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ORIGINAL ARTICLE

pT3 subclassification of renal pelvic cancer considering the tumor location improves the patients' prognostic accuracy

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Abstract

Whether pT3 urothelial carcinoma of the renal pelvis (UCRP) and urothelial carcinoma of the ureter (UCU) have the same prognosis is controversial, this study compared the prognosis of pT3 UCRP with that of pT3 UCU. We retrospectively evaluated 954 patients who underwent nephroureterectomy at our institutions between January 1983 and December 2017. All surgical specimens were reviewed by a single genitourinary pathologist. Cases of pT3 UCRP were subclassified as pT3a (urothelial carcinomas extending only to the renal medulla) and pT3b (urothelial carcinomas extending into the renal cortex and/or peripelvic adipose tissue). Fine and Gray's model was used to predict recurrence-free survival (RFS) and cancer-specific survival (CSS). A total of 493 (51.7%) had UCRP and 461 (48.3%) had UCU. Within this group, 202 patients had pT3 UCRP and 146 had pT3 UCU. The pT3 subclassification of UCRP resulted in 79 cases of pT3a and 120 of pT3b. The difference in 5-year CSS among the pT3a UCRP, pT2 UCRP, and pT2 UCU subgroups was not statistically significant (pT3a UCRP vs pT2 UCRP, HR = 0.69, $p = 0.56$; pT3a UCRP vs pT2 UCU, HR = 0.66, $p = 0.31$) However, RFS and CSS were significantly higher in the pT3a UCRP group than in the pT3b group (pT3a vs pT3b, HR = 2.59, $p = 0.0038$ and pT3a vs pT3b, HR = 3.10, $p = 0.001$). The results suggest that our proposed pT3 subclassification better predicts the prognosis of UCRP patients than does the pT3 of the current AJCC/UICC classification.

Keywords Urothelial carcinoma of the upper urinary tract · pT3 subclassification · Corticomedullary junction · Parenchymal invasion · Prognosis

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon disease that accounts for ~ 10% of all renal tumors and ~ 5% of all urothelial carcinomas [23, 26]. Although ~ 60% of UTUCs are invasive tumors at diagnosis [12], few studies have addressed the pathological prognostic factors in detail. Pathological tumor stage (pT), the presence of lymphovascular invasion (LVI), tumor location, histological grade, and lymph node metastasis are well-known and important pathological prognostic factors [11, 14–16, 20, 29]. Interestingly, in some studies, patients with urothelial carcinoma of the renal pelvis (UCRP) had a significantly better prognosis than those with urothelial carcinoma of the ureter (UCU) [1, 17], whereas in others the prognosis was the same [7, 10, 21].

In the 2017 American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) classification, UCRPs infiltrating the renal parenchyma are defined as pT3 tumors [2, 4]. However, the depth of renal parenchymal infiltration is not considered. In some reports, the degree of infiltration into the renal parenchyma was shown to correlate with the prognosis of patients with pT3 UCRP and several subclassification systems were developed accordingly [22, 24, 25]. However, their usefulness is unclear, as is the mechanism underlying this finding.

In this study, we examined the prognoses of UCRP and UCU patients according to our proposed subclassified UTUC pT classification, which is based on precise anatomical criteria. Our aim was to reveal the exact mechanism underlying the difference in prognosis between pT3 UCRP and pT3 UCU patients.

Materials and methods

In total, 1289 patients with UTUC underwent radical nephroureterectomy (RNU) with bladder cuff excision between January 1983 and December 2017. The records were retrieved from the treating physicians and five participating institutions. Patients with the following characteristics were excluded: multifocal tumors, unknown clinical details, concomitant ipsilateral ureteral cancer, distant metastasis, concomitant invasive bladder cancer, and neoadjuvant chemotherapy. Of the remaining patients, 954 were eligible for this study (Fig. 1). The clinicopathological data included sex, age at diagnosis, laterality, operative method, pathological tumor characteristics, pT, tumor location, WHO/ISUP grade, histological variant, LVI, and pathological lymph node stage (pN). Adjuvant chemotherapy was performed with regimens of methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin.

The primary endpoint of this study was overall survival (OS), which was defined as the time from RNU to death from any cause. The secondary endpoint was recurrence-free survival (RFS) and cancer-specific survival (CSS). RFS was defined as the time from RNU to extravesical recurrence. CSS was defined as the time from RNU to death attributable to a cancer-related complication. Extravesical recurrence (lymph node metastasis, distant metastasis, and local recurrence) was an endpoint in this study, but intravesical recurrence was not.

Pathological evaluation

All HE slides in this study were retrospectively reviewed by one genitourinary pathologist (T.T.). Pathological evaluations were concerned with the pT stage, pN, WHO/ISUP grade, LVI, and histological variant [24].

We subclassified pT3 into pT3a and pT3b according to the depth of tumor invasion, as reported previously [24]. Briefly, pT3a was defined as tumors extending only into the renal medulla, without normal glomeruli surrounded by carcinoma cells. pT3b was defined as tumors extending into the renal cortex (with normal glomeruli surrounded by carcinoma cells) or into the peripelvic adipose tissue (Fig. 2 and Supplementary Figure 1).

Statistical analyses

The clinicopathological features of the two groups were compared using Fisher's exact test for categorical variables and the Wilcoxon signed-rank test for continuous variables. Cumulative incidence curves were used in a competing-risks setting to calculate the probabilities of CSS and RSS. The cumulative incidence curves for patients stratified by tumor stage and location were compared using Gray's test. The influence of prognostic factors on CSS and RFS was estimated using Fine and Gray's model [8]. OS was estimated using the Kaplan–Meier method and compared among groups using the log-rank test. Multivariate analyses using the Cox proportional hazards model were performed to evaluate the influence of prognostic factors for OS. p values < 0.05 were considered significant. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA).

Results

The clinicopathological characteristics of the patients are listed in Table 1. In all, 493 patients (51.7%) with UCRP and 461 patients (48.3%) with UCU were included in the analyses. Average and median patient age was 67.5 and 69 years (range 33–88 years). The median follow-up period was 57 months (range 2–340 months). A total of 896 patients (94%) were diagnosed as pure urothelial carcinomas (renal pelvis 458, ureter 438) and 58 patients (6%) contained variant

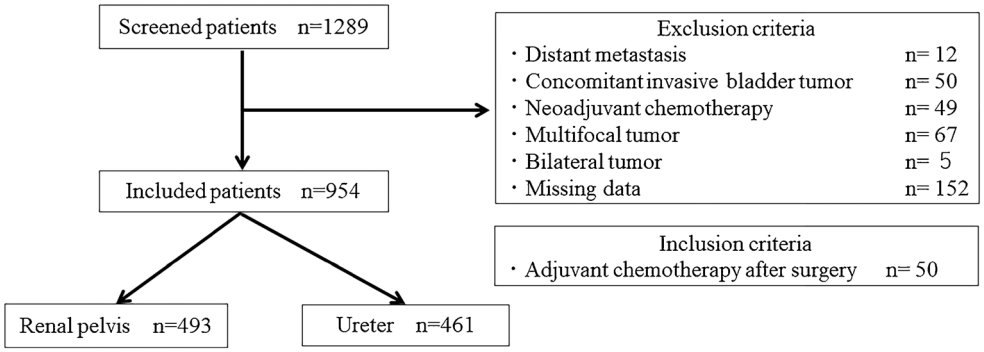

Fig. 1 Exclusion/inclusion criteria in this study. Patients who underwent radical nephroureterectomy with bladder cuff excision between January 1987 and December 2017. The records were retrieved from the treating physicians and five participating institutions

histology (renal pelvis 35, ureter 23). The detail of histology in each organ was shown in Table 1. A total of 202 cases were pT3 UCRP and 146 were pT3 UCU. The pT3 subclassification of UCRP resulted in 79 pT3a and 120 pT3b cases. There were more non-papillary (58% vs 28%), pN-positive (32% vs 8%), and LVI cases (66% vs 19%) among patients with pT3b UCRPs. pT3b tumors tended to have worse prognostic factors.

Recurrence-free survival and cancer-specific survival

Overall, 100 patients (20%) with UCRP and 103 (22%) with UCU experienced extravesical recurrence; 97 (19.6%) and 85 patients (18.4%) died of their disease during follow-up.

The RFS and CSS rates in patients with UCRP and UCU decreased according to the pT stage (Fig. 3). Table 2 shows the 5-year RFS and CSS stratified by pT and location. We examined the hazard ratios (HRs) of RFS and CSS in each pathological stage (Table 3). No significant differences were found in the 5-year RFS or 5-year CSS among pT3a UCRP, pT2 UCRP, and pT2 UCU (5-year RFS, pT3a UCRP 81.7% vs pT2 UCRP 80% ($p = 0.74$) and pT3a UCRP vs pT2 UCU 81.8% ($p = 0.72$); 5-year CSS, pT3a UCRP 80.6% vs pT2 UCRP 87.4% ($p = 0.57$) and pT3a UCRP 81.7% vs pT2 UCU 88.2% ($p = 0.31$)). Both the RFS and CSS rates were significantly higher in pT3a UCRP than in pT3b UCRP patients (5-year RFS, pT3a UCRP 81.7% vs pT3b UCRP 42.9%, HR = 2.59, $p = 0.0038$; 5-year CSS, pT3a UCRP 80.6% vs pT3b UCRP 42%, HR = 3.10, $p = 0.001$) and pT3 UCU patients (5-year RFS, pT3a UCRP 81.7% vs pT3 UCU 40.6%, HR = 2.34, $p = 0.0084$; 5-year CSS, pT3a UCRP 80.6% vs pT3 UCU 50.8%, HR = 2.29, $p = 0.0179$) (Table S1).

According to Fine and Gray's model of RFS, pT stage ($p < 0.001$), pN (HR = 1.72, $p = 0.011$), WHO/ISUP grade (HR = 3.93, $p = 0.008$), and LVI (HR = 1.58, $p = 0.015$) were associated with tumor recurrence (Table 3). Squamous cell differentiation (HR = 1.62, $p = 0.007$) and sarcomatoid change

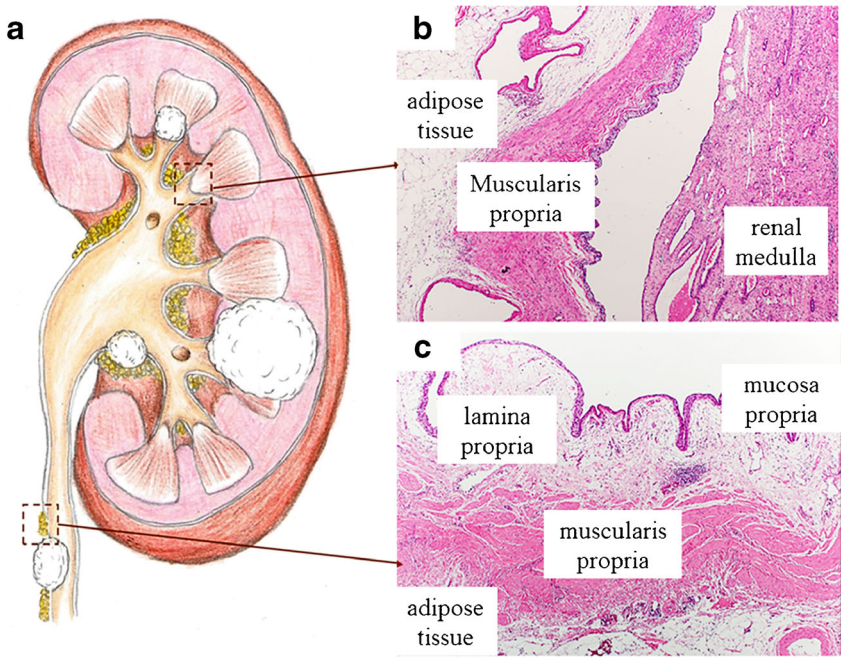

Fig. 2 Anatomical features of the renal pelvis and ureter, and definition of subclassification of pT3 urothelial carcinoma. **a** Proposed pT3 subclassification—pT3a, carcinoma only infiltrates the renal medulla without peripelvic adipose tissue invasion. pT3b, carcinoma infiltrates the renal cortex or the peripelvic adipose tissue. Anatomical features of the renal pelvis and ureter. **b** Note the lack of the muscularis propria in the pyramid (right side). By contrast, the muscularis propria is present adjacent to the adipose tissue on the left side. The pyramid is located at the corticomedullary junction, which lacks a muscularis propria. **c** The ureteral wall is histologically composed of three layers: the mucosa, smooth muscle layer, and adventitia

Table 1 Clinicopathological characteristics of the 954 patients in this study

		Renal pelvis ($N = 493$)	Ureter ($N = 461$)	p value	Number
Age	N (median, range)	493 (69, 22–94)	461 (69, 36–92)	0.1018	954
Sex	M	362 (73%)	320 (69%)	0.1736	682 (71%)
	F	131 (27%)	141 (31%)		272 (29%)
Laterality	R	222 (45%)	225 (49%)	0.2698	447 (47%)
	L	271 (55%)	236 (51%)		507 (53%)
Operative method	Open	233 (47%)	214 (46%)	0.7956	447 (47%)
	Laparoscopic	260 (53%)	247 (54%)		507 (53%)
Follow-up period (years)	N,= (median, range)	493 (4.2, 0–26.9)	461 (3.3, 0–28.6)	0.0153	954
Gross type	Papillary	367 (74%)	248 (54%)	< 0.0001	615 (64%)
	Non-papillary	126 (26%)	213 (46%)		339 (36%)
WHO/ISUP grade	Low	109 (22%)	71 (15%)	0.0101	180 (19%)
	High	384 (78%)	390 (85%)		774 (81%)
Histological variant	UC	458 (93%)	438 (95%)	0.1784	896 (94%)
	Variant histology	35 (7%)	23 (5%)		58 (6%)
	Squamous	17 (3.4%)	15 (3.3%)		32 (3.4%)
	Sarcomatoid	9 (1.8%)	3 (0.7%)		12 (1.2%)
	Small cell	3 (0.6%)	2 (0.4%)		5 (0.5%)
	Glandular differentiation	1 (0.2%)	2 (0.4%)		3 (0.3%)
	Micropapillary	3 (0.6%)	0 (0%)		3 (0.3%)
	Trophoblast	2 (0.4%)	0 (0%)		2 (0.2%)
	Lymphoepithelioma-like	0 (0%)	1 (0.2%)		1 (0.1%)
Lymphovascular invasion	-	370 (75%)	325 (70%)	0.1261	695 (73%)
	+	123 (25%)	136 (30%)		259 (27%)
pT stage	pT1	247 (50%)	202 (44%)	< 0.0001	449 (47%)
	pT2	30 (6%)	106 (23%)		136 (14%)
	pT3	202 (41%)	146 (32%)		348 (36%)
	pT4	14 (3%)	7 (2%)		21 (2%)
pN	pN0	271 (55%)	297 (64%)	0.0064	568 (60%)
	pN1 or pN2	50 (10%)	45 (10%)		95 (10%)
	pNx	172 (35%)	119 (26%)		291 (30%)
Adjuvant chemotherapy	None	394 (80%)	360 (78%)	0.5245	754 (79%)
	Done	99 (20%)	101 (22%)		200 (21%)

p value, Wilcoxon signed-rank test or Fisher's exact test

(HR = 3.54, $p < 0.001$) were also independent risk factors for predicting RFS. The significance of other histological variants was not statistically significant (HR = 1.79, $p < 0.240$). The evaluation for individual of them was impossible because of their small number.

In an analysis of CSS using the same model, pT stage ($p < 0.001$), pN (HR = 2.33, $p < 0.001$), operative method (HR = 0.64, $p = 0.004$), histological variant (HR = 2.27 $p < 0.001$), LVI (HR = 1.46, $p = 0.049$), gross type (HR = 1.58, $p = 0.0099$), and adjuvant chemotherapy (HR = 0.65, $p = 0.037$)

Table 2 The 1-, 3-, 5-year survival rates stratified by tumor stage and location

Tumor location/stage		RFS (%)			p value	CSS (%)			p value	OS (%)			p value
		1 year	3 years	5 years		1 year	3 years	5 years		1 year	3 years	5 years	
Renal pelvis	pTa, pTis, pT1	98.7	95.8	94.7	0.22	99.6	98.2	96.4	0.25	97.9	91.8	86.8	0.19
Ureter		98.4	93.6	91.1		99.5	97	94.7		98.4	93.6	86.3	
Renal pelvis	pT2	92.9	85	80	0.97	100	87.4	87.4	0.8	100	87.4	87.4	0.44
Ureter		93.7	85.6	81.8		97.8	88.2	88.2		93.8	81.3	76.2	
Renal pelvis	pT3	74.8	60.9	59.3	0.03	89.2	66.7	57.9	0.12	88.7	63.7	54.6	0.06
	pT3a	91.1	81.7	81.7	< 0.0001	98.7	85.7	80.6	< 0.0001	98.7	83.3	78.3	< 0.0001
	pT3b	63.7	46	42.9	0.54	82.8	53.7	42	0.21	81.9	50.1	38.2	0.32
Ureter	pT3	69	47.3	40.6		86.4	59.7	50.8		85.1	56.3	44.2	
Renal pelvis	pT4	0	0	0	0.02	16.7	8.3	0	0.42	0	8.3	0	0.41
Ureter		53.3	0	0		51.4	0	0		51.4	0	0	

Table 3 Multivariate analyses of variables predicting recurrence-free survival/cancer-specific survival/Overall survival

Variables			Recurrence-free survival		Cancer-specific survival		Overall survival	
		Number	HR (95% CI)	*p* value	HR(95% CI)	*p* value	HR(95% CI)	*p* value
pT	Renal pelvis pTa/pTis/pT1	247	Ref		Ref		Ref	
	pT2	30	3.11 (1.09–8.91)	0.035	2.60 (0.67–10.02)	0.166	1.18 (0.53–2.65)	0.68
	pT3a	79	2.62 (1.19–5.74)	0.016	3.78 (1.45–9.86)	0.007	1.15 (0.64–2.07)	0.64
	pT3b	123	6.79 (3.31–13.92)	< 0.0001	11.71 (4.97–27.60)	< 0.001	3.60 (2.23–5.82)	< 0.0001
	pT4	14	10.73 (3.05–37.70)	0.0002	57.99 (18.1–185.80)	< 0.001	23.08 (10.3–51.70)	< 0.0001
	Ureter pTa/pTis/pT1	202	1.62 (0.75–3.49)	0.22	1.74 (0.68–4.45)	0.250	1.07 (0.7–1.65)	0.75
	pT2	106	2.29 (1.05–5.01)	0.037	2.48 (0.94–6.55)	0.066	1.67 (1.01–2.76)	0.047
	pT3	146	6.12 (3.01–12.5)	< 0.0001	8.65 (3.61–20.70)	< 0.001	2.69 (1.66–4.36)	< 0.0001
	pT4	7	7.96 (2.88–21.99)	< 0.0001	42.78 (11.30–161.8)	< 0.001	12.53 (4.4–38.7)	< 0.0001
Age		954	1.00 (0.99–1.02)	0.69	1.02 (0.99–1.04)	0.057	1.04 (1.02–1.05)	< 0.0001
Sex	M	682	Ref		Ref		Ref	
	F	272	0.89 (0.65–1.22)	0.46	1.04 (0.76–1.44)	0.800	0.90 (0.69–1.17)	0.44
Laterality	R	447	Ref		Ref		Ref	
	L	507	1.21 (0.89–1.62)	0.21	1.10 (0.81–1.49)	0.560	1.08 (0.85–1.37)	0.51
Operative method	Laparotomy	447	Ref		Ref		Ref	
	Laparoscopic	507	0.91 (0.68–1.19)	0.49	0.64 (0.47–0.87)	0.004	0.73 (0.58–0.93)	0.0098
pN	pN0	568	Ref		Ref		Ref	
	pN1 or pN2	95	1.72 (1.13–2.63)	0.011	2.33 (1.54–3.53)	< 0.001	1.78 (1.22–2.58)	0.0026
	pNx	291	1.04 (0.73–1.49)	0.82	1.20 (0.81–1.77)	0.36	1.09 (0.82–1.46)	0.55
Histological variant	UC	895	Ref		Ref		Ref	
	Variant histology	58	1.60 (0.99–2.58)	0.054	2.27 (1.45–3.54)	< 0.001	1.89 (1.27–2.81)	0.0017
	Squamous	32	1.62 (0.96–2.74)	0.073	2.03 (1.19–3.47)	0.009	1.86 (1.13–3.06)	0.014
	Sarcomatoid	12	3.54 (1.67–7.49)	< 0.001	5.57 (2.57–12.1)	< 0.001	3.65 (1.72–7.74)	< 0.001
	Others	14	1.79 (0.67–4.81)	0.240	1.74 (0.86–4.42)	0.250	1.89 (0.81–4.39)	0.140
WHO/ISUP grade	Low	180	Ref		Ref		Ref	
	High	774	3.93 (1.28–10.35)	0.008	3.12 (0.91–10.80)	0.071	1.02 (0.67–1.56)	0.93
Lymphovascular invasion	–	695	Ref		Ref		Ref	
	+	259	1.58 (1.09–2.23)	0.015	1.46 (1.00–2.14)	0.049	1.45 (1.04–1.9)	0.028
Gross type	Papillary	615	Ref		Ref		Ref	
	Non-papillary	339	1.27 (0.91–1.76)	0.16	1.58 (1.12–2.25)	< 0.001	1.45 (1.12–1.88)	0.005
Adjuvant chemotherapy	None	754	Ref		Ref		Ref	
	Done	200	0.97 (0.67–1.41)	0.88	0.65 (0.43–0.97)	0.037	0.75 (0.55–1.04)	0.082

Ref, reference category

were associated with cancer death (Table 3). Squamous cell differentiation (HR = 2.03, $p < 0.001$) and sarcomatoid change (HR = 5.57, $p < 0.001$) were also independent risk factors for predicting CCS. The significance of other histological variants was not statistically significant (HR = 1.74, $p < 0.250$).

Overall survival

In this cohort, death occurred in 148 patients (30%) with UCRP, and in 144 patients (31.2%) with UCU. Figure 3c shows the OS curves after stratification by tumor location, and Table 2 shows the 5-year OS after stratification by pT and location.

In the Cox regression multivariate analyses, pT stage ($p < 0.001$), age ($p < 0.001$), pN (HR = 1.78 $p = 0.0026$), operative method (HR = 0.73 $p = 0.0098$), histological variant (HR = 1.89, $p = 0.0017$), LVI (HR = 1.45 $p = 0.028$), and gross type (HR = 1.45, $p = 0.005$) were independent risk factors for predicting OS (Table 3). Squamous cell differentiation (HR = 1.86, $p = 0.009$) and sarcomatoid

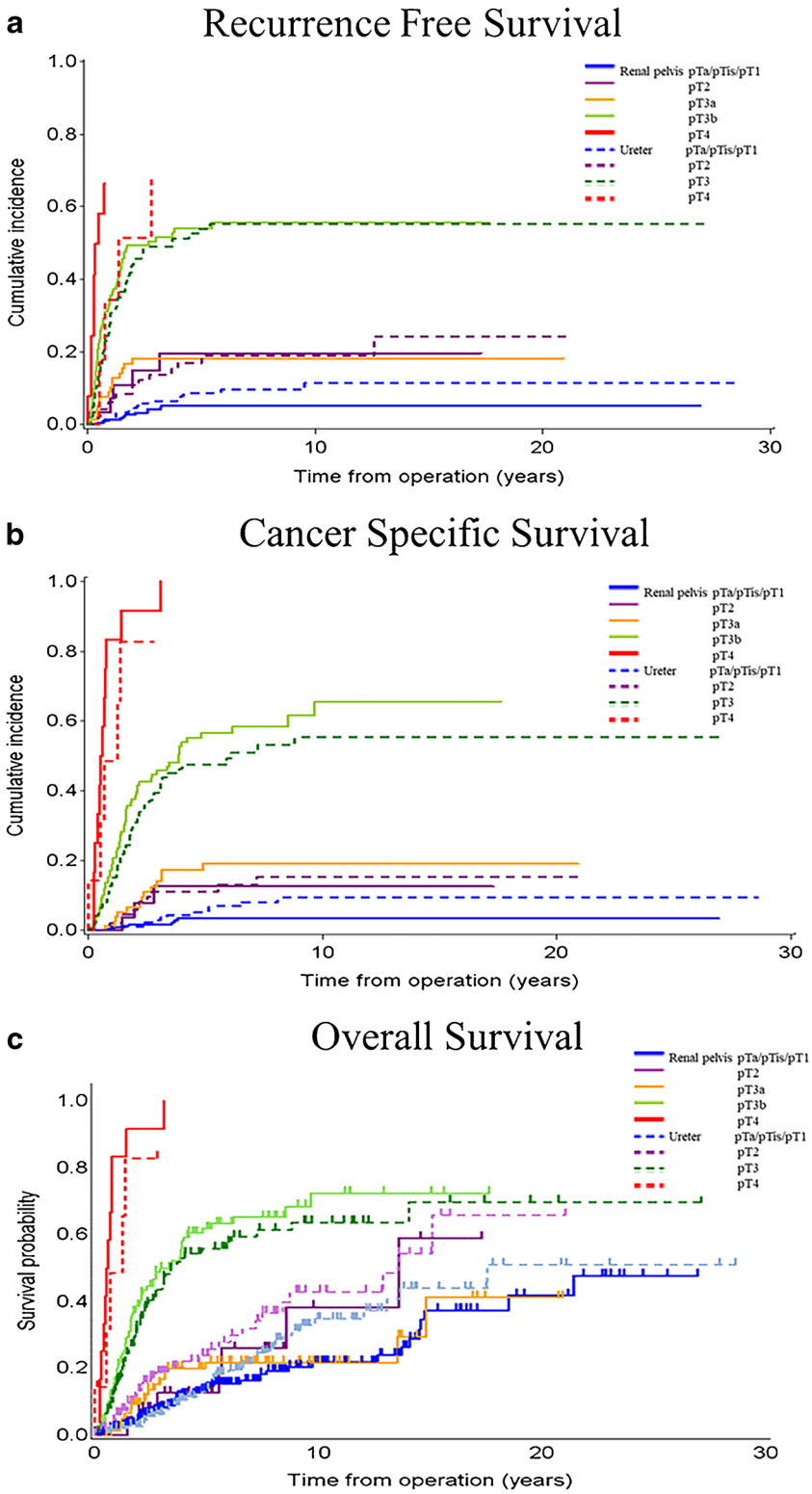

Fig. 3 The cumulative incidence curves for patients stratified by tumor stage and location for recurrence-free survival (**a**) and cancer-specific survival (**b**). Survival curves for patients stratified by tumor stage and location for overall survival (**c**)

change (HR = 3.65, $p < 0.001$) were also independent risk factors for predicting OS. The significance of other histological variants was not statistically significant (HR = 1.89, $p < 0.140$).

Discussion

Few studies have reported the significance of tumor location for oncological outcomes of UTUC, although the anatomical

structure of the renal pelvis differs from that of the ureter [7, 10, 21]. Ouzzane et al. reported that the prognosis of UCRP is better than that of UCU (5-year CSS, UCRP 86.8% vs UCU 68.9%; HR = 1.7, $p = 0.02$) [17].

Park et al. reported that the CSS rate of pT3 UCU patients was significantly lower than that of pT3 UCRP patients, while there was no difference between UCRP and UCU patients with pathological stage pT2 or less [18]. The 5-year CSS was 76.1% in pT3 UCRP patients and 43.1% in pT3 UCU patients ($p = 0.009$). Tai et al. reported a longer RFS in patients with pT3 UCRP than in those with pT3 UCU (5-year RFS, pT3 UCRP 71% vs pT3 UCU 50%, $p = 0.047$), although the difference in CSS was not significant [27].

In contrast to the urothelium, renal calyces are composed of protruding papillae with a thin mucosal layer and the absence of a lamina propria and muscle layers (Fig. 2) [6]. These anatomical structures are different from those of the ureter and renal pelvis, located outside the kidney. Considering these anatomical differences, we determined two patterns of tumor invasion in pT3 UCRP [24]: (1) pT3a, carcinoma cells extend into the collecting duct, with limited invasion of the renal medulla; (2) pT3b, carcinoma cells invade the renal cortex or peripelvic adipose tissue. In general, the former pattern showed minimal parenchymal invasion, while the latter was characterized by extensive invasion. Therefore, we hypothesized that the renal medulla plays the same role as the muscularis propria of the ureter and renal pelvis outside the kidney.

Although our study showed that the depth of tumor invasion into the renal parenchyma is a critical prognostic determinant, it is not considered by the current AJCC TNM classification. As a result, UCRPs that infiltrate only into the renal medulla are classified as pT3, not pT1 or pT2. Cho et al. proposed that tumors with invasion limited to the renal medulla be classified as pT2, while those with invasion extending into the renal cortex should be considered as pT3 [5]. However, we reclassified renal medullary invasion as pT3a, and renal cortical invasion as pT3b, because pT2 in the current TNM staging system corresponds to tumor invasion into the muscle layer, not the renal parenchyma. Restricting the degree of modification of the pT classification will avoid unnecessary confusion. Patients with pT3b UCRP had a significantly worse prognosis than those with pT3a tumors. The 5-year CSS rates for pT3a and pT3b patients were 84.6% and 37.3% ($p = 0.008$), respectively.

Several authors have proposed cutoffs for the depth of parenchymal invasion (Table S2). Yoshimura et al. demonstrated that the degree of parenchymal invasion (not deeper than 5 mm from the basement membrane or deeper than 5 mm) influenced the prognosis of UCRP patients [30] (3-year cause-specific survival; 76.4% [≤ 5 mm] vs 25.2% [> 5 mm], $p < 0.0001$). Wu et al. also found that superficial parenchymal invasion (not deeper than 5 mm) was associated with a better oncological outcome than extensive parenchymal invasion (deeper than 5 mm) or peripelvic and periureteral adipose tissue invasion, in a study of 72 patients with pT3 UTUC located in either the renal pelvis or the ureter [29]. However, Park did not find evidence of a survival difference according to parenchymal invasion depth (5-year RFS, microscopic 84.6% vs extensive 60.5%, $p = 0.218$; 5-year CSS, microscopic 92.3% vs extensive 81.7%, $p = 0.864$). Rather, the prognosis of patents with tumors invading the peripelvic adipose tissue was worse than that of patients whose tumors invaded the renal parenchyma [19].

Shariat et al. classified pT3 UCRPs into pT3a (microscopic parenchymal invasion) and T3b (macroscopic parenchymal invasion or invasion into peripelvic adipose tissue). In their study of 266 patients with pT3 UCRP, those with pT3b had significantly lower 10-year RFS and CSS rates than patients with pT3a (RFS, 58% vs 38%; CSS, 60% vs 39%; $p < 0.001$ and $p = 0.002$, respectively) [25]. Roscigno et al. assessed the prognostic value of the pT3 subclassification in 284 international patients with pT3 UCRPs. Those with pT3b tumors were shown to be at increased risk of disease recurrence and cancer-specific mortality. However, in multivariate analyses, the subclassification of pT3 tumors was not associated with tumor recurrence or CSS [22].

In the categories proposed by Yoshimura or Shariat, microscopic invasion includes minimal or limited renal medulla invasion, in contrast to extensive parenchymal invasion. However, their categories are subjective and have no quantitative basis. Junior residents with little experience often evaluate the macroscopic findings, but the findings of senior pathologists may differ. Therefore, the subclassification may not be reliable [28]. Our proposed boundary at the corticomedullary junction was clear and reproducible. In this study, we validated this subclassification of pT3 UCRPs in a larger number of patients. We reconfirmed that patients with pT3b UCRPs have a significantly worse prognosis than pT3a UCRPs (5-year RFS, pT3a 81.7% vs pT3b 42.9%, $p = 0.0038$; 5-year CSS, pT3a 80.6% and pT3b 42%, $p = 0.001$).

Furthermore, we compared the oncological results of both UCRP and UCU in a relatively large number of patients. The prognosis of patients with our proposed pT3a UCRP was similar to that of patients with pT2 UCRP or UCU. Moreover, the prognosis of pT3b UCRP was similar to that of pT3 UCU. These results show that the renal parenchyma had a protective effect against tumor invasion in the renal pelvis where it lacks a muscular layer. Our proposed subclassification, which distinguishes pT3a from pT3b, clearly showed a correlation between TNM stage and the oncological results.

Multivariate analyses revealed that patients who received adjuvant chemotherapy had a better CSS than patients who did not. Current clinical guidelines do not strongly recommend adjuvant chemotherapy and many reports suggest that adjuvant therapy for UTUC has no impact on prognosis. However, some retrospective studies of UTUC patients (pT3N0M0) have shown that adjuvant chemotherapy improves CSS [9, 13].

The recent randomized and prospective POUT study showed that combination platinum-based chemotherapy containing cisplatin or carboplatin (GC or GCarbo therapy), administered within 90 days to patients undergoing RNU, improved the 3-year DFS and 3-year PFS rates [3]. Most of our patients are treated with platinum-based regimens such as MVAC, GC, or GCarbo as adjuvant therapy, which may have helped to improve the CSS of our cohort.

Our distinct and reproducible criteria for classification of the degree of parenchymal invasion at the corticomedullary boundary allowed one genitourinary pathologist to accurately evaluate a large number of specimens. We therefore believe that this subclassification will be useful for precisely predicting the prognosis of pT3 UCRP patients.

Our study had several limitations. The data were collected retrospectively, and the research was multi-institutional. Surgical procedures including lymphadenectomy and the chemotherapy regimen have changed over the past 30 years and are determined by physicians' choice. Nevertheless, the large number of enrolled patients provided reliable results.

In conclusion, we examined the validity of the pT3 classification for UCRP from an anatomical point of view. Our results suggest that our proposed pT3 subclassification predicts the prognosis of UCRP more accurately than pT3 of the current AJCC/UICC classification, that is, pT3a UCRP had almost the same prognosis as pT2 UCRP and UCU, whereas pT3b UCRP had almost the same prognosis as pT3 UCU. An accurate diagnosis of pT3a makes it possible to avoid unnecessary postoperative chemotherapy. A prospective trial is needed to examine the usefulness of postoperative chemotherapy.

Our findings on the proposed pT3 subclassification may enhance the predictive value of UCRP prognosis than the current AJCC/UICC classification.

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Compliance with ethical standards

This study is approved by institutional review boards of Nagoya University Hospital and all affiliated institutions.

Conflicts of interest Toyonori Tsuzuki: honoraria, AstraZeneca, Chugai.

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