



Preintervention risk stratification of renal pelvic cancer and ureteral cancer should differ

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Purpose: To identify different preintervention prognostic factors between renal pelvic cancer (RPe) and ureteral cancer (Uc) and to develop different preintervention risk stratifications for each cancer type.

Materials and Methods: A total of 1,768 patients with organ-confined upper urinary tract urothelial carcinoma (1,067 patients with RPe and 701 with Uc) who presented between 2004 and 2015 were selected from the Surveillance, Epidemiology, and End Results database. Clinicopathologic characteristics were compared between RPe and Uc. Univariable and multivariable Cox regression models were used to examine the prognostic ability of the clinicopathologic characteristics with respect to oncology outcomes.

Results: Age greater than 75 years was significantly associated with cancer-specific survival (CSS) in RPe patients but not in Uc patients. Tumor size had a significant influence on CSS in Uc patients but not in RPe patients; in contrast, age had an influence in RPe but not in Uc. Unlike CSS, age was significantly associated with overall survival (OS) in both RPe and Uc. Tumor size had an effect on OS in Uc patients but not in RPe patients.

Conclusions: The preintervention prognostic factors differed between RPe and Uc. Thus, we should develop separate preintervention risk stratification standards for RPe and Uc. Using these specific preintervention risk stratifications, we may be able to select the most appropriate surgical options for patients in the clinic.

Keywords: Prognosis; Risk factors; Ureteral neoplasms

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INTRODUCTION

According to the guidelines of the European Association of Urology (EAU), as well as most clinical studies, renal pelvic cancer (RPe) and ureteral cancer (Uc) are considered an integral group and are collectively referred to as upper urinary tract urothelial carcinoma (UTUC). The rationale for this combined grouping is that both the renal pelvis and the ureter are derived from the mesoderm, and their cancers show similar etiology, clinical features, and diagnosis [1]. In the clinical treatment of RPe and Uc, only one preinter-

vention risk stratification standard is used to divide patients into low-risk and high-risk groups, and a surgical procedure is then selected according to the results of the risk stratification: kidney-sparing surgery (KSS) for low-risk patients and radical nephroureterectomy (RNU) for high-risk patients.

However, the renal pelvis and the ureter are two different organs with specific anatomic structures and surrounding tissues. These variations result in differences between RPe and Uc. For example, patients with Uc are more likely to experience hydronephrosis, which can cause flank pain and become very noticeable to the patient, whereas patients

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with RPc do not experience this symptom. In addition, Uc can directly invade the surrounding tissues, whereas RPc must invade the renal parenchyma before it invades the surrounding Gerota fascia [2]. In addition to the abovementioned differences, the tumor characteristics of each cancer also differ; for instance, 55% to 75% of Uc cases are low-grade and low-stage, approximately 85% of RPc cases are papillary, and squamous cell cancers are six times as frequent in the renal pelvis as in the ureter [3,4]. Moreover, an increasing number of recent studies have reported different oncologic outcomes of RPc and Uc, even if the stage or grade of the cancers was similar [2,5-7].

Considering these differences, some authors disagree that the same preintervention risk stratification standard be used for both RPc and Uc [2,5,8]. Therefore, whether we can still use this risk stratification standard for both RPc and Uc remains controversial.

In the present study, owing to the small number of patients with UTUC, we aimed to use the Surveillance, Epidemiology, and End Results (SEER) database to identify different preintervention prognostic factors for patients with RPc and Uc, which enabled us to develop a preintervention risk stratification for each of these cancers and to select a more appropriate treatment approach for patients.

MATERIALS AND METHODS

1. Data source and patients

In this study, data were obtained from the SEER database released in 2018. SEER*Stat software (ver. 8.3.5) was used in client-server mode to perform all data queries. We obtained access to the SEER database, along with additional information, for research purposes only.

After identifying patients with RPc or Uc (the primary cancer site located in the renal pelvis or ureter using the code C65.9 or C66.9, respectively), we excluded patients with non-organ-confined (pT3+ or N+ or M+) cancer. We focused on patients with organ-confined disease (\leq pT2 and N0M0) because KSS can only be considered when the cancer is not invasive and when patients can be distinguished from those with pT3 or higher disease by preoperative clinical examination; in contrast, those with pT1 and pT2 disease cannot be clinically distinguished from each other before surgery. The other exclusion criteria were as follows: 1) patients diagnosed before 2004, 2) patients without primary site surgery, 3) patients with more than one primary tumor, 4) patients who underwent radiotherapy and/or chemotherapy, and 5) patients with incomplete information on tumor stage, grade, size, chemotherapy, radiation, and survival.

2. Variables

From the SEER database, we gathered information on the location of the tumor, age, sex, race, year of diagnosis, laterality, tumor stage, grade, size, histologic type, additional therapy information (chemotherapy and radiation), and follow-up information (survival months, cause-specific death, and other cause of death).

Patients were divided into five groups according to age (\leq 54, 55–64, 65–74, 75–84, and \geq 85 years). According to this group, we sought to determine whether age has a prognostic role, and if so, at what age patients have a worse prognosis. Diagnosis was divided into two groups according to year (2004–2009 and 2010–2015) because we collected data for 12 years and divided the time period in half for balance. Patients were also divided into three groups based on race/ethnicity (white, black, and other). For tumor grade, we combined grade I (well differentiated) and grade II (moderately differentiated) tumors into one group because most tumors classified as grade II according to the 1973 World Health Organization (WHO) classification were reassigned as low-grade carcinoma according to the 2004 WHO classification [9]. Histologic type was classified as transitional cell carcinoma or variant histology.

The outcomes were cancer-specific survival (CSS) (failure was patient death due to UTUC) and overall survival (OS) (failure was patient death due to any cause).

3. Statistical analyses

Patients were divided into two groups according to the primary tumor location, and the chi-square test and Fisher's exact method were used to evaluate the association between tumor location and clinicopathologic features. We estimated Kaplan–Meier survival functions and performed log-rank tests to assess associations between tumor location and time to survival. Next, univariable and multivariable Cox proportional hazards regression models were used to examine the prognostic role of each clinicopathologic characteristic in patients with RPc and Uc, respectively. All p-values are two-sided, and statistical significance was set at less than 0.05. All analyses were performed with PASW Statistics (ver. 18.0; SPSS Inc, Chicago, IL, USA).

RESULTS

We identified 15,080 patients with either RPc or Uc who presented from 2004 to 2015. According to the exclusion criteria mentioned above, a total of 1,768 patients met our inclusion criteria for further analysis. The exclusion details are shown in Supplementary Fig. 1.

Of the 1,768 patients, 1,067 (60.4%) were diagnosed with RPc and 701 (39.6%) were diagnosed with Uc. Detailed information on the patients' clinical characteristics is listed in Table 1. Compared with the RPc group, the Uc group was more likely to contain older patients. Sex, laterality, and tumor grade were similar between the two groups; however, patients with RPc were more likely to be black and to have more T1 stage tumors, a larger tumor size, and lower pathologic variation.

A Kaplan–Meier analysis revealed that patients with Uc had lower CSS and OS than did patients with RPc (p=0.003 and 0.003, respectively) (Fig. 1). To further investigate the impact of the preintervention prognostic factors on survival, we performed a Cox regression analysis of patients with either RPc or Uc. As shown in Table 2, age greater than 75

years had a significant association with CSS in RPc patients but not in Uc patients. Tumor grade had prognostic roles in CSS in both RPc and Uc patients, but notably, only grade IV cancer had a negative influence on CSS in Uc patients. Interestingly, tumor size had a significant influence on CSS in Uc patients but not in RPc patients, just as age had an influence in RPc but not in Uc.

The Cox regression analysis of the association between variables and OS in patients with RPc and Uc is shown in Table 3. Unlike CSS, age demonstrated a significant association with OS not only in RPc but also in Uc, although this association was only observed when the age of Uc patients was greater than 75 years. The association of tumor grade with OS remained in both RPc and Uc patients. Similar to CSS, tumor size had an effect on OS in Uc patients but not

Table 1. Characteristics of 1,768 patients with organ-confined upper urinary tract urothelial carcinoma

Variable	Total	Renal pelvis	Ureter	p-value
No. of patients	1,768	1,067	701	
Year of diagnosis				0.039
2004–2009	805 (45.5)	507 (47.5)	298 (42.5)	
2010–2015	963 (54.5)	560 (52.5)	403 (57.5)	
Age (y)				0.002
≤54	150 (8.5)	109 (10.2)	41 (5.8)	
55–64	341 (19.3)	222 (20.8)	119 (17.0)	
65–74	552 (31.2)	325 (30.5)	227 (32.4)	
75–84	532 (30.1)	299 (28.0)	233 (33.2)	
≥85	193 (10.9)	112 (10.5)	81 (11.6)	
Sex				0.762
Male	996 (56.3)	598 (56.0)	398 (56.8)	
Female	772 (43.7)	469 (44.0)	303 (43.2)	
Race				0.007
White	1,537 (86.9)	925 (86.7)	612 (87.3)	
Black	80 (4.5)	60 (5.6)	20 (2.9)	
Other	151 (8.5)	82 (7.7)	69 (9.8)	
Laterality				0.554
Left	888 (50.2)	542 (50.8)	346 (49.4)	
Right	880 (49.8)	525 (49.2)	355 (50.6)	
Stage				<0.001
pT1	1,152 (65.2)	771 (72.3)	381 (54.4)	
pT2	616 (34.8)	296 (27.7)	320 (45.6)	
Grade				0.099
I and II	563 (31.8)	344 (32.2)	219 (31.2)	
III	397 (22.5)	255 (23.9)	142 (20.3)	
IV	808 (45.7)	468 (43.9)	340 (48.5)	
Tumor size (cm)				<0.001
≤1	145 (8.2)	53 (5.0)	92 (13.1)	
>1 and ≤3	756 (42.8)	436 (40.9)	320 (45.6)	
>3	867 (49.0)	578 (54.2)	289 (41.2)	
Histological type				0.045
TCC	1,718 (97.2)	1,030 (96.5)	688 (98.1)	
Variant	50 (2.8)	37 (3.5)	13 (1.9)	

Values are presented as number only or number (%).
TCC, transitional cell carcinoma.

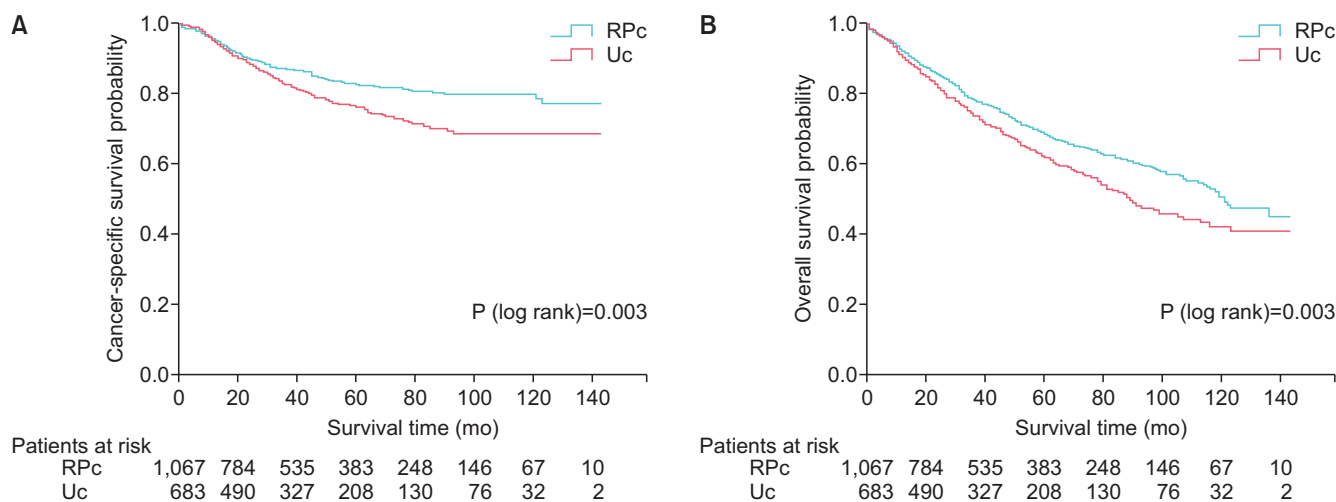


Fig. 1. Kaplan–Meier curves of cancer-specific survival (A) and overall survival (B). RPc, renal pelvic cancer; Uc, ureteral cancer.

in RPc patients.

DISCUSSION

The information described above supports that RPc and Uc are undoubtedly two different tumors. However, for these two cancer types, only one preintervention risk stratification has been used, and surgical options, KSS or RNU, have been confirmed according to the results of the tumor risk stratification. Moreover, although some previous studies have identified the prognostic factors of UTUC, such as tumor stage and grade, among others [10-15], it is notable that all these studies considered RPc and Uc as one integral group, and the differences between them mentioned above were ignored; thus, their conclusions may not be appropriate for patients with one of these two types of cancer. To select more appropriate surgical options, we aimed to determine the different preintervention prognostic factors between RPc and Uc and to develop risk stratification criteria for each type of cancer.

We used the SEER database in this study because of the low number of UTUC cases. Thus, we focused on organ-confined disease (\leq pT2, N0, and M0) for the two reasons described below. First, KSS should be considered only if the tumor is not invasive, but it is difficult to distinguish between pT1 and pT2 tumors according to preoperative examinations, such as preoperative computerized tomography and/or magnetic resonance imaging. However, pT2 stage or less can be roughly distinguished from pT3 or greater. Therefore, for this study, we selected patients from the SEER database with pT2 or lower-stage tumors. Second, some predictive tools for non-organ-confined disease have been developed in some studies [14,16,17] and reviews [18,19], but to our knowledge, no

prediction tool has been established for organ-confined cancer.

Interestingly, after the multivariate analysis, we found that advanced age was significantly associated with both the CSS and OS of RPc patients, whereas in Uc, advanced age was associated with OS only. Large multi-institutional studies have not identified age as a prognostic factor for survival [20,21], even though it has been associated with survival in more aggressive tumors [22]. In the EAU guideline for UTUC, age is no longer considered an independent prognostic factor, and therefore it was not included in the preintervention risk stratification standard of UTUC. However, as mentioned above, most of these studies considered RPc and Uc as a single group and ignored the differences between them.

Similar to age, the prognostic role of tumor size in survival outcomes remains unclear [23,24] despite the worse influence of larger tumors [25,26]. Tumors larger than 1 cm are considered high-risk tumors in the EAU guidelines [27], and some studies have shown that tumors >3 to 4 cm may be associated with a worse survival and a higher risk for bladder cancer recurrence [26,28,29]. Therefore, we divided patients into three groups (≤ 1 cm, 1 to 3 cm, >3 cm) according to tumor size and found that tumor size was associated with Uc only and not RPc, which was the opposite of that observed for age. The reason behind this observation may be that Uc can be detected early because it is more likely to cause hydronephrosis and flank pain. On the basis of this result, we can include tumor size in the preintervention risk stratification standard for Uc but not the standard for RPc.

Our study had several limitations. First, this study was nonrandomized and retrospective in nature, which inevitably leads to data limitations. Moreover, some preoperative

Table 2. Results of Cox regression analyses evaluating variables associated with cancer-specific survival

Variable	Renal pelvic cancer				Ureter cancer			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of diagnosis								
2004–2009	Reference				Reference			
2009–2015	0.819 (0.580–1.155)	0.255			0.819 (0.568–1.181)	0.284		
Age (y)								
≤54	Reference		Reference		Reference			
55–64	1.27 (0.580–2.802)	0.545	1.166 (0.530–2.565)	0.703	0.577 (0.239–1.394)	0.222		
65–74	1.514 (0.726–3.158)	0.269	1.429 (0.684–2.984)	0.342	1.143 (0.537–2.432)	0.730		
75–84	2.956 (1.459–5.990)	0.003	2.537 (1.249–5.152)	0.010	1.221 (0.574–2.595)	0.604		
≥85	6.103 (2.926–12.731)	<0.001	5.385 (2.577–11.25)	<0.001	2.140 (0.963–4.754)	0.062		
Sex								
Male	Reference				Reference			
Female	0.975 (0.708–1.342)	0.875			1.200 (0.854–1.686)	0.294		
Race								
White	Reference				Reference			
Black	1.981 (0.481–2.005)	0.959			1.250 (0.510–3.063)	0.625		
Other	1.483 (0.882–2.494)	0.137			1.500 (0.911–2.470)	0.111		
Laterality								
Left	Reference				Reference			
Right	1.166 (0.849–1.602)	0.342			1.188 (0.844–1.671)	0.323		
Grade								
I and II	Reference		Reference		Reference		Reference	
III	2.489 (1.562–3.968)	<0.001	2.219 (1.388–3.546)	0.001	1.582 (0.928–2.697)	0.092	1.600 (0.938–2.729)	0.085
IV	2.650 (1.717–4.090)	<0.001	2.376 (1.535–3.676)	<0.001	2.395 (1.545–3.711)	0.000	2.468 (1.592–3.827)	<0.001
Tumor size (cm)								
≤1	Reference				Reference		Reference	
>1 and ≤3	1.207 (0.483–3.015)	0.687			2.347 (1.122–4.908)	0.023	2.525 (1.207–5.284)	0.014
>3	1.586 (0.645–3.899)	0.315			2.745 (1.317–5.722)	0.007	2.899 (1.390–6.044)	0.005
Histological type								
TCC	Reference				Reference			
Variant	0.811 (0.333–1.979)	0.646			2.228 (0.911–5.449)	0.079		

HR, hazard ratio; CI, confidence interval; TCC, transitional cell carcinoma.

factors that have been shown to have a prognostic effect, such as body mass index (BMI), ECOG-PS (Eastern Cooperative Oncology Group Performance Status), obesity (BMI>30 kg/m²), and sessile architecture, among others, are not available in the database. Second, we did not consider recurrence-free survival or intravesical recurrence, which is necessary for cancer outcome. Therefore, more clinical research is

needed to confirm our results. Third, surgery details are unavailable from the SEER database, which may affect the results because of significant variations between different institutions.

Table 3. Results of Cox regression analyses evaluating variables associated with overall survival

Variable	Renal pelvic cancer				Ureter cancer			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of diagnosis								
2004–2009	Reference				Reference			
2009–2015	0.837 (0.649–1.080)	0.172			0.773 (0.583–1.024)	0.073		
Age (y)								
≤54	Reference		Reference		Reference		Reference	
55–64	1.785 (0.971–3.283)	0.062	1.672 (0.909–3.078)	0.099	0.893 (0.391–2.040)	0.778	0.817 (0.357–1.870)	0.632
65–74	2.406 (1.360–4.254)	0.003	2.301 (1.300–4.072)	0.004	2.062 (0.993–4.282)	0.052	1.898 (0.913–3.945)	0.086
75–84	4.571 (2.622–7.968)	<0.001	4.103 (2.348–7.169)	<0.001	2.881 (1.400–5.928)	0.004	2.596 (1.259–5.351)	0.010
≥85	10.218 (5.763–18.12)	<0.001	9.413 (5.301–16.716)	<0.001	4.752 (2.248–10.05)	<0.001	4.316 (2.036–9.147)	<0.001
Sex								
Male	Reference				Reference			
Female	0.889 (0.713–1.108)	0.296			1.099 (0.856–1.411)	0.457		
Race								
White	Reference				Reference			
Black	1.277 (0.827–1.971)	0.270			1.183 (0.607–2.306)	0.621		
Other	1.098 (0.729–1.653)	0.656			1.239 (0.835–1.838)	0.287		
Laterality								
Left	Reference				Reference			
Right	0.992 (0.798–1.234)	0.945			1.261 (0.981–1.621)	0.070		
Grade								
I and II	Reference				Reference		Reference	
III	1.777 (1.326–2.381)	<0.001	1.528 (1.137–2.054)	0.005	1.573 (1.095–2.261)	0.014	1.300 (0.901–1.875)	0.161
IV	1.854 (1.410–2.437)	<0.001	1.618 (1.229–2.130)	0.001	1.890 (1.386–2.578)	<0.001	1.827 (1.338–2.495)	<0.001
Tumor size (cm)								
≤1	Reference				Reference		Reference	
>1 and ≤3	1.080 (0.610–1.910)	0.792			1.814 (1.141–2.882)	0.012	1.843 (1.158–2.934)	0.010
>3	1.185 (0.675–2.080)	0.555			1.658 (1.038–2.649)	0.034	1.632 (1.020–2.610)	0.041
Histological type								
TCC	Reference				Reference			
Variant	0.488 (0.231–1.033)	0.061			1.623 (0.765–3.442)	0.207		

HR, hazard ratio; CI, confidence interval; TCC, transitional cell carcinoma.

CONCLUSIONS

The preintervention prognostic factors differed between RPc and Uc, which should serve as the basis for developing separate preintervention risk stratification standards for RPc and Uc (advanced age should be included in the risk stratification standard for RPc, and tumor size should be in-

cluded in the risk stratification for Uc). With these specific preintervention risk stratifications, we may be able to choose the most appropriate surgical intervention for patients in a clinical setting.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Jinhai Fan and Dalin He. Data acquisition: Tao Yang, Nan Zhang, and Bo Yang. Statistical analysis: Tao Yang and Junjie Fan. Data analysis and interpretation: Tao Yang and Jinhai Fan. Drafting of the manuscript: Tao Yang. Critical revision of the manuscript: Dalin He. Obtaining funding: Jinhai Fan. Administrative, technical, or material support: Dalin He. Supervision: Jinhai Fan and Dalin He. Approval of the final manuscript: Jinhai Fan.

SUPPLEMENTARY MATERIAL

Scan this QR code to see the supplementary material, or visit <https://www.icurology.org/src/sm/icurology-61-397-s001.pdf>.



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