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ORIGINAL ARTICLE

Subclassification of pT3 upper tract urothelial carcinoma: a multicenter retrospective study

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Abstract

Purpose The prognosis of patients with pT3 upper tract urothelial carcinoma (UTUC) varies. The current study aimed to further classify patients with pT3 UTUC into different survival outcome groups based on tumor location and site of invasion.

Methods This retrospective study included 323 patients with pT3 UTUC who underwent nephroureterectomy at 11 hospitals in Japan. Histological and clinical data were obtained via a chart review. Univariate and multivariate Cox proportional hazards analyses showed the effect of different variables on recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).

Results The median age of the patients was 72 years. Patients with pT3 UTUCs were divided into two groups: those with renal parenchymal invasion only (pT3a, $n=95$) and those with peripelvic or periureteral fat invasion (pT3b, $n=228$). pT3b UTUC was significantly associated with hydronephrosis, low preoperative estimated glomerular filtration rate (eGFR), histological nodal metastasis, nuclear grade 3, lymphovascular invasion (LVI), carcinoma in situ, and positive surgical margin. Based on the univariate analyses, patients with pT3b UTUC had a significantly lower 5-year RFS (42.4% vs. 70.1%, $p<0.0001$), 5-year CSS (54.3% vs. 80.0%, $p=0.0002$), and 5-year OS (47.8% vs. 76.8%, $p<0.0001$) than those with pT3a UTUC. According to the multivariate analyses, nodal metastasis, LVI, adjuvant chemotherapy, preoperative eGFR, nuclear grade (RFS only), surgical margin (RFS only), and Charlson comorbidity index (OS only), but not pT3b stage, were associated with survival.

Conclusion Compared with pT3a UTUC, pT3b UTUC was significantly associated with worse histological features, consequently resulting in unsatisfactory survival outcomes.

Keywords Classification · Nephroureterectomy · Renal pelvis · Survival · Upper tract urothelial carcinoma · Urothelial carcinoma

Abbreviations

UTUC	Upper tract urothelial carcinoma
CSS	Cancer-specific survival
RFS	Recurrence-free survival
eGFR	Estimated glomerular filtration rate
LN	Lymph node
OS	Overall survival
LVI	Lymphovascular invasion

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease, accounting for only 5–10% of all urothelial carcinoma cases [1]. Radical nephroureterectomy with bladder cuff excision is the standard treatment for UTUC without distant metastasis [1]. Although surgery has excellent survival outcomes in non-muscle-invasive UTUC, the prognosis of patients with locally advanced-stage disease varies, and it is not satisfactory. The 5-year cancer-specific survival (CSS) rate of pT3 UTUC is 46–56% [2–4].

To improve patient prognosis, previous studies have investigated the efficacy of pre- and/or postsurgical systemic

chemotherapy [5–8]. Recently, a multicenter prospective randomized trial has shown that postsurgical adjuvant platinum-based chemotherapy improved the recurrence-free survival (RFS) of patients with pT2–4 UTUC (POUT trial) [9]. Further, the updated guidelines recommend this treatment for locally advanced-stage disease after surgery [10, 11]. However, patients with UTUC commonly present with insufficient renal function. Thus, they cannot receive systemic cisplatin-based chemotherapy. After surgery, the patients' median estimated glomerular filtration rate (eGFR) is 42–48/1.73 mL/min/m^2 [12–15].

pT3 UTUC is a heterogeneous disease. That is, it includes both renal pelvic and ureteral cancers. pT3 renal pelvic cancer is defined as invasion of either renal parenchyma or peripelvic adipose tissue. Meanwhile, pT3 ureteral cancer is defined as invasion into periureteral adipose tissue [16, 17]. Although several previous studies have proposed the subclassifications of pT3 UTUC, they have not been adopted by the international classification system yet [18–21]. The identification of pT3 UTUC subgroups with different oncological outcomes could facilitate the more sophisticated application of postsurgical adjuvant chemotherapy. The current study aimed to further classify patients with pT3 UTUC into groups with different prognoses.

Materials and methods

Patient population

This study was approved by the institutional review board of The University of Tokyo Graduate School of Medicine (approval number 11032) and that of each participating institution and was conducted in accordance with the Declaration of Helsinki. The need for a written informed consent was waived due to the retrospective nature of the research. In total, 968 patients with UTUC underwent nephroureterectomy at 11 institutions in Japan between 1995 and 2016. Their medical records were retrospectively reviewed.

Patients with distant metastasis, cT4 disease, and non-urothelial carcinoma, those without cancerous lesion (pT0) at the final pathological examination, those with prior or synchronous development of invasive bladder cancer or contralateral UTUC, those who received chemotherapy prior to nephroureterectomy (neoadjuvant chemotherapy), and those who had undergone ureteral segmentectomy before were excluded from the analysis. After further exclusion of patients without sufficient follow-up data, 826 patients were included in the study. Among them, 336 had pT3 UTUC. However, 13 had no detailed pathology. Finally, 323 patients were included in the current analysis (Supplementary Fig. 1).

Treatment and follow-up

Standard radical nephroureterectomy with bladder cuff excision was performed at each institution. The execution and the extent of lymph node (LN) dissection were based on presurgical imaging and intraoperative findings and were determined by the attending physician.

Adjuvant chemotherapy was offered and selected after a discussion between the treating physicians and patients.

Although a standardized follow-up protocol was not required due to the retrospective and multicenter nature of this study, patients were generally assessed every 3 months within the 1st year, every 3–6 months within the 2nd and 3rd years, every 6 months within the 4th and 5th years, and annually thereafter. Patients who presented with suspicious symptoms between the scheduled visits were evaluated immediately. The follow-up consisted of examining patients' medical history and performing a physical examination, blood laboratory investigations, urine cytology, cystoscopy, and imaging studies. Imaging studies included chest radiography and chest, abdominal, and pelvic computed tomography scan. Bone scintigraphy was performed if clinically indicated.

All nephroureterectomy specimens were subjected to routine pathological examination. Histological diagnosis was determined according to the World Health Organization (WHO) classification system [22], and nuclear morphology was graded according to the 1973 WHO classification [23]. The primary tumors and LNs were restaged based on the 2017 American Joint Committee on Cancer/Union for International Cancer Control TNM Classification [16, 17]. Histological information was obtained from the medical records, and a centralized histological review of specimens was not conducted.

Laboratory data

Data on serum creatinine values within a month before surgery and at 2–8 weeks after surgery were obtained from the medical records. eGFR was examined using the international modification of diet in the renal disease equation modified for Japanese population [24].

Statistical analyses

The outcomes were RFS, CSS, and overall survival (OS). Recurrence was defined as local recurrence or distant metastasis. Development of urothelial cancer in the remnant urothelium (urothelial bladder cancer and contralateral UTUC) was not included. RFS, CSS, and OS were calculated from the date of nephroureterectomy to the date of

tumor recurrence, death due to urothelial cancer, and death due to any cause, respectively (or was censored at the date of the last follow-up).

Differences in group characteristics were compared using the chi-square test or the Mann–Whitney *U* test. Kaplan–Meier plots were used to estimate survival after nephroureterectomy. Univariate and multivariate Cox regression models were used to assess RFS, CSS, and OS after nephroureterectomy. Variables that were statistically significant in the univariate analyses and other potentially relevant factors (such as age and adjuvant chemotherapy) were included in the multivariate analyses.

Statistical analysis was performed with JMP® Pro 15.1.0 (SAS Institute, Cary, NC, the USA). A p value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of the patients

Table 1 shows the characteristics of the patients. There were 197 (61.0%) men and 126 (39.0%) women with a median age of 72 (interquartile range 65–78) years. The median follow-up durations were 41 months in all patients and 67.5 months in those who were alive at the final follow-up.

During the follow-up, 153 (47.4%) patients developed local recurrence or distant metastasis. The median duration from surgery to recurrence/metastasis was 10 (interquartile range 5–19) months. In total, 113 (35.0%) and 148 (45.8%) patients died of urothelial cancer and any cause, respectively. The 5-year RFS, CSS, and OS were 50.8%, 61.9%, and 56.1%, respectively.

Subclassification of pT3 UTUC

First, patients were divided into three groups according to the location of tumors classified as pT3 (renal pelvis, $n = 175$; ureter, $n = 138$; or both, $n = 10$). Patients with tumors classified as pT3 at the renal pelvis had a better survival than those with tumors classified as pT3 at the ureter, and those at both renal pelvis and ureter (multifocal pT3 invasion) (Fig. 1a–c). Then, 175 patients with pT3 renal pelvic cancer were further divided into two groups: those with renal parenchymal invasion only (without peripelvic fat invasion, $n = 95$) and those with peripelvic fat invasion ($n = 80$). The survival rates of the patients with peripelvic fat invasion were significantly lower than those of the patients with renal parenchymal invasion alone (RFS, $p = 0.0023$; CSS, $p = 0.0004$; and OS, $p = 0.0004$) and were almost identical to those of patients with pT3 ureteral cancer (periureteral fat invasion) (RFS, $p = 0.7193$; CSS, $p = 0.5744$; and OS, $p = 0.7928$) (Supplementary Fig. 2). Therefore, patients with pT3 UTUC were finally divided into two groups: those with renal parenchymal invasion alone (pT3a, $n = 95$) and those with peripelvic or periureteral fat invasion (pT3b, $n = 228$).

Table 1 shows the characteristics of patients with pT3a and pT3b UTUC. pT3b UTUC was significantly associated with preoperative hydronephrosis, histological nodal metastasis, nuclear grade 3, lymphovascular invasion (LVI), carcinoma in situ, and a higher incidence of positive surgical margin. The preoperative eGFR of patients with pT3a UTUC was significantly higher than that of patients with pT3b UTUC (56.4 vs. 49.1 mL/min/1.73 m^2, $p = 0.0014$). However, there was no significant difference in postoperative eGFRs (42.4 vs. 43.5 mL/min/1.73 m^2, $p = 0.9009$).

In the univariate analyses, pT3b UTUC was significantly associated with lower survival rates compared with pT3a UTUC (Table 2). Figure 1d–f shows the Kaplan–Meier estimates of RFS, CSS, and OS stratified according to pT3a or pT3b subclassifications. Patients with pT3a UTUC had significantly better 5-year RFS (70.1% vs. 42.4%, $p < 0.0001$), 5-year CSS (80.0% vs. 54.3%, $p = 0.0002$), and 5-year OS (76.8% vs. 47.8%, $p < 0.0001$) than those with pT3b UTUC (Fig. 1d–f).

Based on the multivariate analyses, histological nodal metastasis, LVI, adjuvant chemotherapy, preoperative eGFR, nuclear grade (RFS only), soft-tissue surgical margin (RFS only), and Charlson comorbidity index (OS only), but not pT3b stage, were associated with survival (Table 2).

Supplementary Fig. 3 depicts the Kaplan–Meier estimates of RFS, CSS, and OS stratified according to pT stages including pT3a and pT3b subclassification. The RFS, CSS, and OS of patients with pT3a UTUC and those with pT2 UTUC did not significantly differ ($p = 0.0802$, 0.3274, and 0.3164, respectively). The RFS, CSS, and OS of patients with pT3b UTUC were better than those of patients with pT4 UTUC ($p < 0.0001$, $p = 0.0004$, and $p = 0.0030$).

Discussion

This retrospective study showed that pT3b UTUC defined by peripelvic/periureteral fat invasion was associated with significantly worse survival rates compared with pT3a UTUC defined by renal parenchymal invasion only (without fat invasion). pT3b UTUC was correlated with a significantly higher incidence of histological nuclear grade 3, CIS, LVI, and nodal metastasis. The positive surgical margin rate was higher in pT3b UTUC because fat itself is a resection margin. These malignant features of pT3b UTUC result in worse survival outcomes, although the subclassification of pT3a/pT3b itself was not significant based on the multivariate analyses.

pT3 UTUC is heterogeneous. That is, it includes renal pelvic cancer invading renal parenchyma or peripelvic

Table 1 Characteristics of the patients

Characteristics	All patients ($N=323$)	Patients with renal parenchymal invasion only (pT3a, $n=95$)	Patients with peripelvic or periureteral fat invasion (pT3b, $n=228$)	p value
	Number (%) or median (IQR)	Number (%) or median (IQR)	Number (%) or median (IQR)	
Age (years)	72 (65–78)	73 (66–78)	72 (65–78)	0.7505
Sex				
Male	197 (61.0%)	55 (57.9%)	142 (62.3%)	0.4615
Female	126 (39.0%)	40 (42.1%)	86 (37.7%)	
Smoking habit				
No	100 (42.0%)	25 (40.3%)	75 (42.6%)	0.7533
Yes (current or previous)	138 (58.0%)	37 (59.7%)	101 (57.4%)	
Unknown	85	33	52	
Charlson comorbidity Index				
0	152 (47.2%)	47 (49.5%)	105 (46.3%)	0.8120
1	64 (19.9%)	17 (17.9%)	47 (20.7%)	
≥ 2	106 (32.9%)	31 (32.6%)	75 (33.0%)	
Unknown	1	0	1	
History of bladder cancer				
No	273 (84.5%)	84 (88.4%)	189 (82.9%)	0.2109
Previous or synchronous	50 (15.5%)	11 (11.6%)	39 (17.1%)	
Hydronephrosis				
No	134 (41.6%)	69 (72.6%)	65 (28.6%)	< 0.0001
Yes	188 (58.4%)	26 (27.4%)	162 (71.4%)	
Unknown	1	0	1	
Surgical procedure				
Open	190 (59.0%)	58 (61.0%)	132 (58.1%)	0.6291
Laparoscopic	132 (41.0%)	37 (39.0%)	95 (41.9%)	
Unknown	1	0	1	
Tumor side				
Left	174 (53.9%)	53 (55.8%)	121 (53.1%)	0.6551
Right	149 (46.1%)	42 (44.2%)	107 (46.9%)	
Tumor location				
Renal pelvis	134 (41.5%)	79 (83.2%)	55 (24.1%)	< 0.0001
Ureter	121 (37.5%)	0	121 (53.1%)	
Renal pelvis and ureter	68 (21.1%)	16 (16.8%)	52 (22.8%)	
Number of lesions				
Solitary	242 (74.9%)	77 (81.1%)	165 (72.4%)	0.1009
Multiple	81 (25.1%)	18 (19.0%)	63 (27.6%)	
Histology				
Pure UC	275 (85.1%)	82 (86.3%)	193 (84.7%)	0.7012
UC with variant histology	48 (14.9%)	13 (13.7%)	35 (15.4%)	
Grade				
G1	1 (0.3%)	0	1 (0.5%)	< 0.0001
G2	87 (27.7%)	45 (48.4%)	42 (19.0%)	
G3	226 (72.0%)	48 (51.6%)	178 (80.5%)	
Unknown	9	2	7	
pN stage				
pNx	203 (62.8%)	71 (74.7%)	132 (57.9%)	0.0024
pN0	64 (19.8%)	19 (20.0%)	45 (19.7%)	
pN1	31 (9.6%)	3 (3.2%)	28 (12.3%)	
pN2	25 (7.7%)	2 (2.1%)	23 (10.1%)	

Table 1 (continued)

Characteristics	All patients ($N=323$)	Patients with renal parenchymal invasion only (pT3a, $n=95$)	Patients with peripelvic or periureteral fat invasion (pT3b, $n=228$)	p value
	Number (%) or median (IQR)	Number (%) or median (IQR)	Number (%) or median (IQR)	
Lymphovascular invasion				
Negative	101 (31.5%)	48 (51.1%)	53 (23.4%)	< 0.0001
Positive	220 (68.5%)	46 (48.9%)	174 (76.6%)	
Unknown	2	1	1	
Carcinoma in situ				
Negative	216 (66.9%)	78 (82.1%)	138 (60.5%)	0.0002
Positive	107 (33.1%)	17 (17.9%)	90 (39.5%)	
Soft tissue surgical margin				
Negative	290 (91.2%)	95 (100%)	195 (87.4%)	0.0003
Positive	28 (8.8%)	0 (0%)	28 (12.6%)	
Unknown	5	0	5	
Number of lymph nodes resected	0 (0–2)	0 (0–0)	0 (0–2)	0.0108
Adjuvant chemotherapy				
No	184 (57.0%)	62 (65.3%)	122 (53.5%)	0.0519
Yes	139 (43.0%)	33 (34.7%)	106 (46.5%)	
Preoperative eGFR (mL/min/1.73 m^2)	51.6 (38.8–62.9)	56.4 (45.9–65.0)	49.1 (36.5–61.1)	0.0014
Postoperative eGFR (mL/min/1.73 m^2)	43.1 (35.9–51.2)	42.4 (36.4–51.2)	43.5 (35.6–51.2)	0.9009

IQR interquartile range, *UC* urothelial carcinoma, *eGFR* estimated glomerular filtration rate

adipose tissue and ureteral cancer invading periureteral adipose tissue. Previous studies have proposed the subclassification of pT3 UTUC, particularly pT3 renal pelvic cancer: renal pelvicalyceal cancer with and without peripelvic fat invasion (Asan group) [21], peripelvic fat invasion or macroscopic parenchymal invasion and microscopic renal parenchymal invasion only (Cornell group) [20], and peripelvic fat invasion or renal parenchymal invasion beyond the corticomedullary junction and renal parenchymal invasion within cortico-medullary junction (Nagoya group) [19]. Our proposal is similar to the Asan group.

Park et al. applied these three classifications on their own cohort with pT3 UTUC and investigated which classification had the best discriminative ability [25]. Results showed that the Cornell group classification had the best c-index (0.742 and 0.758 for RFS and CSS, respectively). The Nagoya (0.731 and 0.747) and Asan (0.706 and 0.733) classifications had slightly lower c-index values. Furthermore, Seisen et al. recently confirmed that two subgroups defined by the Cornell group classification had significantly different survival outcomes via a centralized pathological review of specimens [26]. Thus, the Cornell classification may be the most promising.

However, microscopic or macroscopic parenchymal invasion adopted in the Cornell classification is based on the gross inspection of resected specimens, and its interobserver reproducibility has not been confirmed yet. A similar issue in the differential diagnosis of pT3a/b bladder cancer has been identified [27]. pT3 urothelial bladder cancer, defined as the presence of extravesical adipose tissue invasion, is further subclassified into two categories (extravesical adipose tissue invasion at the microscopic [pT3a] or macroscopic [pT3b] level) [16, 17]. Tretter et al. reported that the macroscopic evaluation of radical cystectomy specimens was underreported without adequate educational intervention [27]. By contrast, the current subclassification system, which is identical with the Asan group, is quite simple. With this subclassification, renal pelvic cancer with peripelvic adipose tissue invasion (pT3b renal pelvic cancer) had almost identical survival outcomes with ureteral cancer with periureteral adipose tissue (pT3b ureteral cancer) (Supplementary Fig. 2). It was correlated with significantly worse survival outcomes compared with renal pelvic cancer with renal parenchymal invasion only (pT3a renal pelvic cancer, Supplementary Fig. 2). Moreover, the numbers of patients in the two groups were well-balanced. That is, 95 and 80 cases of renal pelvic cancers were classified as pT3a and pT3b, respectively. Thus, the present definition of pT3a/b may be considered for further subclassification of pT3 UTUC.

In our study, the multivariate analyses revealed that adjuvant chemotherapy significantly improved the RFS, CSS, and OS of patients with pT3 UTUC, although the

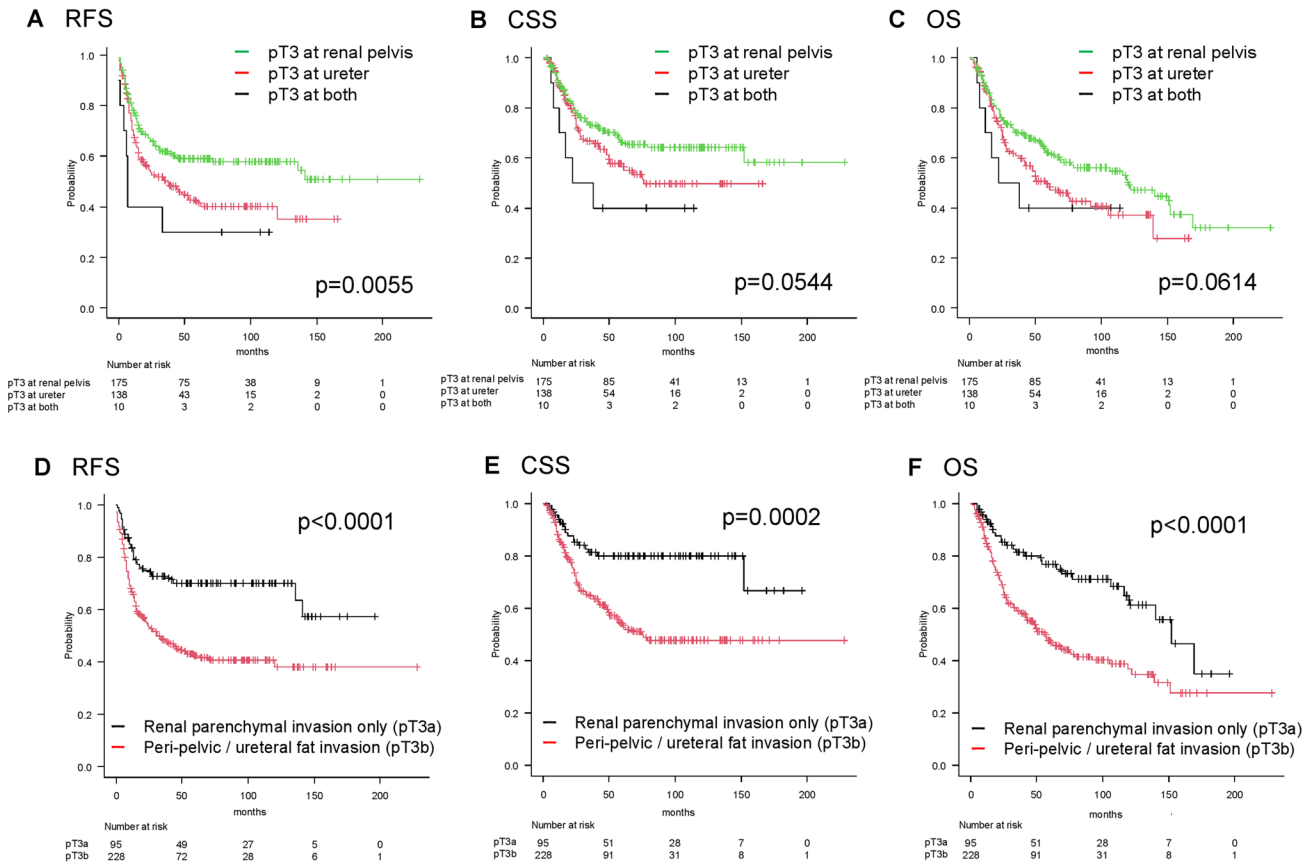

Fig. 1 (A, B, C) Kaplan–Meier plots of recurrence-free survival (**A**), cancer-specific survival (**B**), and overall survival (**C**) rates of patients with pT3 UTUC stratified according to tumor location (renal pelvis, ureter, and both). **D**–**F** Kaplan–Meier plots of recurrence-free survival (**D**), cancer-specific survival (**E**), and overall survival (**F**) rates of patients with pT3 UTUC with renal parenchymal invasion only and with peripelvic/ureteral adipose tissue

statistical significance was marginal in the univariate analyses (Table 2). Improvement in survival was in accordance with the results of several retrospective studies and a recent prospective randomized study [5–9]. Our retrospective study was not consistent in terms of regimens and the number of administered cycles. Despite adjustment with age, preoperative eGFR, and comorbidity (Table 2), bias could not be prevented due to unknown confounding factors. Thus, further studies must be conducted to assess the efficacy of adjuvant chemotherapy.

Our study had several limitations. First, it was based on the routine pathology report of resected specimens, without a centralized histological review. The lack of centralized review might lead to any misclassification. Second, due to the retrospective multicenter design of the study, surgical procedure, particularly execution and templates for LN dissection, and follow-up schedule were not standardized. Role of prior dietary or environmental carcinogen exposure (e.g., Chinese herb and arsenic) could not be analyzed other than smoking [28]. Third, the present study and the other similar one by Asan group [21] were based on data of Asian population. These results need to be validated using data from other populations of different ethnicities. Finally, genetic analysis of the surgical samples was not performed for the present study. Genetic testing has been incorporated into clinical decision-making in breast, colorectal, and lung cancers. Identification of genetic factors to classify UTUC would be an urgent and important research topic [29, 30].

Conclusions

Compared with pT3a UTUC defined by renal parenchymal invasion only, pT3b UTUC defined by peripelvic/periureteral fat invasion was significantly associated with worse histological features (nuclear grade, LVI, and nodal metastasis) and a high incidence of positive surgical margin. Consequently, patients with pT3b UTUC had a significantly worse survival than those with pT3a UTUC. Differences in outcomes between pT3a UTUC and pT3b UTUC can be taken into account when considering postsurgical adjuvant

Table 2 Univariate and multivariate analyses of survival

Factors	References	Recurrence-free survival			Cancer-specific survival			Overall survival		
		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
		p value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value
Age (continuous)		0.1839	0.995 (0.975–1.016)	0.6300	0.4118	0.990 (0.966–1.014)	0.3940	0.0575	1.002 (0.980–1.024)	0.8689
Sex, male	Female	0.5550			0.9032			0.6939		
Smoking, yes	No	0.7820			0.3627			0.3369		
CCI, ≥ 2	0–1	0.2210			0.1811			0.0028	1.531 (1.074–2.183)	0.0185
Previous or simultaneous UCB, yes	No	0.8619			0.7964			0.7000		
Hydronephrosis, yes	No	0.0018	1.112 (0.745–1.658)	0.6036	0.0050	1.033 (0.655–1.630)	0.8875	0.0054	0.974 (0.655–1.448)	0.8955
Procedure, laparoscopic	Open	0.3511			0.5484			0.5667		
Laterality, left	Right	0.6871			0.2020			0.1895		
Lesion, multiple	Solitary	0.1319			0.0798			0.1168		
Variant histology, yes	No	0.1846			0.0941			0.2504		
Nuclear grade, G3	G1–2	0.0002	1.735 (1.118–2.693)	0.0140	0.0013	1.541 (0.923–2.573)	0.0982	0.0093	1.164 (0.773–1.755)	0.4668
pN stage, pN1–2	pN0/pNx	< 0.0001	2.310 (1.561–3.418)	< 0.0001	< 0.0001	2.596 (1.652–4.079)	< 0.0001	< 0.0001	2.375 (1.564–3.609)	< 0.0001
CIS, positive	Negative	0.0739			0.0811			0.0761		
LVI, positive	Negative	< 0.0001	1.759 (1.115–2.775)	0.0152	< 0.0001	2.357 (1.323–4.201)	0.0036	< 0.0001	2.088 (1.301–3.351)	0.0023
Surgical margin, positive	Negative	< 0.0001	2.113 (1.300–3.435)	0.0025	< 0.0001	1.676 (0.948–2.961)	0.0756	< 0.0001	1.612 (0.937–2.774)	0.0845
Adjuvant chemotherapy, yes	No	0.1606	0.688 (0.478–0.990)	0.0443	0.1335	0.630 (0.411–0.967)	0.0347	0.0147	0.626 (0.428–0.915)	0.0155
Preoperative eGFR (continuous) (mL/min/1.73 m^2)		< 0.0001	0.984 (0.975–0.994)	0.0017	0.0001	0.981 (0.969–0.993)	0.0018	0.0008	0.990 (0.980–0.999)	0.0493
Postoperative eGFR (continuous) (mL/min/1.73 m^2)		0.0862			0.3178			0.3880		

Table 2 (continued)

Factors	References	Recurrence-free survival			Cancer-specific survival			Overall survival			
		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis		
		p value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value
Peripelvic or periureteral fat invasion, yes (pT3b)	No (renal parenchymal invasion only, pT3a)	< 0.0001	1.308 (0.804–2.127)	0.2796	0.0002	1.375 (0.770–2.457)	0.2822	< 0.0001	1.500 (0.930–2.418)	0.0964

HR hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *UCB* urothelial bladder cancer, *CIS* carcinoma in situ, *LVI* lymphovascular invasion, *eGFR* estimated glomerular filtration rate

chemotherapy, planning follow-up scheme in individual patients, and revising the current TNM system.

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Author contributions YY involved in project development, data collection, data analysis and interpretation, and manuscript writing. TN took part in project development, data management, data analysis and interpretation, and manuscript writing. JM involved in project development, data collection, data analysis and interpretation, and critical revision. TK took part in project development, data collection, interpretation of data, and critical revision. ST involved in project development, data collection, interpretation of data, and critical revision. MT involved in data collection, interpretation of data, and critical revision. TK involved in data collection, interpretation of data, and critical revision. AI took part in data collection, interpretation of data, and critical revision. HM involved in data collection, interpretation of data, and critical revision. YK took part in data collection, interpretation of data, and critical revision. AM involved in data collection, interpretation of data, and critical revision. AN involved in data collection, interpretation of data, and critical revision. MH took part in data collection, interpretation of data, and critical revision. YF involved in interpretation of data and critical revision. YA took part in interpretation of data and critical revision. YY involved in interpretation of data and critical revision. YS involved in interpretation of data and critical revision. AN took part in interpretation of data and critical revision. DY involved in interpretation of data and critical revision. TM took part in data collection, interpretation of data, and critical revision. MS took part in interpretation of data and critical revision. YE took part in interpretation of data and critical revision. HN involved in data collection, interpretation of data, and critical revision. TT took part in interpretation of data and critical revision. YT involved in interpretation of data and critical revision. HK took part in interpretation of data, critical revision, and supervision. All authors had read and approved the final manuscript.

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Declarations

Conflict of interest None declared.

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