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Impact of tumour location versus multifocality in patients with upper tract urothelial carcinoma treated with nephroureterectomy and bladder cuff excision: a homogeneous series without perioperative chemotherapy

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Accepted for publication 26 July 2011

Study Type – Prognosis (case series)
Level of Evidence 5

OBJECTIVE

- To examine the significance of ureteral and renal pelvic location of upper tract urothelial carcinoma in a large multi-institutional study.

MATERIALS AND METHODS

- We collected and pooled a database of 637 patients with upper tract urothelial carcinoma who underwent radical nephroureterectomy and bladder cuff excision in nine international academic centres.
- Univariate and multivariate models examined the effect of tumour location on recurrence-free survival (RFS) and cancer-specific survival (CSS) rates.
- Collected variables included age, gender, race, presence of lymphovascular invasion, concomitant carcinoma *in situ*, pathological stage, lymph node dissection and type of surgery (open vs laparoscopic).

What's known on the subject? and What does the study add?
It is well established that upper tract urothelial carcinoma is a rare cancer with an aggressive course. Currently, radical nephroureterectomy with bladder cuff excision remains the standard of care in the treatment of these tumours. Previous studies demonstrate that stage, grade and lymphovascular invasion have prognostic significance on recurrence and outcome whereas the prognostic impact of tumour location remains unclear.

This study provides an accurate analysis of the impact of tumour location and multifocality on prognosis in patients with upper tract urothelial carcinoma following nephroureterectomy with bladder cuff excision. Ureteral tumour location, particularly when associated with multifocal disease in the renal pelvis, is significantly associated with an increased risk of disease recurrence and cancer-specific death after surgery.

RESULTS

- Anatomically, 34% of tumours were ureteral, 59% were renal pelvic and 7% were multifocal. Median follow-up for patients alive was 42 months (interquartile range: 19–76).
- Race, type of surgery, pathological stage and presence of lymphovascular invasion were significantly different across the three subgroups of patients (all P values <0.05). Age, gender, grade, presence of concomitant carcinoma *in situ* and follow-up duration were similar among the three subgroups.
- On multivariable Cox regression analyses, ureteral tumour location was an independent predictor of worse RFS (hazard ratio 2.1, $P = 0.006$) and CSS (hazard ratio 2.0, $P = 0.027$).
- When associated with renal pelvic disease, ureteral location was an even stronger independent predictor of worse RFS (hazard ratio 4.6, $P < 0.001$) and CSS (hazard ratio 4.0, $P < 0.001$).

CONCLUSION

- Ureteral tumour location, particularly in association with multifocal disease in the renal pelvis, is an independent prognostic factor for higher disease recurrence and cancer-specific mortality.

KEYWORDS

multifocality, nephroureterectomy, prognosis, recurrence, tumour location, urinary tract cancer, urothelial carcinoma

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) arises anywhere along the urothelial lining of the urinary tract from the renal calyces to the ureteral orifice. It is a rare cancer and accounts for only 5–10% of all renal tumours, and 5–6% of all urothelial tumours. Tumours are more frequently located in the renal pelvis and 25% are in the ureter [1–3]. Currently, radical nephroureterectomy (RNU) with bladder cuff excision continues to be the therapy of choice in the treatment of these tumours [4].

According to retrospective data, nodal and distant metastases develop in up to 50% of patients with UTUC and a significant proportion of these patients will succumb to their disease [3,5,6]. As such, efforts were put forth to identify independent prognostic factors that may aid in selecting patients at high risk who can be counselled to receive adjuvant chemotherapy as well as establishing specific surveillance protocols. While some data have suggested that tumour stage, grade and lymphovascular invasion and to a lesser extent age, gender and multifocality of disease may have prognostic significance in recurrence and outcome [4,7–11], there remains debate as to whether tumour location (renal pelvis vs ureter) is similarly prognostic. Some small retrospective studies have shown worse outcomes in patients with ureteral tumours [12–14], but others have shown the opposite [15]. Finally, larger recent databases failed to show any differences in survival or recurrence according to tumour location [6,7,16].

Acknowledging this disparity in results, we collected and reviewed a multi-institutional database of patients with UTUC who were homogeneously treated with RNU and bladder cuff excision without perioperative chemotherapy to further elucidate whether tumour location is prognostic in this population.

PATIENTS AND METHODS

This was an institutional review-board-approved study with all participating sites providing the necessary institutional data-sharing agreements before initiation of the study. A total of nine international academic centres provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database comprised 785 patients who underwent RNU with ipsilateral bladder cuff resection since 1990. Following exclusion of patients who received neoadjuvant chemotherapy ($n = 4$) or adjuvant chemotherapy ($n = 63$) and patients in whom tumour location was unknown ($n = 81$), the 637 remaining patients were the subjects of the present analysis. Surgery was performed according to standard criteria for RNU, i.e. extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of bladder cuff. Hilar and regional lymph nodes adjacent to ipsilateral great vessels were generally resected at the discretion of the treating physician. Extended lymphadenectomy was not routinely performed.

All surgical specimens were processed according to standard pathological procedures at each institution. Tumours were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [17].

Tumour grading was assessed according to the 1973 WHO/International Society of Urologic Pathology consensus classification [18]. Lymphovascular invasion was defined as the presence of tumour cells within an endothelium-lined space without underlying muscular walls.

Patients were generally observed every 3 to 6 months for the first year after RNU, every 6 months from the second through to the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scan, chest CT and MRI were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e. death within 30 days of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

Fisher's exact test and chi-squared test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Kruskall–Wallis test. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All reported P values are two-sided.

TABLE 1 Association of tumour location with clinical and pathological characteristics of 637 patients treated with radical nephroureterectomy and bladder cuff excision for upper tract urothelial carcinoma

		Tumour location			
	Cases (%)	Renal pelvis (n = 376, 59%)	Ureter (n = 215, 34%)	Both (n = 46, 7%)	P value
Age (years; median and IQR)	68 (61–75)	68 (60–74.9)	69 (62.1–75.1)	68 (61–73)	0.369
Gender, *n* (%)					
Male	430 (68)	249 (66)	149 (69)	32 (70)	0.709
Female	207 (32)	127 (34)	66 (31)	14 (30)	
Race, *n* (%)					
Caucasian	520 (82)	299 (80)	175 (81)	46 (100)	0.003
Asiatic	117 (18)	77 (20)	40 (19)	0	
Type of surgery, *n* (%)					
Open RNU	591 (93)	340 (90)	206 (96)	45 (98)	0.02
Laparoscopic RNU	46 (7)	36 (10)	9 (4)	1 (2)	
Lymph node dissection, *n* (%)					
Performed	130 (20)	81 (21)	44 (20)	5 (11)	0.238
Not performed	507 (80)	295 (79)	171 (80)	41 (89)	
Pathological stage, *n* (%)					
pTa	151 (24)	99 (26)	46 (21.5)	6 (13)	
pTis	8 (1)	5 (1)	3 (1)	0	
pT1	167 (26)	93 (25)	61 (28.5)	13 (28)	0.007
pT2	132 (21)	62 (17)	61 (28.5)	9 (20)	
pT3	165 (26)	106 (28)	43 (20)	16 (35)	
pT4	14 (2)	11 (3)	1 (0.5)	2 (4)	
Grade, *n* (%)					
G1	92 (14)	59 (16)	29 (13)	4 (9)	0.462
G2	191 (30)	112 (30)	68 (32)	11 (24)	
G3	354 (56)	205 (54)	118 (55)	31 (67)	
Architecture, *n* (%)*					
Papillary	281 (44)	187 (85)	86 (80)	8 (89)	0.379
Sessile	55 (9)	32 (15)	22 (20)	1 (11)	
Number of removed lymph nodes (median and IQR)	4 (2–6)	3 (2–6)	5 (2–7)	2 (2.5–3.5)	0.153
Lymphovascular invasion, *n* (%)					
Absent	525 (82)	299 (82)	189 (89)	37 (80)	0.041
Present	100 (16)	68 (18)	23 (11)	9 (20)	
Concomitant carcinoma *in situ*, *n* (%)					
Absent	565 (89)	338 (90)	188 (87)	39 (84)	0.454
Present	72 (11)	38 (10)	27 (13)	7 (15)	
Lymph node stage, *n* (%)					
N0	110 (17)	67 (18)	39 (18)	4 (9)	0.448
Nx	507 (80)	295 (78)	171 (80)	41 (89)	
N1/2	20 (3)	14 (4)	5 (2)	1 (2)	
Follow-up duration (median and IQR)	37 (18–68)	37 (18–72)	38 (19–67)	31 (13–57.7)	0.423

**Missing in 301 cases. IQR, interquartile range; RNU, radical nephroureterectomy.*

Analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In all, 376 (59%) tumours were located in the renal pelvis, and 215 (34%) in the ureter. Forty-six tumours (7%) were multifocal, involving both renal pelvis and ureter. Table 1 shows the association between tumour location and clinical and pathological features in this cohort. Patients' race, type of surgery, pathological T stage, and prevalence of lymphovascular invasion were significantly different across the three subgroups of patients (all P values <0.05). Notably, follow-up duration was similar in the three subgroups (P = 0.423)

The median follow-up of the entire cohort was 37 months (interquartile range 18–68 months). At the last follow-up, 104 patients (16%) had developed disease recurrence and

90 (14%) were dead as the result of UTUC. An additional 92 patients (14%) experienced non-cancer-related deaths. The median follow-up for the 455 patients alive at the last follow-up was 42 months (interquartile range 19–76 months). The overall 2-year and 5-year recurrence-free survival (RFS) estimates were 86.7% (SE 1.4%) and 81.2% (SE 1.8%), respectively. The overall 2-year and 5-year CSS estimates were 90.7% (SE 1.2%) and 82.7% (SE 1.8%), respectively.

Ureteral tumour location, when associated with renal pelvic disease, was significantly associated with an increased risk of disease recurrence and cancer-specific death. Specifically, the 5-year RFS estimates were 85.3% (SE 2.1%), 79.6% (SE 3.3%) and 56.4% (SE 8.2%), for tumours in the renal pelvis, in the ureter and in both renal pelvis and ureter, respectively (Fig. 1; log-rank pooled over strata *P* value <0.001; renal pelvis vs ureter: $P = 0.229$; both renal pelvis and ureter vs renal pelvis: $P < 0.001$; both renal pelvis and ureter vs ureter: $P = 0.001$). Similarly, the 5-year CSS estimates were 85.4% (SE 2.2%), 83.0% (SE 3.1%) and 59.7% (SE 8.3%), for tumours in the renal pelvis, in the ureter and in both renal pelvis and ureter, respectively (Fig. 2; log-rank pooled over strata *P* value <0.001; renal pelvis vs ureter: $P = 0.502$; both renal pelvis and ureter vs renal pelvis: $P < 0.001$; both renal pelvis and ureter vs ureter: $P = 0.001$).

Tables 2 and 3 summarize univariable and multivariable analyses for RFS (Table 2) and CSS (Table 3), respectively. On univariable analyses, ureteral tumour location was significantly associated with an increased risk of disease recurrence and cancer-related death (*P* for trends <0.001). On multivariable Cox regression analyses that included age, gender, race, surgical type, stage, grade, presence of concomitant CIS and presence of lymphovascular invasion, ureteral tumour location, particularly when associated with multifocal disease in the renal pelvis, was an independent predictor of both RFS (*P* for trend <0.001; ureter vs renal pelvis: hazard ratio 2.1, $P = 0.006$; both renal pelvis and ureter vs renal pelvis: hazard ratio 4.6, $P < 0.001$) and CSS (*P* for trend 0.001; ureter vs renal pelvis: hazard ratio 2.0, $P = 0.027$; both renal pelvis and ureter vs renal pelvis: hazard ratio 4.0, $P < 0.001$).

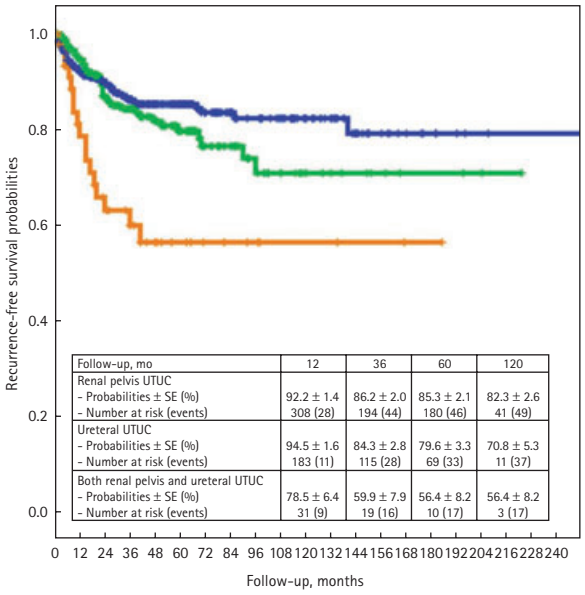

FIG. 1.
Kaplan–Meier curves of recurrence-free survival stratified by tumour location in 637 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. Blue curve: patients with tumours in the renal pelvis; green curve: patients with tumours in the ureter; yellow curve: patients with tumours in both the renal pelvis and ureter. Log-rank pooled over strata P *value <0.001; renal pelvis vs ureter:* P = *0.229; both renal pelvis and ureter vs renal pelvis:* P < *0.001; both renal pelvis and ureter vs ureter:* P = *0.001.*

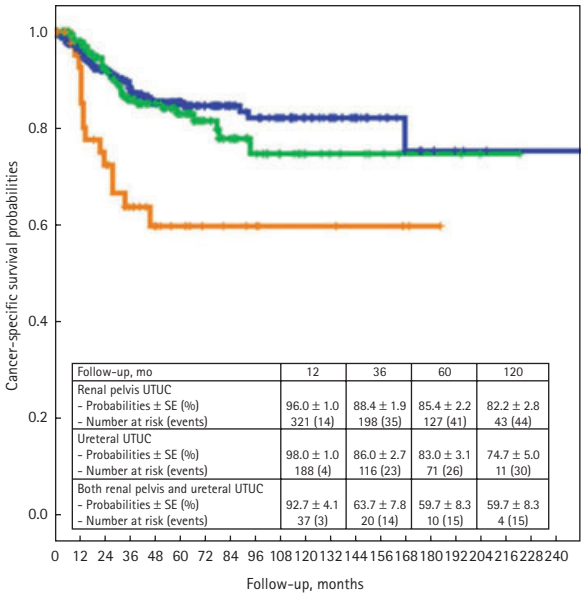

FIG. 2.
Kaplan–Meier curves of cancer-specific survival stratified by tumour location in 637 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. Blue curve: patients with tumours in the renal pelvis; green curve: patients with tumours in the ureter; yellow curve: patients with tumours in both the renal pelvis and ureter. Log-rank pooled over strata P value <*0.001; renal pelvis vs ureter:* P = *0.502; both renal pelvis and ureter vs renal pelvis:* P < *0.001; both renal pelvis and ureter vs ureter:* P = *0.001.*

DISCUSSION

These data confirm the prognostic role of established variables in predicting survival and recurrence of UTUC after RNU. More importantly, it shows that ureteral tumour location, particularly when associated with multifocal disease in the renal pelvis is significantly associated with an increased risk of disease recurrence and cancer-specific death after RNU.

Some clinical and pathological variables have consistently been shown in recent reviews of UTUC to correlate with outcomes [6–9]. This was similarly the case in this study in which pathological stage, concomitant carcinoma *in situ* and lymphovascular invasion were independent prognostic factors for recurrence and cancer-specific mortality. The focus of this analysis was an assessment of the role that tumour location plays in predicting recurrence and survival in patients after RNU for UTUC.

With regards to the clinical and pathological characteristics of the patients with different

TABLE 2 Univariable and multivariable Cox regression analyses of tumour location for prediction of disease recurrence in 637 patients treated with radical nephroureterectomy ipsilateral bladder cuff excision for upper tract urothelial carcinoma (104 recurrences)

	Univariable analysis			Multivariable analysis		
Parameter	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.0	0.99–1.043	0.068	1.01	1.0–1.04	0.318
Race	1.0	0.9–1.2	0.602	1.1	1.0–1.3	0.108
Gender	0.9	0.6–1.3	0.468	1.05	0.6–1.7	0.844
Type of surgery	0.4	0.1–1.4	0.154	0.4	0.5–2.2	0.223
Tumour location			<0.001			<0.001
Renal pelvis only	1	Reference	–	1	Reference	–
Ureter only	1.3	0.8–2.0	0.239	2.1	1.2–3.6	0.006
Both ureter and renal pelvis	3.2	1.9–5.6	<0.001	4.6	2.4–9	<0.001
Pathological stage			<0.001			<0.001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	0.9	0.4–2.0	0.781	0.5	0.2–1.6	0.252
pT2	3.2	1.6–6.5	0.001	2.0	0.8–5	0.146
pT3	6.0	3.2–11.6	<0.001	3.0	1.2–7.5	0.021
pT4	25.1	10–63.0	<0.001	6.8	1.9–24.5	0.003
Grade			<0.001			0.096
G1	1	Reference	–	1	Reference	–
G2	2.2	0.7–6.4	0.159	1.7	0.3–8.5	0.528
G3	6.1	2.2–16.7	<0.001	2.3	0.7–14.5	0.120
Concomitant carcinoma *in situ*	2.9	1.9–4.5	<0.001	2.0	1.1–3.7	0.018
Lymphovascular invasion	3.9	2.6–5.9	<0.001	2.3	1.4–4	0.002
Lymph node stage			<0.001			0.508
N0	1	Reference	–	1	Reference	–
Nx	0.8	0.5–1.4	0.483	1.06	0.6–1.9	0.849
N1/2	3.9	1.8–8.5	0.001	1.7	0.7–4.6	0.264

HR, hazard ratio; 95% CI, 95% confidence interval.

tumour locations, in our patient population, renal pelvic tumours displayed significantly higher pathological stages and trended towards more high-grade tumours and positive nodal stage, which was similar to what was reported by Isbarn *et al.* [16] in an analysis of the Surveillance, Epidemiology and End Results (SEER) registry evaluating more than 2800 patients. One explanation for this discrepancy could be that ureteral tumours become symptomatic earlier because of obstruction at lower stages and grades and hence become detectable by endoscopy earlier compared with renal pelvic tumours that may progress before any symptomatic manifestation of disease or obstruction.

Whereas some earlier publications showed a trend towards worse prognosis for ureteral location [12–14], more recent large cohorts have failed to make any correlation between location and outcome [7,16,19]. Specifically, Isbarn *et al.* found that patients with renal pelvis UTUC had lower CSS estimates, compared with those with ureteral cancers in univariate analysis; tumour location, however, failed to be an independent predictor of survival in multivariate analysis that adjusted for the effect of other clinical and pathological covariates [16]. Raman *et al.* [19] reported in a large multi-institutional collaboration that patients with renal pelvis and ureter tumours had similar outcomes and tumour location was not an independent predictor of patients' outcomes.

Our present study shows on multivariate analysis that ureteral location with or without multifocal disease is an independent prognostic factor for both worse disease recurrence and cancer-specific mortality. However, on Kaplan–Meier survival analysis, ureteral tumour location, only when associated with multifocal disease in the renal pelvis, becomes associated with significantly worse RFS and CSS compared with unifocal locations. Although the multifocality of disease has been previously addressed in the literature and been shown to be possibly associated with worse outcomes, the location of the multiple foci was not made clear and included multiple tumours occurring within the same anatomic location [20–23]. As far as we know, this is the first report to show this important distinction in which ureteral location of tumours with synchronous renal pelvic foci imparts a worse prognosis compared with single location only. The nature of this association still remains unclear, but the implications are important for the prognostication and counselling of this subset of patients with UTUC.

One postulated hypothesis to explain the worse outcome with ureteral tumours is that the presence of a thinner layer of adventitia containing an extensive plexus of blood vessels and lymphatics surrounding the ureter facilitates tumour lymphatic and haematogenous spread. Furthermore, the smooth muscle layer of the ureter is thinner, allowing for higher stage when minimal tumour invasion occurs. Comparatively, the renal pelvis displays a thicker adventitial layer with associated abundant renal parenchyma that allows for wider surgical resection margins, which may provide a protective role.

One strength of this study is that, unlike some of the earlier publications, which had smaller population samples and reflected the single-institution experiences of tertiary centres, this study reflected the experience of multiple large institutions from several countries, rendering these results more generalizable. Furthermore, this study has some marked differences compared with the recent large studies by Isbarn *et al.* [16] and Margulis *et al.* [7], which failed to show a significant difference in outcomes between ureteral and renal pelvic tumour locations. First, whereas those studies included all patients who underwent an RNU regardless of whether a bladder cuff excision was performed; all patients had a bladder cuff excision in the present study. Recognizing that a bladder cuff excision alongside RNU is currently widely considered the standard therapy [1,24,25], excluding patients who did not undergo bladder cuff excision reflected a more homogeneous standard of

care therapy. Second, Isbarn *et al.* [16] performed a population-based analysis of the SEER database, which does not capture some pertinent parameters such as tumour characteristics (tumour architecture, lymphovascular invasion, concomitant carcinoma *in situ*, multifocality) and longitudinal parameters such as use of adjuvant therapy and recurrence information. These variables were included in our analysis and may have also contributed to the discrepancy in results. Lastly, when comparing available cohorts overall, the study by Margulis *et al.* [7] included all patients who had received adjuvant chemotherapy (13% of their cohort, 43% of lymph-node-positive patients) in their analyses. Our analysis excluded these patients because the indication for adjuvant therapy in UTUC is primarily based on the presence of nodal metastasis. As most patients in this study, as well as in the study by Margulis *et al.* [7], did not undergo lymphadenectomy, including patients who received adjuvant chemotherapy would have introduced a significant bias on the analysis.

Our study has its limitations, such as its retrospective nature and the fact that previous endo-urological and percutaneous therapies as well as the time lapse between diagnosis and surgical intervention were not reported, we believe that in the absence of a prospective randomized controlled trial comparing ureteral and renal pelvic tumour locations head-to-head, it provides an accurate analysis of the impact of tumour location and multifocality on prognosis in patients with UTUC after RNU with bladder cuff excision. Moreover, although the study period spans two decades and the data may not represent current practice patterns, 60% of the patients in the study were treated in the year 2000 or thereafter.

Ureteral tumour location, particularly in association with multifocal disease in the renal pelvis, is an independent prognostic factor for both higher disease recurrence and cancer-specific mortality. Whether ureteral tumours have a different biology or whether anatomic variation affects disease dissemination remains unknown. As such, these patients with invasive multifocal disease could be candidates for exploring adjuvant therapy and may require closer surveillance.

TABLE 3 Univariable and multivariable Cox regression analyses of tumour location for prediction of cancer-specific mortality in 637 patients treated with radical nephroureterectomy with ipsilateral bladder cuff excision for upper tract urothelial carcinoma (90 cancer-specific deaths)

	Univariable analysis			Multivariable analysis		
Parameter	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.03	1–1.05	0.023	1.02	1.0–1.06	0.106
Race	0.9	0.8–1.1	0.460	1.1	0.9–1.3	0.335
Gender	0.7	0.4–1.2	0.190	0.9	0.5–1.5	0.576
Type of surgery	0.3	0.3–1.7	0.148	0.3	0.3–2.0	0.196
Tumour location			0.001			0.001
Renal pelvis only	1	Reference	–	1	Reference	–
Ureter only	1.2	0.7–1.7	0.520	2.0	1.1–3.6	0.027
Both ureter and renal pelvis	3.0	1.7–53.4	<0.001	4.0	1.9–8.2	<0.001
Pathological stage			<0.001			<0.001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.0	0.4–2.4	0.935	0.6	0.2–2.2	0.464
pT2	2.9	1.3–6.4	0.008	2.1	0.7–6.2	0.203
pT3	6.9	3.4–14.2	<0.001	3.7	1.2–11.1	0.018
pT4	36.5	13.9–95.7	<0.001	10.1	2.4–42.0	0.001
Grade			<0.001			0.276
G1	1	Reference	–	1	Reference	–
G2	2.0	0.7–5.9	0.215	1.4	0.3–7.3	0.713
G3	5.1	1.8–13.9	0.002	2.4	0.5–11.1	0.269
Concomitant carcinoma *in situ*	2.8	1.8–4.6	0.001	2.0	1.04–4.0	0.037
Lymphovascular invasion	4.2	2.7–6.6	<0.001	2.4	1.3–4.3	0.005
Lymph node stage			<0.001			0.197
N0	1	Reference	–	1	Reference	–
Nx	1.1	0.6–2.1	0.727	1.4	0.7–2.8	0.347
N1/2	6.1	2.6–14.3	<0.001	2.6	0.9–7.3	0.071

HR, hazard ratio; 95% CI, 95% confidence interval.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **UTUC**, upper tract urothelial carcinoma; **RNU**, radical nephroureterectomy; **RFS**, recurrence-free survival; **CSS**, cancer-specific survival; **SEER**, Surveillance, Epidemiology and End Results.