Urothelial Carcinoma of the Renal Pelvis and Ureter: Does Location Make a Difference?

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Conflict of Interest

Declarations of interest (all authors): None

MicroAbstract

There has been a scarcity of data on outcomes of upper tract urothelial carcinoma. We queried a large, cancer registry and have found a strong association between survival and location of tumor. Patients with ureteral urothelial carcinoma were found to be treated with less radical surgery and found to have worse survival than those with renal pelvis urothelial carcinoma. These patients may suffer from poor initial staging and suboptimal treatments.

Abstract

Objectives: There is a paucity of data on outcomes of upper tract urothelial carcinoma (UTUC) arising from the renal pelvis (RPUC) versus UTUC arising from the ureter (UUC). The published literature is conflicting, and there is no consensus on patient prognosis based on disease location. The aim of this study is to compare clinical and survival outcomes based on location of primary tumor using a large, national registry.

Methods: The National Cancer Database was queried from 2010-2016 for patients with localized (cN0M0) UTUC. Patients were stratified based on location of tumor. Survival analysis was performed using Cox proportional hazard regression and inverse probability of treatment weighting (IPTW) -adjusted Kaplan-Meier curves. We also performed exploratory analyses based on tumor stage.

Results: We identified 11,922 patients who underwent surgical treatment. Median follow-up was 32.1 months. RPUC patients presented with higher tumor stage and grade. UUC patients were treated with less radical nephroureterectomy (56.4 vs 84.3%, p<.01). IPTW-adjusted Kaplan-Meier curves demonstrated higher median OS for RPUC versus UUC (71.1 vs 66.8 months, respectively; P=0.01). This benefit was consistent across tumor stage subgroups reaching statistical significance in patients with T1 disease. On multivariable analysis, ureteral location of tumor was a predictor of worse survival.

Conclusion: Patients with UUC were found to be treated with less radical surgery and found to have worse survival than those with RPUC. These patients may suffer from poor initial staging

and suboptimal treatments.. Further studies are needed to evaluate potential biological differences of UTUC based on tumor location.

Keywords: upper tract urothelial carcinoma; outcomes; renal pelvis urothelial carcinoma; ureteral urothelial carcinoma; survival

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Introduction

Upper tract urothelial carcinoma (UTUC) is defined as urothelial carcinoma arising from the ureter or renal collecting system. UTUC is relatively rare comprising 5-10% of all urothelial tumors.[1] The great majority occur unilaterally; however, bilateral disease can occur in approximately 1.6% of cases.[2] Most cases arise in the renal pelvis (RPUC); however, the frequency of ureteral disease (UUC) has been rising in the past 50 years and estimated to occur in 25-33% of patients with UTUC.[2-4] For decades, treatment has consisted of radical nephroureterectomy with excision of bladder cuff, but segmental and endoscopic interventions are now well-recognized options in select cases based on location, size, and histological parameters.[5]

The literature is conflicting in describing the prognostic impact of UTUC location. Small series have reported no difference in outcomes between UUC versus RPUC.[3,4,6-9] Others have reported increased recurrence for UUC[10-16]. Hypotheses of why UUC may have worse outcomes have been postulated. The adventitia and smooth muscle covering of the upper tract is thinner with a rich blood and lymphatic supply than compared to the bladder; thus, allowing for direct tumor invasion and earlier metastases[3,7]. However, there is lack of concrete evidence on outcomes and optimal management based on UTUC location.

In this study, we aimed to first evaluate current practice patterns for treatment of UTUC based on tumor location using a large, national cancer registry. Secondly, we analyze patient and clinical

characteristics as well as overall survival (OS) differences of UTUC patients treated in the United States.

Materials and Methods

Data source and patient selection

We used data from the National Cancer Data Base (NCDB), a hospital-based registry database of Commission on Cancer (CoC)-accredited hospitals, representing more than 70% of newly diagnosed cancer cases in the U.S.[17] The NCDB was queried for patients diagnosed with localized (cN0M0) UTUC (histology codes 8120 and 8130) with complete treatment and follow-up data from the years 2010 to 2016 (Supplemental table 1). International Classification of Diseases for Oncology, Third Edition oncologic codes included topographical codes C65.9 (renal pelvis) and C66.9 (ureter). Only patients with known tumor stage, known treatment, and known surgical management were included. Those who received perioperative systemic therapy were excluded.

Baseline characteristics

Patient demographics included age (continuous), gender (male and female), race (White, Black, and Other), ethnicity (Non-Hispanic and Hispanic), insurance status (not insured, private insurance, Medicaid/Medicare, and other/unknown), income quartile (<$38 000, $38 000-$62 999, and ≥$63 000), education (>93%, 79.0%-93%, and <79.0% achieving high-school diploma), Charlson-Deyo comorbidity score (0, 1, and 2 or more), and year of diagnosis (2010-2011, 2012-2013, and 2014-2015). Disease characteristics included clinical T-stage (<T1, T1, T2, and T3/T4),

World Health Organization (WHO) or International Society of Urological Pathology (ISUP) grade as documented in the pathology report (low grade and high grade), and presence of lymphovascular invasion. Treatment characteristics included site-specific surgery codes. CoC cancer programs are required to identify treatment their patients received from all sources. This refers to the final treatment of the primary site, cumulative for all procedures, which may have occurred at any facility. Treatment was stratified into three groups: 1. endoscopic local tumor destruction (laser ablation or electrosurgery), 2. nephron-sparing treatment (segmental ureterectomy or partial resection), and 3. radical surgery (nephroureterectomy with bladder cuff excision).

Statistical analysis

Descriptive statistics for clinical and sociodemographic characteristics were compared based on tumor location. Differences in proportions between categorical variables were assessed using the $\chi 2$ test. Wilcoxon test was used to assess differences for continuous variables. Univariable and multivariable Cox proportional hazards models were used to determine potential differences in survival between patients with ureteral versus renal pelvis lesions. Kaplan-Meier survival analyses was adjusted for age, gender, race, primary surgery, tumor grade and tumor size through the inverse probability treatment weighted (IPTW) approach. We performed exploratory analyses for each T-stage and compared differences with the log-rank test. SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) was used to generate figures. Statistical significance was set at $P < 0.05$.

Results

In total, we identified 11,922 cases: 5,448 patients diagnosed with UUC and 6,474 with RPUC. Patient demographics and univariable analyses are detailed in Table 1. Median follow-up was 32.1 months (31.6 UUC vs. 32.4 RPUC, p=0.37). Higher proportion of male gender, White race, Non-Hispanic ethnicity, and Medicaid/Medicare insured patients were seen in the UUC group.

When examining disease and treatment characteristics, patients with RPUC presented with more non-organ confined disease, and more high grade tumors (both, p<0.01). RPUC patients were treated with radical surgery more often than UUC patients (84.3 vs 56.4% received nephroureterectomy, p<0.01) (Table 2).

IPTW-adjusted Kaplan-Meier curves showed higher median OS for patients with RPUC versus those with UUC (71.1 vs 66.8 months, respectively; P=0.01). Non-significant improved survival was seen in RPUC stages <T1, T2, and T3/4 when compared to UUC cases, while a significantly better OS was seen in patients with T1 tumors (68.8 vs 59.6 months, respectively, p <0. 01) (Figure 1). When adjusting for age, gender, stage, grade, performance status, lymphovascular invasion and treatment modality; ureteral tumor location continued to be an independent predictor of worse survival (hazard ratio 1.15; 95% CI: 1.08-1.22; p<0.01).

Discussion

Due to its rarity, there is scarcity of data on the management of patients with UTUC. In this population-based study, we report on contemporary national practice patterns for treatment of UTUC and associated survival outcomes. Firstly, we found patients with UUC underwent less radical treatment when compared to patients with RPUC. Secondly, patients with RPUC showed improved OS compared to UUC after adjusting for clinical and pathologic variables. Survival impact was greater in those with T1 disease and ureteral tumor location was found as an independent predictor of worse survival.

There have been conflicting findings in regards to prognosis between UUC and RPUC patients. A meta-analysis by Wu et al. did not find significant differences between UUC or RPUC in presentation of pT3-T4 or pN+ disease after radical nephroureterectomy although UUC was found to have worse recurrence free survival and cancer specific survival on multivariable analyses[12]. Multiple hypotheses exist on the poorer outcomes of patients with ureteral vs renal pelvis tumors. It is possible that the ureteral adventitia is thinner with surrounding lymphatics and vascular network to help facilitate tumor metastases. In addition, it has been postulated that the surrounding renal parenchyma and adipose tissue of the kidney act as a barrier to RPUC spread[3,7]. Intuitively, UUC could be observed with higher stages and extra-ureteral disease although this has not been proven to be true in multiple studies.

Favaretto et al. analyzed 325 UTUC patients and found no differences in recurrence and survival based on location but rather on pathologic stage and nodal status[7]. Other studies have echoed these findings with tumor stage and grade as better predictors of outcomes.[3,6] Although higher stages were seen in our RPUC cohort, this may be confounded by the more thorough staging from a

radical nephroureterectomy although our findings are similar to previous reports of higher incidence of T3-T4 disease in RPUC[4,13]. Nevertheless, research continues to be needed to study potential biological differences of ureteral and renal pelvis UTUC along with predictive models to help estimate non-organ, confined disease and better discern patients that could benefit from improved staging modalities prior to proceeding with organ-sparing treatments.

Joshi et al similarly analyzed the National Cancer Database (n=8,284 from 1998-2011) in patients with localized disease and demonstrated worse survival in patients with larger tumor size but no difference in survival on location[8]. They demonstrated an overall 5 year OS of 51.6% and on multivariate analysis, tumor size ≥3.5cm was independent predictive of worse OS[8]. The difference in findings can be attributed to baseline population differences of years analyzed (1998-2011) along with coding differences. In addition, they only included patients that underwent radical nephroureterectomy with or without bladder cuff excision[8]. Thus our findings could be considered a more contemporary view on current practice patterns with the increased adoption of endoscopic treatments for treating UTUC. It is our hope we continue to evaluate the efficacy and appropriateness of organ-sparing approaches for optimal patient selection and counseling.

We found UUC patients to be treated with more endoscopic and nephron sparing treatments. Although difficult to interpret due to inherent selection bias, a reason for the poorer outcomes may be the difficulty to visualize diseased tissue and ensure a clear surgical margin when endoscopically treating ureteral tumors. However, it is unlikely that one factor solely attributes to worse outcomes in UUC, but instead a culmination of presentation, treatment, and anatomical factors. Better imaging and techniques for accurate staging of UUC are needed to help clinical

decision-making and patient counseling prior selection of surgical approach in those with tumors appropriate for nephron-sparing treatment. In addition, these patients may benefit from closer surveillance follow-up and prompt intervention at the time of recurrence.

There has been insufficient long-term data to base recommendations for perioperative systemic therapy for UTUC. Current evidence is conflicting adding uncertainty in disease management. Some evidence supports cisplatin-based adjuvant chemotherapy after radical nephroureterectomy for pT3/T4 and/or pN+ UTUC due to observed OS benefit[18]. Recently, Necchi et al found adjuvant chemotherapy did not improve OS compared with observation for patients with ≥pT2 and/or pN1–3 after nephroureterectomy in large multicenter study[19]. High level evidence continues to be scarce given the rarity of the disease. Current studies on adjuvant chemotherapy have been in the setting after radical nephroureterectomy; thus, studies continue to be needed on the safety and efficacy of nephron-sparing and endoscopic approaches for those select patients with amenable tumors.

Limitations of this study include its retrospective nature which brings inherent weaknesses such as selection bias and confounding. We were unable to evaluate patient and surgeon reasons for using certain surgical approaches. Due to limitations of the NCDB, we were unable to evaluate recurrence and disease specific survival. We were also unable to identify those with renal insufficiency or other factors precluding a radical nephroureterectomy. Prospective studies are still needed to confirm the impact of increased adoption of endoscopic treatments. Given the paucity of predictive clinical tools, distinguishing aggressive UTUC phenotypes and providing appropriately aggressive treatment remains a challenge for this rare cancer.

Conclusion

In this large retrospective study examining national treatment patterns, patients with ureteral UTUC were found to be treated with less radical treatment and have worse survival than patients with renal pelvis UTUC. Patients with ureteral tumors may suffer from poor initial staging and suboptimal treatments.Further studies are needed to evaluate potential biological differences of UTUC based on tumor location.

Clinical Practice Points

1. There is a scarcity of data on outcomes of upper tract urothelial carcinoma (UTUC) arising from the renal pelvis (RPUC) versus UTUC arising from the ureter (UUC).
2. In this study, we found patients with UUC underwent less radical treatment when compared to patients with RPUC.
3. Patients with RPUC showed improved OS compared to UUC after adjusting for clinical and pathologic variables.
4. Survival impact was significantly noted in those with T1 disease and ureteral tumor location was found as an independent predictor of worse survival.
5. Patients with UUC may suffer from poor initial staging and suboptimal treatment.

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Table 1: Socio-demographic differences between renal pelvis versus ureteral UC patients

Variables	Ureteral UC	Renal Pelvis UC	p-value
Patients	5448	6474	
Age (year), median (IQR)	73 (66-81)	73 (65-80)	**0.001**
Follow-up (month), median (IQR)	31.6 (16.3-51.6)	32.4 (15.4-53.2)	0.366
Gender			**<0.001**
Male	3443 (63.2)	3883 (60)	
Female	2005 (36.8)	2591 (40)	
Race			**0.015**
White	5085 (93.3)	5953 (92)	
Black	200 (3.7)	294 (4.5)	
Other	163 (3)	227 (3.5)	
Ethnicity			**0.006**
Non-hispanic	5108 (96.7)	6055 (96.5)	
Hispanic	174 (3.3)	219 (3.5)	
Income			0.228
<$38,000	730 (13.4)	939 (14.6)	
$38,000-47,999	1241 (22.9)	1509 (23.4)	
$48,000-62,999	1536 (28.3)	1786 (27.7)	
$63,000 or more	1922 (35.4)	2214 (34.3)	
Education			0.315
21% or more	690 (12.7)	871 (13.5)	
13-20.9%	1327 (24.4)	1631 (25.3)	
7-12.9%	1937 (35.7)	2241 (34.7)	
<7%	1477 (27.2)	1709 (26.5)	
Charlson-Deyo score			0.311
0	3458 (63.5)	4188 (64.7)	
1	1377 (25.3)	1603 (24.8)	
2 or more	613 (11.3)	683 (10.5)	
Insurance status			**0.001**
Private/Managed care	1193 (21.9)	1531 (23.6)	
Medicaid/Medicare	4068 (74.7)	4697 (72.6)	
Other/Unknown	129 (2.4)	134 (2.1)	
Not insured	58 (1.1)	112 (1.7)	
Year of diagnosis			0.063
2010-2011	1715 (31.5)	2150 (33.2)	
2012-2013	1844 (33.8)	2195 (33.9)	
2014-2015	1889 (34.7)	2129 (32.9)	

Table 2: Clinical and treatment differences between renal pelvis versus ureteral UTUC

Variables	Ureteral UC	Renal Pelvis UC	p-value
Patients	5448	6474	
Primary procedure			**<0.001**
Endoscopic/Laser/Thermal	1229 (22.6)	790 (12.2)	
Nephron-sparing/Segmental	1147 (21.1)	229 (3.5)	
Radical treatment	3072 (56.4)	5455 (84.3)	
Tumor stage			**<0.001**
<T1	2862 (52.5)	2993 (46.2)	
T1	1565 (28.7)	2015 (31.1)	
T2	604 (11.1)	411 (6.3)	
≥T3	417 (7.7)	1055 (16.3)	
WHO/ISUP			**<0.001**
Low grade	2161 (39.7)	2168 (33.5)	
High grade	2866 (52.6)	3852 (59.5)	
Unknown	421 (7.7)	454 (7)	
Lymphovascular invasion			**<0.001**
None	3626 (66.6)	4299 (66.4)	
Present	455 (8.4)	700 (10.8)	
Unknown	1367 (25.1)	1475 (22.8)	

Table 3: Multivariable survival analysis after treatment of upper tract urothelial carcinoma in the United States based on tumor location

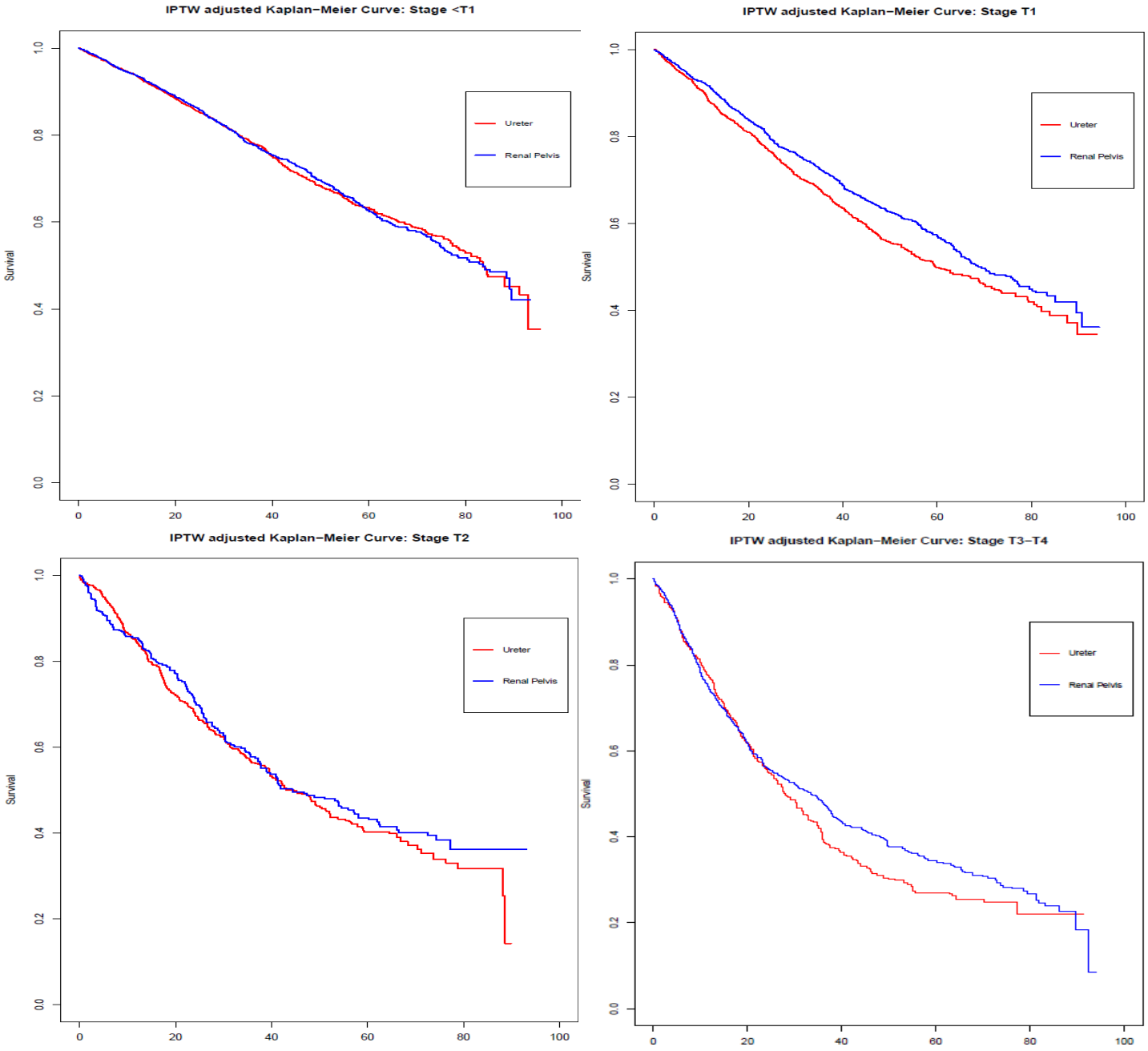
Variables	Hazard ratio (95%CI)			
	Univariable	**p-value**	**Multivariable[&]**	**p-value**
Location				
• Renal pelvis	Ref		Ref	
• Ureter	1.10 (1.03-1.17)	0.003	1.15 (1.08-1.22)	<0.001

[&] Adjusted for age, gender, stage, grade, performance status, lymphovascular invasion and treatment modality

Supplemental Table 1 (Online Only): Inclusion criteria

Patient Group	**Included**	**Excluded**
Include histology of UC of renal pelvis and ureter (2010-2016)	37,087	2,095
Include localized disease (cN0M0)	27,495	9,592
Include known tumor stage	18,521	8,974
Include known treatment given	17,422	1,099
Include no perioperative systemic therapy given	14,897	2,525
Include complete follow-up	12,580	2,317
Include known surgical management	11,922	658
Final Analytic Cohort (N) =	11,922	

Figure 1: IPTW adjusted 5-year overall survival based on tumor stage



Stage	Renal Pelvis			Ureter			P[b]
	# of deaths	median	OS(5 yr)	# of deaths	median	OS(5 yr)	
<T1	778 (25.99%)	83.65	63%	810 (28.30%)	83.65	63%	0.94
T1	653 (32.41%)	68.76	57%	624 (39.87%)	59.60	50%	<0.01
T2	177 (43.07%)	44.35	44%	301 (49.83%)	43.10	40%	0.51
T3-T4	591 (56.02%)	33.51	35%	266 (63.79%)	27.93	27%	0.19

[a]adjusted for age, gender, race, primary surgery, tumor grade and tumor size
[b]derived from IPTW logrank test