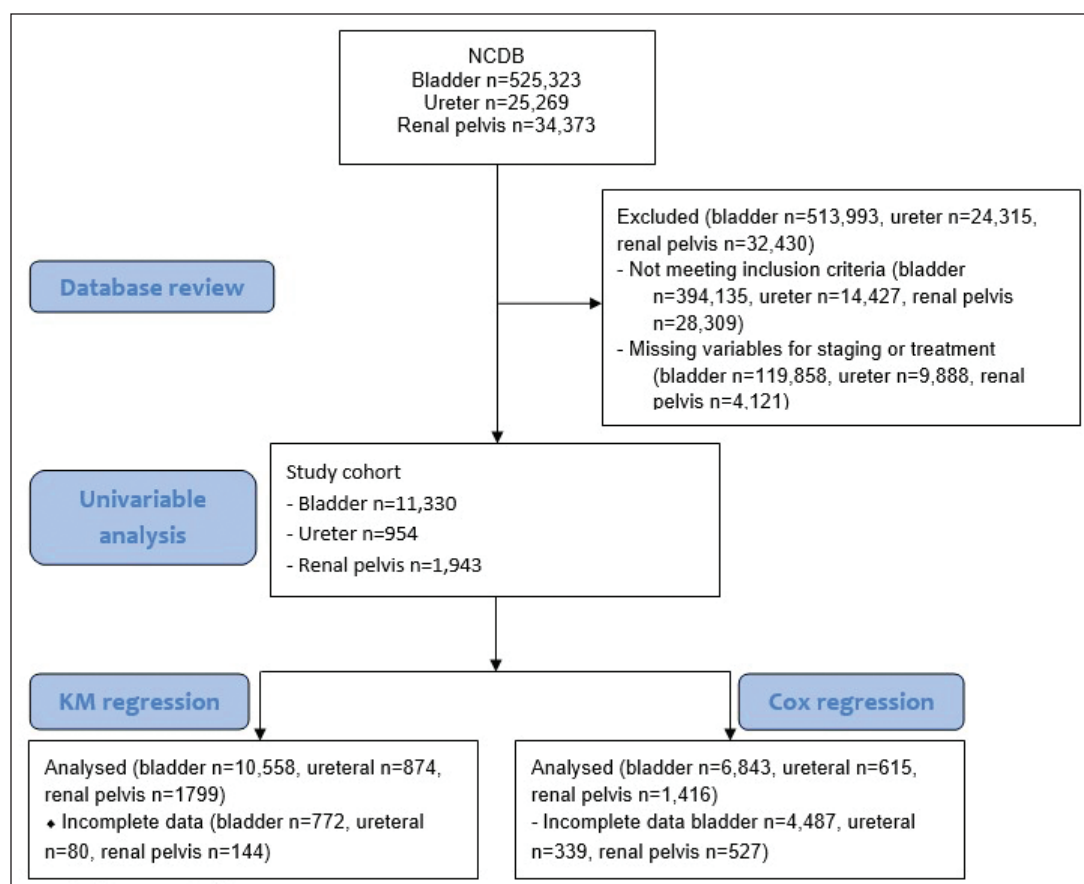
Fig. 1. Consort diagram. NCDB: National Cancer Database.

points with missing variables are automatically excluded from Cox regression analysis.

Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY). Reported p-values are two-sided, with statistical significance set at p<0.05.

Results

Descriptive statistics

A total of 11 330 patients with bladder (BUC), 954 patients with ureteral (UUC), and 1943 patients with renal pelvis (RPUC) urothelial carcinoma were analyzed. The demographic data is summarized in Table 1. Mean followup was 43.3, 39.4, and 41.4 months for bladder, ureteral, and renal pelvis, respectively. The median ages for UUC and RPUC were both 74 years, while that for BUC was 70 years (p<0.001). The proportion of females that were affected by disease differed by location — 24.1% of BUC, 43.5% of UUC, and 44.8% of RPUC (p<0.001). There was no difference in Charlson-Deyo scores between the three groups (p=0.605). Patients with RPUC presented more frequently with pT3 disease (67.7%) compared to BUC and UUC (38.2% and 46.1%, respectively, p<0.001). A greater proportion of BUC had IOC-O-3 grade 3 and 4 disease (54.5% and 40.8%, respectively) compared to UUC (51.6% and 33.1%, respectively) and RPUC (48.8% and 33.6%, respectively) (p<0.001). There was a greater delay to surgery for BUC vs. UTUC. The median number of days to surgery was 47 (interquartile range [IQR] 29–70) for BUC, 26 (3.5–46) for UUC, and 21 (0–40) for RPUC (p<0.001).

Convalescence time was longest for BUC patients. The number of days from surgery to discharge for BUC was 8 (IQR 6–11) vs. 5 (IQR 3–7) for UUC and 5 (IQR 3–7) for RPUC (p<0.001). Similarly, patients with BUC had a higher rate of 30-day re-admission (11%) compared to those with UUC or RPUC (4.9% and 5.1%, respectively, p<0.001). Thirty-day mortality was statistically similar between the three groups (p=0.105), though 90-day mortality was significantly worse in both BUC and RPUC (7.5% and 6.3%, respectively) vs. UUC (5.6%, p=0.001).

Survival analysis

The Kaplan-Meier curve for OS of all patients, stratified by location, is shown in Fig. 2. There was a significant difference in OS between BUC and UUC (p<0.001), and UUC and RPUC (p=0.028). Median survival was 49.2 months (95% confidence interval [CI] 47.0–51.4) for BUC, 39.2 months (95% CI 34.2–4.2) for UUC, and 46.5 (95% CI 42.3–50.6) for RPUC (Supplementary Table 1). Kaplan-Meier functions were also stratified by pT stage (Figs. 3A–C). Figure 3A shows that OS was worse for pT2 UUC compared to both BUC (61.3 vs. 80.4 months, p=0.007) and RPUC (61.3 vs. 80.5 months, p=0.014). For pT3, OS was greater for RPUC compared to both BUC (42.5 vs. 28.6 months, p<0.001) and UUC (42.5 vs. 25.7 months, p<0.001). BUC also displayed a survival advantage over UUC (28.6 vs. 25.7 months, p=0.003). For pT4, BUC was associated with greater OS than RPUC (17.7 vs. 11.4 months, respectively, p<0.001). Comparison of BUC vs. UUC did not reach statistical significance (p=0.847).

Multivariable Cox proportional hazards regression, stratified by pT stage, is summarized in Tables 2A–C. Renal pelvis location was associated with a 20% decreased risk of mortality for pT3 disease (hazard ratio [HR] 0.80, 95% CI 0.72–0.88, p<0.001). Location was not a predictor of mortality for either pT2 or pT4 disease. For all patients, regardless of pT stage, increasing number of nodes obtained for pathological diagnosis was associated with a decreased risk of mortality, while a positive surgical margin was associated with an increased risk of mortality. Increasing tumor size and days from surgery to discharge were weak risk factors for mortality.

Discussion

To date, there have been multiple outcome comparisons between UTUC and bladder carcinoma, with conflicting results. Several studies, including a comprehensive literature review, suggest that the differences in outcomes are attributed to tumor stage and grade rather than on location itself.[2,4,8-13] Nevertheless, the EAU guidelines conclude that when controlling for stage, patients with ureteral tumors have a worse prognosis than those with renal tumors.[14] Our findings further support their statement.

We excluded patients who received any type of neoadjuvant and adjuvant therapy, due to the low usage rate for UTUC, and patients with evidence of metastatic disease. Ureteral location was associated with worse OS for both pT2 and pT3 disease on univariable analysis. This may be attributable to the high rate of positive surgical margins for UUC. When controlling for surgical margins on multivariable Cox regression, ureteral location was not a predictor of mortality. However, renal pelvis location was associated with improved median OS and decreased risk of mortality compared to both bladder and ureteral location for pT3 disease. When examining the AJCC grading system used to stage upper tract tumors, invasion of peri-pelvic fat and renal parenchyma are classified as pT3; this closely mirrors that for bladder disease, though the prognostic significance may differ when surrounding fat or surrounding organs are involved. We postulate that benefits of renal pelvis location may be attributed to the bulk of renal parenchyma shielding from invasion of surrounding tissues. Notably, Park et al reported

Table 1. Demographic information of patients with pT2-T4, node negative, non-metastatic urothelial call carcinoma of the urinary tract who received definitive surgical therapy from 2004–2015

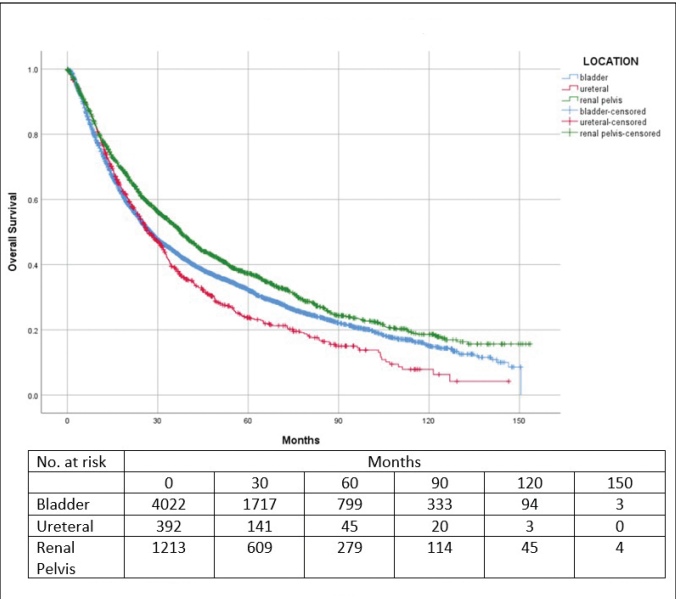|	Bladder (n=11 330)	Ureter (n=954)	Renal pelvis (n=1943)	p
Age (years) (median, IQR)	70 (62–77)	74 (66–81)	74 (65–81)	<0.001
Gender (%)				<0.001
Male	8603 (75.9)	539 (56.5)	1072 (55.2)	
Female	2727 (24.1)	415 (43.5)	871 (44.8)	
Race (%)				<0.001
White	10 353 (92.3)	872 (92.4)	1780 (92.7)	
Black	631 (5.6)	35 (3.7)	84 (4.4)	
Other	183 (1.6)	32 (3.4)	47 (2.4)	
Unknown	52 (0.5)	5 (0.5)	10 (0.5)	
Median income quartile (%)				0.001
Less than $38 000	1931 (17.3)	182 (19.3)	299 (15.7)	
$38 000–47 999	2963 (26.6)	231 (24.5)	464 (24.3)	
$48 000–62 999	3125 (28)	257 (27.2)	516 (27)	
Greater than $63 000	3134 (28.1)	274 (29)	629 (33)	
Year of diagnosis (%)				0.032
2004–2006	3388 (29.9)	286 (30)	572 (29.4)	
2007–2009	2787 (24.6)	233 (24.4)	489 (25.2)	
2010–2012	2741 (24.2)	209 (21.9)	417 (21.5)	
2013–2015	2414 (21.3)	226 (23.7)	465 (23.9)	
Facility type (%)				<0.001
Community cancer program	752 (6.7)	85 (8.9)	147 (7.6)	
Comprehensive community cancer	4099 (36.3)	419 (44)	812 (42.1)	
Academic program	5424 (48.1)	355 (37.3)	759 (39.3)	
Integrated network cancer program	1011 (9)	94 (9.9)	212 (11)	
Distance to facility of diagnosis (miles) (median, IQR)	14.9 (5.8–42.9)	11.2 (4.7–31.4)	11.1 (4.5–29.8)	<0.001
Charlson/Deyo score (%)				0.605
0	7685 (67.8)	626 (65.6)	1305 (67.2)	
1	2689 (23.7)	248 (26)	470 (24.2)	
2 or more	956 (8.4)	80 (8.4)	168 (8.6)	
T stage (%)				<0.001
pT2	6002 (53)	472 (49.5)	474 (24.4)	
pT3	4331 (38.2)	440 (46.1)	1316 (67.7)	
pT4	997 (8.8)	42 (4.4)	153 (7.9)	
ICD-O-3 tumor grade (%)				<0.001
1	95 (0.9)	36 (4.2)	88 (5.1)	
2	389 (3.8)	94 (11.1)	217 (12.6)	
3	5629 (54.5)	439 (51.6)	843 (48.8)	
4	4212 (40.8)	281 (33.1)	580 (33.6)	
Tumor size (cm) (median, IQR)	3.7 (2.5–5.2)	3 (2–5)	4 (2.8–5.5)	<0.001
Bilateral disease (%)	n/a	0 (0)	1 (0.1)	<0.001
Positive surgical margins (%)	699 (6.4)	148 (15.8)	117 (6.1)	<0.001
Lymphadenectomy (%)	10,421 (92)	411 (43.1)	697 (35.9)	<0.001
Nodes examined (median, IQR)	10 (4–17)	0 (0–2)	0 (1–6)	<0.001
Days to definitive surgery (median, IQR)	47 (29–70)	26 (3.5–46)	21 (0–44)	<0.001
Days to discharge (median, IQR)	8 (6–11)	5 (3–7)	4 (3–6)	<0.001
Readmission within 30 days of surgery (%)	1219 (11)	46 (4.9)	97 (5.1)	<0.001
Mortality within 30 days of surgery (%)	355 (3.4)	26 (3)	48 (2.7)	0.105
Mortality within 90 days of surgery (%)	797 (7.5)	49 (5.6)	113 (6.3)	0.023

Univariable analysis was completed with Chi-squared tests for categorical variables and Kruskal-Wallis test for continuous variables. IQR: interquartile range.
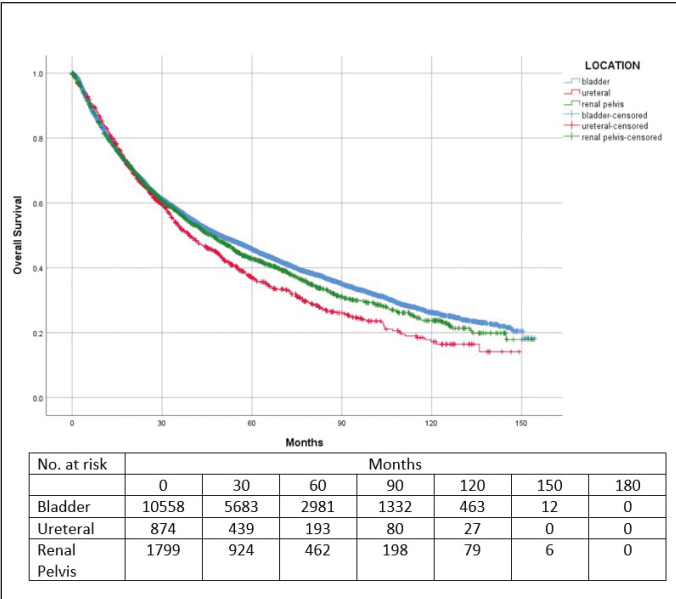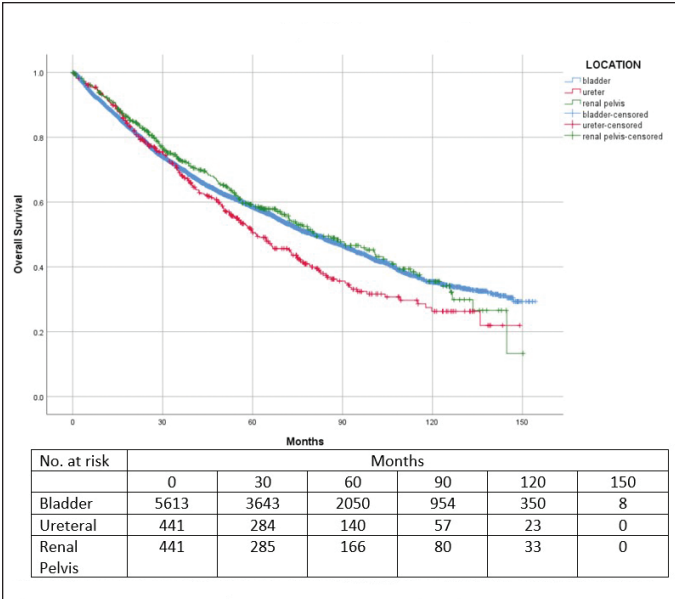
Fig. 2. Kaplan-Meier curve for overall survival of all patients, stratified by location. Bladder vs. ureteral p<0.001; bladder vs. renal pelvis p=0.087; ureteral vs. renal pelvis p=0.028.

No. at risk	Months						
	0	30	60	90	120	150	180
Bladder	10558	5683	2981	1332	463	12	0
Ureteral	874	439	193	80	27	0	0
Renal Pelvis	1799	924	462	198	79	6	0

Fig 3A. Kaplan-Meier curves for overall survival stratified by pT2 stage: bladder vs. ureteral p=0.007; bladder vs. renal pelvis p=0.531; ureteral vs. renal pelvis p=0.014.

No. at risk	Months					
	0	30	60	90	120	150
Bladder	5613	3643	2050	954	350	8
Ureteral	441	284	140	57	23	0
Renal Pelvis	441	285	166	80	33	0

that peri-pelvic fat invasion was associated with a 3.47 HR for cancer-specific survival compared with renal parenchymal invasion in a retrospective review.[15] The NCDB data set does not allow for determination of peri-pelvic or renal parenchymal invasion for pT3. Other studies have reported the protective effect of renal pelvis location, including a large multicenter study by Ouzzane et al and a small single-surgeon study by Akdogan et al.[16,17] These studies did not stratify by tumor pathological stage, however.
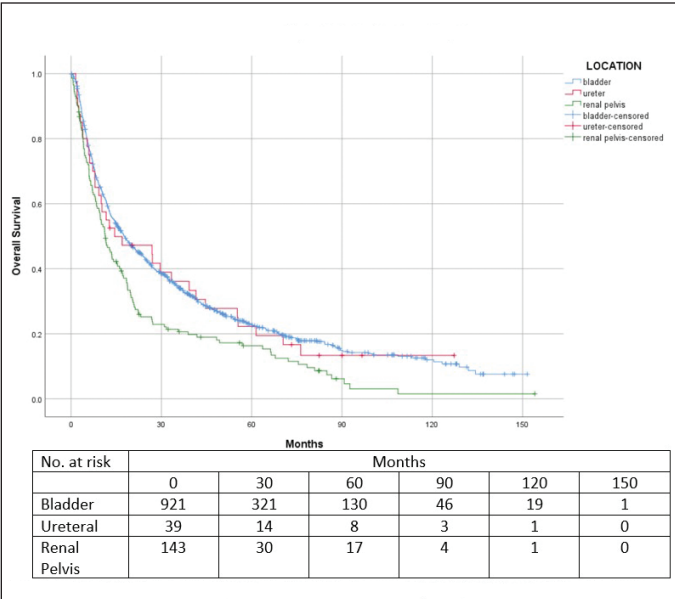
The largest study comparing bladder and UTUC found that location had an impact on survival only for pT4 disease. Rink et al completed a multicenter, retrospective study with 4335 BUC, 877 UUC, and 1615 RPUC patients treated with radical surgery. They reported no differences in cancer-specific survival for pT2-pT3 but worse survival for pT4 in the upper tract.[8] In contrast, we found that only pT4 RPUC did worse than BUC, though RPUC was not a predictor of mortality on Cox regression (p=0.108). The inclusion of patients with posi-

Fig. 3B. Kaplan-Meier curves for overall survival stratified by pT3 stage: bladder vs. ureteral p=0.003; bladder vs. renal pelvis p<0.001; ureteral vs. renal pelvis p<0.001.

No. at risk	Months					
	0	30	60	90	120	150
Bladder	4022	1717	799	333	94	3
Ureteral	392	141	45	20	3	0
Renal Pelvis	1213	609	279	114	45	4

Fig 3C. Kaplan-Meier curves for overall survival stratified by pT4 stage: bladder vs. ureteral p=0.847; bladder vs. renal pelvis p<0.001; ureteral vs. renal pelvis p=0.102.

No. at risk	Months					
	0	30	60	90	120	150
Bladder	921	321	130	46	19	1
Ureteral	39	14	8	3	1	0
Renal Pelvis	143	30	17	4	1	0

Table 2A. Multivariable Cox regression examining predictors of mortality for patients with pT2 disease

	Hazard ratio	95% CI	p
Location			
Bladder	Ref		
Ureteral	0.99	0.85–1.14	0.856
Renal pelvis	0.89	0.76–1.04	0.125
Age (continuous)	1.04	1.03–1.04	<0.001*
Gender			
Male	Ref		
Female	0.94	0.85–1.03	0.176
Charlson/Deyo score			
0	Ref		
1	1.26	1.14–1.39	<0.001*
2 or more	1.66	1.43–1.92	<0.001*
ICD-O-3 tumor grade			
1	Ref		
2	0.91	0.66–1.26	0.559
3	1.20	0.90–1.59	0.213
4	1.18	0.89–1.58	0.255
Tumor size (continuous)	1.001	1.000–1.002	0.004*
Positive surgical margins	1.55	1.27–1.88	<0.001*
Nodes examined (continuous)	0.99	0.986–0.995	<0.001*
Days to discharge (continuous)	1.01	1.004–1.010	<0.001*
Readmission within 30 days of surgery	1.11	0.97–1.27	0.122

*Statistically significant. CI: confidence interval.

Table 2B. Multivariable Cox regression examining predictors of mortality for patients with pT3 disease

	Hazard ratio	95% CI	p
Location			
Bladder	Ref		
Ureteral	0.98	0.86–1.12	0.793
Renal pelvis	0.80	0.72–0.88	<0.001*
Age (continuous)	1.03	1.02–1.03	<0.001*
Gender			
Male	Ref		
Female	0.89	0.82–0.96	0.002*
Charlson/Deyo score			
0	Ref		
1	1.24	1.14–1.34	<0.001*
2 or more	1.59	1.42–1.78	<0.001*
ICD-O-3 tumor grade			
1	Ref		
2	1.20	0.86–1.68	0.286
3	1.54	1.13–2.09	0.006*
4	1.45	1.06–1.97	0.019*
Tumor size (continuous)	1.003	1.003–1.004	<0.001*
Positive surgical margins	1.66	1.48–1.86	<0.001*
Nodes examined (continuous)	0.99	0.98–0.99	<0.001*
Days to discharge (continuous)	1.01	1.01–1.01	<0.001*
Readmission within 30 days of surgery	1.02	0.91–1.15	0.724

*Statistically significant. CI: confidence interval.

tive nodes, who received adjuvant chemotherapy, and lack of surgical margin status may explain this disparity. Interestingly, their Kaplan-Meier survival curve for pT3 showed that renal pelvis location had improved OS when compared to both bladder and ureter, but they did not include a Cox regression.[8] Moschini et al compared survival in patients with unresectable, pN+, and metastatic UTUC and bladder cancer treated with chemotherapy and reported no significant differences in survival when stratified by location.[18] Yet, inclusion of nonlocalized disease poses a confounding factor since metastatic sites display heterogeneity from the primary tumor, and is oftentimes highly anaplastic.[19]

Several studies have attempted to study the impact of location on outcomes in UTUC following radical surgery but included patients with positive nodes and who received chemotherapy, and do not stratify by pT stage.[2,3,6,7,9] Catto et al conducted a multicenter, retrospective analysis and reported that for muscle-invasive disease, location was not a predictor of mortality on univariable analysis; multivariable analysis was not included.[2] Though not reaching statistical significance, both Favaretto et al and Williams et al published a Kaplan-Meier curve showing that OS for RPUC and UUC diverge, with RPUC having improved survival.[3,9] Moussa et al found no difference in OS for pT2 or greater between bladder and UTUC treated with radical surgery, but

did not substratify UUC and RPUC in their analysis.[6] NCDB data from 1998–2011 suggests no increased risk of death for RPUC vs. UUC following radical nephroureterectomy. However, all pT stages are included in their Cox analysis, and 47% of their cohort consisted of pT1 tumors and lower,[20] confounding comparison with our cohort.

UTUC and bladder carcinoma may represent phenotypically distinct diseases. The urothelium of the upper tract and bladder are derived from different germ layers, with the bladder deriving from endoderm and both ureter and renal pelvis deriving from mesoderm. Heterogeneity in the urothelium is suggested when examining risk factors for urothelial carcinoma. In Lynch syndrome, disease in the upper tract is more common than in the bladder.[21] While the incidence of bladder cancer is also increased, it is unclear whether this is from seeding or from an intrinsic defect from mutations of Lynch syndrome. Consider that aristolochic acid exposure is associated with increased incidence of UTUC but not bladder cancer.[22] The mutational patterns between the UTUC and BUC have been shown to differ.[11,12] Audenet et al showed that UTUC was more frequently associated with alterations in FGFR3 and HRAS, whereas TP53, RB1, and ERBB2 were more frequently altered in BUC.[13] In patients with a history of UTUC and subsequent bladder UC, the tumors were "always clonally related," suggesting downstream seeding. The role

Table 2C. Multivariable Cox regression examining predictors of mortality for patients with pT4 disease

	Hazard ratio	95% CI	p
Location			
Bladder	Ref		
Ureteral	0.98	0.66–1.43	0.899
Renal pelvis	1.19	0.96–1.46	0.108
Age (continuous)	1.02	1.01–1.03	<0.001*
Gender			
Male	Ref		
Female	1.19	1.00–1.41	0.056
Charlson/Deyo score			
0	Ref		
1	1.01	0.85–1.21	0.898
2 or more	1.43	1.14–1.81	0.002*
ICD-O-3 tumor grade			
1	Ref		
2	1.51	0.56–4.08	0.414
3	2.20	0.89–5.44	0.089
4	1.83	0.74–4.54	0.193
Tumor size (continuous)	1.001	1.000–1.001	0.100
Positive surgical margins	1.71	1.45–2.02	<0.001*
Nodes examined (continuous)	0.99	0.985–0.992	0.034*
Days to discharge (continuous)	1.01	1.01–1.02	<0.001*
Readmission within 30 days of surgery	1.25	0.99–1.58	0.062

*Statistically significant. CI: confidence interval.

of estrogen receptors on urothelial carcinoma has yet to be defined, though expression has been shown in a few studies to predict survival.[23-25] The clinical significance of this marker is relevant when considering that the gender disparity for BUC is much more pronounced than for UTUC.[1]

The greatest limitation of this study is the lack of cancer-specific survival variables in the database. We opted to use OS and sought to control for confounders by including Charlson-Deyo scores, days to discharge, and 30-day re-admission in our multivariable analysis as a proxy for overall health. We acknowledge that OS is not a perfect substitute, but it likely correlates with cancer-specific survival in patients with muscle-invasive cancer. The retrospective observational design of this study introduces several biases, including selection, misclassification, and non-standardization of variables. Additionally, the NCDB does not provide details about pT stage — re-classification of renal parenchymal invasion into pT2 may nullify the survival advantage of pT3 RPUC. While the NCDB boasts large numbers, a small proportion of data points are incomplete and have missing variables. Despite these limitations, we feel that our large study population across the U.S. and long duration of followup bolsters the generalizability of this study. To our knowledge, this is the largest national study comparing survival between bladder and upper tract disease.

Conclusions

UTUC and BUC were historically viewed as identical diseases in different locations. Past literature may not have shown differences because analyses were not stratified by pT stage or chemotherapy received. When stratifying by pT stage and controlling for use of neoadjuvant and adjuvant therapies, pT3 in the renal pelvis is associated with a lower risk of mortality. This may be a consequence of embryological and genetic differences between the upper tract and bladder. Conceivably, subclassification of pT3 to separate parenchymal and peri-pelvic fat invasion may also explain this finding.[26] While treatment strategies for bladder cancer continue to evolve, strategies for UTUC have lagged behind. With the advent of targeted therapies, dedicated prospective studies are necessary to validate use in UTUC, rather than treating it as a subset on BUC, as was historically done.

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Supplementary Table 1. Estimated median overall survival with 95% CI (months) for all patients with pT2-pT4 disease with node-negative disease who did not receive any chemotherapy, radiation, or immunotherapy

	Bladder Median OS, 95% CI, n	Ureter Median OS, 95% CI, n	Renal pelvis Median OS, 95% CI, n
pT2-T4	49.2 (47.0–51.4) n=10 559	39.2 (34.2–44.2) n=875	46.5 (42.3–50.6) n=1800
pT2	80.4 (76.4–84.5) n=5614	61.3 (52.1–70.5) n=442	80.5 (65.4–95.7) n=442
pT3	28.6 (26.7–30.5) n=4023	25.7 (22.1–29.3) n=393	42.5 (38.1–46.8) n=1214
pT4	17.7 (15.0–20.4) n=922	14.5 (0–36.9) n=40	11.4 (8.5–14.3) n=144

The n for each strata subset is included as well. CI: confidence interval; OS: overall survival.