



Platinum Priority – Urothelial Cancer

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Subclassification of pT3 Urothelial Carcinoma of the Renal Pelvicalyceal System is Associated With Recurrence-Free and Cancer-Specific Survival: Proposal for a Revision of the Current TNM Classification

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Abstract

Background: The clinical course of pT3 upper tract urothelial carcinoma (UTUC) is highly variable.

Objectives: The aim of the current study was to validate the clinical and prognostic importance of pT3 subclassification in the renal pelvicalyceal system in a large international cohort of patients.

Design, setting, and participants: From a multi-institutional international database, 858 renal pelvicalyceal tumors treated with radical nephroureterectomy (RNU) were systematically reevaluated by genitourinary pathologists. Category pT3 pelvic tumors were categorized as pT3a (infiltration of the renal parenchyma on a microscopic level only) versus pT3b (macroscopic infiltration of the renal parenchyma and/or infiltration of peripelvic adipose tissue).

Intervention: RNU.

Measurements: Associations of pT3 subclassifications with clinicopathologic features were assessed with the chi-square test. Prognostic impact was assessed with the log-rank test and multivariable Cox regression analyses.

Results and limitations: Of 858 patients with renal pelvicalyceal tumors, 266 (31%) had pT3 disease. Of these, 146 (54.9%) were classified as pT3a and 120 (45.1%) as pT3b. Compared with pT3a, pT3b cancers were associated with higher tumor grade, nodal disease, and tumor necrosis. Ten-year recurrence-free (pT3a 58% vs pT3b 38%; $p < 0.001$) and cancer-specific (pT3a 60% vs pT3b 39%; $p = 0.002$) survival rates were lower for patients with pT3b disease. In multivariable analyses, classification pT3b was an independent predictor of both disease recurrence (hazard ratio [HR]: 1.8, $p = 0.003$)

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and cancer-specific mortality (HR: 1.7; $p = 0.02$). The major limitation is the retrospective character of the study.

Conclusions: Subclassification of pT3 renal pelvicalyceal UTUC helps identify patients who are at increased risk of disease progression and cancer-related death. Further research may help assess the value of subclassification and its inclusion in future editions of the American Joint Committee on Cancer–International Union Against Cancer TNM classification system.

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1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) accounts for approximately 10% of all renal neoplasms and approximately 5% of all urothelial carcinomas [1,2]. Radical nephroureterectomy (RNU) with bladder-cuff excision remains the gold standard treatment [3]. A significant proportion of patients will experience disease recurrence and associated death attributable to metastatic UTUC [3]. While there is currently no evidence supporting the benefit of adjuvant therapies [4], identification of patients at high risk of failure with RNU alone is important for accurate prognostication, patient counseling, and design of clinical trials using integrated multimodal therapy.

To date, however, most of our clinical decision making is based on tumor stage and grade. For UTUC located in the renal pelvicalyceal system, pT3 classification is defined by the American Joint Committee on Cancer (AJCC)–International Union Against Cancer (UICC) TNM system as any tumor infiltration into renal parenchyma and/or peripelvic adipose tissue [5]. Conversely, in bladder cancer, a subclassification of pT3 into pT3a (microscopic infiltration of perivesical fat) and pT3b (macroscopic perivesical fat infiltration) disease has been implemented in the AJCC–UICC TNM system [5]. Cho et al. reported that renal parenchymal invasion beyond the corticomedullary junction has a strong prognostic impact for renal caliceal urothelial carcinomas and proposed a novel staging scheme based on the extent of invasion relative to the corticomedullary junction [6]. We previously demonstrated in a single-center series including 53 patients with pT3 pelvic UTUC that pT3 disease of the renal pelvicalyceal system represents a heterogeneous population with regard to oncologic outcome [7].

Prior to integration into management algorithms, prognostic factors need to be validated in larger cohorts of patients to ensure generalizability [8]. Therefore, we sought to externally validate our previous observations [7] through evaluation of a large independent multi-institutional cohort of patients managed with RNU for UTUC of the renal pelvicalyceal system.

2. Patients and methods

2.1. Patient selection

This was an institutional review board-approved study with all participating sites providing the necessary institutional data-sharing agreements prior to initiation of the study. Eight centers worldwide provided data. Patients with a history of muscle-invasive urothelial carcinoma (UC) of the urinary bladder were excluded. 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. Prior to final analysis, the database was frozen and the final data set was produced for the current analysis.

The study population comprised 858 patients who underwent RNU with bladder cuff resection for renal pelvicalyceal UTUC between 1987 and 2007. Regional lymphadenectomy was generally performed in patients with suspicious lymph nodes on preoperative imaging or with suspicious findings intraoperatively. Extended lymphadenectomy was not routinely performed. Adjuvant chemotherapy regimens were administered to 169 (11.6%) patients. No patient received preoperative systemic chemotherapy, preoperative radiotherapy, or adjuvant radiotherapy.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures, and all slides were re-reviewed by genitourinary pathologists according to identical strict criteria. All pathologists were blinded to clinical outcomes. All specimens were histologically confirmed to be UC. Tumors were staged according to the TNM classification [5]. Tumor grading was performed according to the 2004 World Health Organization–International Society of Urologic Pathology consensus classification [9]. Histopathologic assessment included concomitant carcinoma in situ (CIS), tumor architecture (papillary vs sessile), lymphovascular invasion (LVI), and tumor necrosis (defined as the presence of microscopic coagulative necrosis in >10% of the tumor area [10]).

Only tumors located in the renal pelvicalyceal system were chosen for this study. All tumor specimens were examined according to a pathologic-consensus protocol, which was determined prior to study initiation. The definitions for pathologic examination of specimen and depth of invasion has been previously described [7]. The charts with the original macroscopic descriptions and the hematoxylin- and eosin-stained slides from routinely formalin-fixed and paraffin-embedded material were systematically reevaluated by a genitourinary pathologist. pT3 tumors of the renal pelvicalyceal system were subdivided according to different patterns of tumor involvement as follows: (1) tumors invading renal parenchyma on a microscopic level only, (2) tumors with macroscopic renal parenchyma invasion discerned from the gross appearance of the resection specimen, and (3) tumors with spread into peripelvic fat. Category 1 was defined as pT3a; categories 2 and 3 were combined to stage pT3b.

2.3. Surveillance regimen

Patients were generally followed every 3–4 mo for the first year following RNU, every 6 mo from the second through the fifth year, 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 scans, chest computerized tomography, or magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as tumor relapse in the operative field, regional lymph node and/or distant metastasis. Occurrences of UC

in the bladder or contralateral upper tract were not considered as disease recurrence. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only patients who had UC listed in the death certificate were considered to have died of UTUC for this study. All patients who were coded as dead of cancer had previous disease recurrence. In addition, perioperative mortality (any death within 30 d of surgery or before discharge) was censored at time of death for urothelial cancer-specific survival (CSS) analyses.

2.4. Statistical analysis

Associations of pT3 subclassification with categorical variables were assessed using the chi-square test. The difference in age between pT3 subclassifications was assessed using the Mann-Whitney U test. The impact of pT classification (including pT3 subclassification), grade, lymph node status, and LVI on recurrence-free survival (RFS) and CSS were determined. Univariable RFS and CSS probabilities after RNU were estimated using the Kaplan-Meier method and log-rank statistics. Multivariable Cox regression models addressed RFS and CSS after RNU. Two multivariable models were evaluated: (1) exclusively pT3 cancers ($n = 266$), including pT3 subclassification (pT3b vs pT3a), tumor grade,

lymph node status, tumor necrosis, and LVI and (2) all 858 pelvic tumors assessing all pT categories (pTa as reference category), grade, lymph node status, and LVI. Predictive accuracy (PA) estimates of pT3 substratification outcomes were quantified using the area under the curve (AUC) of the receiver operator characteristic. In Cox regression models, the AUC is substituted by Harrell's concordance index [11,12]. This method was selected to quantify increments in PA associated with the addition of pT3 substaging to a base set of predictor variables. Internal validation with 200 bootstrapping samples was performed to reduce overfit bias [13]. Predictive accuracy estimates were expressed as proportions and compared with the Mantel-Haenszel test. All reported p values are two-sided and statistical significance was set at ≤ 0.05 . Statistical analyses were performed with S-Plus Professional software (MathSoft Inc., Seattle, WA, USA).

3. Results

3.1. Clinicopathologic associations

Out of 858 patients with UTUC located in the renal pelvicalyceal system, 266 (31%) were classified as having

Table 1 – Association of pT3 subclassification with clinical and pathologic characteristics in 266 patients treated with radical nephroureterectomy for pT3 urothelial carcinoma of the renal pelvicalyceal system

Characteristic	Patients, no.	pT3 subclassification		p value
		pT3a ($n = 146$; 54.9%)	pT3b ($n = 120$; 45.1%)	
Age, yr, median, (interquartile range, range)	266	68.9 (15.3, 27.0–91.0)	70.0 (14.0, 36.0–97.1)	0.306
Gender, n (%)				0.595
Males	183	98 (53.6)	85 (46.4)	
Females	83	48 (57.8)	35 (42.2)	
ECOG PS, n (%)				0.137
0	193	100 (51.8)	93 (48.2)	
1	62	38 (61.3)	24 (38.7)	
2/3	11	8 (72.7)	3 (27.3)	
History of previous bladder cancer, n (%)				0.089
Absent	199	103 (51.8)	96 (48.2)	
Present	67	43 (64.2)	24 (35.8)	
Previous endoscopic procedures, n (%)				0.839
Absent	239	132 (55.2)	107 (44.8)	
Present	27	14 (51.9)	13 (48.1)	
Adjuvant chemotherapy, n (%)				0.238
Negative	179	103 (57.5)	76 (42.5)	
Positive	87	43 (49.4)	44 (50.6)	
Procedure, n (%)				0.566
Open	202	113 (55.9)	89 (44.1)	
Laparoscopic	64	33 (51.6)	31 (48.4)	
Grade, n (%)				0.037
Low	16	13 (81.3)	3 (18.8)	
High	250	133 (53.2)	117 (46.8)	
Lymph node status, n (%)				0.005
pNx	93	59 (63.4)	34 (36.6)	
pN0	120	68 (56.7)	52 (43.3)	
pN1-2	53	19 (35.8)	34 (64.2)	
Tumor necrosis, n (%)				0.027
Absent	138	85 (61.6)	53 (38.4)	
Present	128	61 (47.7)	67 (52.3)	
Lymphovascular invasion, n (%)				0.102
Absent	163	96 (58.9)	67 (41.1)	
Present	103	50 (48.5)	53 (51.5)	
Architecture, n (%)				0.381
Papillary	157	90 (57.3)	67 (42.7)	
Infiltrative	109	56 (51.4)	53 (48.6)	
Concomitant carcinoma in situ, n (%)				0.526
Negative	167	89 (53.3)	78 (46.7)	
Positive	99	57 (57.6)	42 (42.4)	

ECOG PS = Eastern Cooperative Oncology Group performance status.

pT3 disease. pT subclassification resulted in 146 (54.9%) pT3a and 120 (45.1%) pT3b tumors. Median patient age was 69.7 yr (range: 27–97 yr). The clinicopathologic characteristics of the 266 patients and their associations with pT3 subclassification are listed in Table 1. Compared with pT3a subcategory, pT3b cancers were more likely to be of high grade (98% vs 91%; $p = 0.04$), node positive (28% vs 13%; $p = 0.005$), and to have tumor necrosis (56% vs 42%; $p = 0.03$). There was, however, no difference between pT3a and pT3b tumors with regard to patient age, gender, performance status, history of previous bladder cancer, previous endoscopic treatment of UTUC, type of RNU (open or laparoscopic), use of adjuvant chemotherapy, LVI, and concomitant CIS.

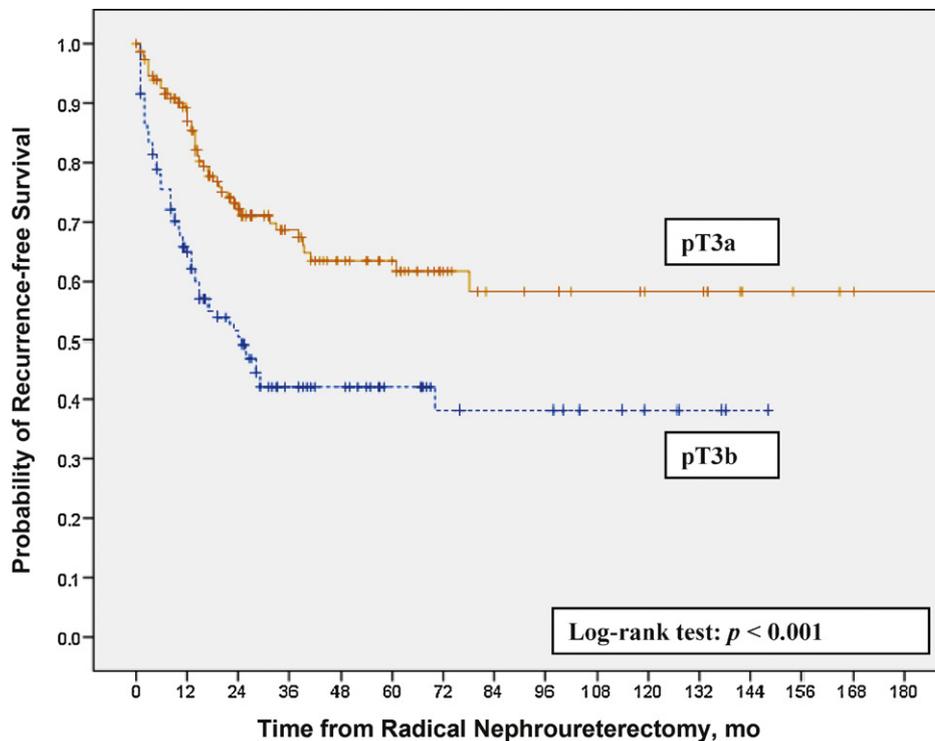
3.2. Associations with recurrence-free survival and cancer-specific survival

Median follow-up of all 858 renal pelvicalyceal UTUC patients and the pT3 only cohort was 48 mo (range: 0.1–250 mo) and 35 mo (range: 1–231 mo), respectively, for patients alive at last follow-up. Median follow-up of all 858 renal pelvicalyceal UTUC patients and the pT3-only cohort was 46 mo (range: 1–250 mo) and 34 mo (range: 1–231 mo),

respectively, for patients without disease recurrence. Disease recurrence was noted in 107 of 266 (40.2%) patients with pT3 pelvic cancer. Median time to disease recurrence was 20 mo (range: 4–169 mo). One hundred nine (41%) patients died: 86 (32.3%) from UTUC and 23 (8.6%) from non-UTUC-related reasons.

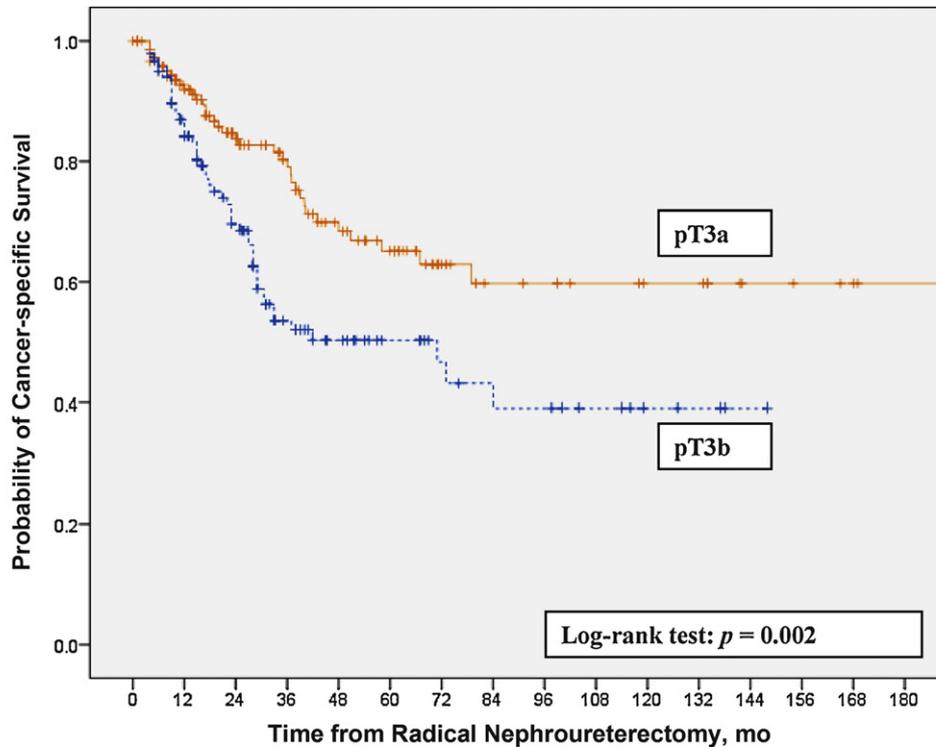
In univariable analyses (Figs. 1 and 2), patients with pT3a tumors had a significantly better outcome compared with pT3b subclassification (10-yr RFS and CSS estimates: 58% vs 38% and 60% vs 39%, respectively; $p < 0.001$ and $p = 0.002$, respectively). Median RFS and CSS in patients with pT3b cancers were 25 mo and 71 mo, respectively. In pT3a cancer patients, median RFS and CSS were not reached. Using univariable Cox regression analyses, pT3 subclassification was associated with RFS (hazard ratio [HR]: 2.2; 95% confidence interval [CI], 1.5–3.2; $p < 0.001$) and CSS (HR: 1.9; 95% CI, 1.3–3.0; $p = 0.003$).

In multivariable analyses restricted to patients with pT3 tumors ($n = 266$) (Table 2), pT3 subclassification was an independent predictor of both RFS ($p = 0.003$) and CSS ($p = 0.02$). The bias-corrected prediction of disease recurrence and CSS after RNU using a base model including tumor grade, LVI, tumor necrosis, and lymph node status were 0.68 and 0.64, respectively. Adding pT3 substaging to the model



	No. of patients at risk for disease recurrence															
	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
All	266	183	119	82	63	51	32	25	24	18	14	13	6	4	3	2
pT3a	136	102	66	50	39	30	20	16	14	11	10	8	5	4	3	1
pT3b	116	66	41	25	19	13	10	9	8	5	4	2	1	0	0	0

Fig. 1 – Recurrence-free survival probabilities according to subclassification of pT3 urothelial cancers located in the renal pelvicalyceal system: pT3a versus pT3b, $p < 0.001$.



	No. of patients at risk for cancer-specific death															
	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
All	266	211	146	99	73	56	36	28	26	20	15	14	7	5	4	2
pT3a	136	104	75	59	44	31	21	17	15	12	11	9	6	4	3	1
pT3b	115	88	56	32	22	16	13	11	9	6	4	2	1	0	0	0

Fig. 2 – Cancer-specific survival probabilities according to subclassification of pT3 urothelial cancers located in the renal pelvicalyceal system: pT3a versus pT3b, $p = 0.002$.

increased its accuracies for disease recurrence and CSS to 0.71 and 0.67, respectively ($p < 0.001$).

In multivariable analyses that included all patients with renal pelvicalyceal tumors ($n = 858$) (Table 3), pT3 subclassification was independently associated with both RFS and CSS. Adjustment for the effects of adjuvant chemotherapy did not alter the statistical significance of pT3 subclassification in any of the analyses.

4. Discussion

We confirmed the independent prognostic value of pT3 subclassification for predicting both RFS and CSS in a large international series of UTUC renal pelvic tumors. In addition, we showed a stepwise increase of risk of advancing pT classification for cancer-related outcomes in multivariable analysis. Of note, the HR difference

Table 2 – Multivariable Cox regression analyses predicting disease recurrence and cancer-specific death in 266 patients treated with radical nephroureterectomy for pT3 urothelial carcinoma of the renal pelvicalyceal system

Factor	Disease recurrence			Cancer-specific death		
	Hazard ratio	95% CI	<i>p</i> value	Hazard ratio	95% CI	<i>p</i> value
pT3b vs pT3a	1.843	1.229–2.763	0.003	1.713	1.088–2.696	0.020
Lymphovascular invasion	1.343	0.897–2.012	0.152	1.193	0.754–1.889	0.451
Tumor necrosis	1.969	0.708–5.477	0.194	1.934	0.689–5.431	0.211
Lymph node status			0.081			0.080
pNx vs pN0	1.274	0.778–2.086	0.336	1.398	0.801–2.438	0.238
Node positive vs pN0	1.740	1.072–2.823	0.025	1.868	1.080–3.229	0.025

CI = confidence interval; Nx = lymphadenectomy not performed.

Table 3 – Multivariable Cox regression analyses predicting disease recurrence and cancer-specific death in 858 patients treated with radical nephroureterectomy for urothelial carcinoma of the renal pelvicalyceal system

Factor	Disease recurrence			Cancer-specific death		
	Hazard ratio	95% CI	<i>p</i> value	Hazard ratio	95% CI	<i>p</i> value
pT classification			<0.001			<0.001
pT1 vs pTa	2.488	1.156–5.354	0.020	2.386	0.998–5.703	0.050
pT2 vs pTa	5.061	2.434–10.524	<0.001	5.282	2.324–12.007	<0.001
pT3a vs pTa	5.879	2.814–12.279	<0.001	7.197	3.171–16.330	<0.001
pT3b vs pTa	10.592	5.056–22.192	<0.001	12.211	5.349–27.878	<0.001
pT4 vs pTa	25.358	11.409–56.362	<0.001	30.926	12.779–74.843	<0.001
Lymphovascular invasion	1.259	0.911–1.740	0.163	1.153	0.793–1.676	0.455
High pathologic grade	2.027	1.201–3.420	0.008	1.819	1.039–3.185	0.036
Lymph node status			<0.001			<0.001
pNx vs pN0	1.615	1.110–2.350	0.012	1.418	0.934–2.154	0.101
Node positive vs pN0	1.724	1.228–2.421	0.002	1.869	1.267–2.754	0.002

CI = confidence interval; Nx = lymphadenectomy not performed.

between pT3b and pT3a was considerably larger than that between pT3a and pT2.

Few other attempts regarding subclassification of renal pelvic UTUC have been published. Previously, Cho et al. showed that renal parenchymal invasion beyond the corticomedullary junction was a predictor for worse outcomes in renal pelvicalyceal tumors and thus a new staging system might lead to more precise outcomes prognostication [6]. Our data are in line with two studies from Japan reporting that pT3 pelvic cancers with extensive parenchymal invasion (defined as invasion deeper than 5 mm) had a prognosis similar to that of pT4 cancers, whereas pT3 cancers without extensive parenchymal invasion (including cases with intraductal spread only) had a prognosis similar to that of pT1/pT2 disease. Sample size, however, was limited in these two series with 21 and 70 patients, respectively [14,15]. In another small study, Komatsu et al. found that none of six patients with pT3 pelvic cancers limited to the kidney died of their disease and that their prognosis was significantly better than that of 11 patients with pT3 disease invading peripelvic and/or periureteral fat [16]. Olgac et al. subdivided 39 pT3 pelvic cancers into three groups: invasion into sinus fat, invasion into renal parenchyma invasion, and invasion into hilar fat [17]. At the time of last follow-up, all four patients with sinus fat invasion were alive (one of them with metastatic disease). In a study of 72 patients with pT3 UTUC located in either renal pelvis or ureter, Wu et al. found that superficial parenchymal invasion (not deeper than 5 mm) was associated with better outcomes compared with extensive parenchymal invasion (deeper than 5 mm), and peripelvic and periureteral fat invasion [18]. Recently, Park et al. reported that pT3 renal pelvis tumors ($n = 122$) had a better outcome than pT3 ureteral tumors ($n = 102$). They found that renal pelvis tumors limited to renal parenchyma invasion were associated with a better prognosis than other renal pelvic tumors and ureteral tumors invading adipose tissue. The authors concluded that renal parenchyma may provide a protective barrier against cancer spread [19].

Taken together, patients with pT3 UTUC of the renal pelvicalyceal system are a heterogeneous population with

variable outcomes. While previous reports elucidated potential categorization that could allow stratification of pT3 patients into differential risk groups, the sample sizes were insufficient to make conclusive recommendations. Using our large multi-institutional data base [3], we show that pT3 subclassification is an independent predictor with respect to both RFS and CSS. Together with data from previous studies, this suggests the inclusion of pT3 subclassification into the TNM classification of renal pelvic UTUC.

In bladder cancer, a subclassification of pT3 disease into pT3a (microscopic invasion of perivesical adipose tissue) and pT3b (macroscopic fat invasion) tumors has been implemented in the current TNM classification system [5]. The prognostic relevance of this subclassification remains controversial, however. Boudreaux et al. described no significant differences in outcomes between node-negative pT3a and pT3b bladder cancers in a population of 75 patients [20]. Furthermore, in a larger series, Bastian et al. found no difference in outcomes between pT2b ($n = 172$) and pT3a ($n = 88$) tumors [21]. In contrast, pT3b tumors ($n = 121$) had a significantly worse outcome with a 1.8-fold increased risk of recurrence and a 2-fold increased death rate [21]. The prognostic accuracy of pT classification alone is too inaccurate to allow individual outcome prediction. Combination of pT classification with other published clinicopathologic features of prognostic relevance, such as vascular invasion [7], lymphovascular invasion [22], lymph node density [23], tumor architecture [24], number of resected lymph nodes [25], and tumor necrosis [10] may improve outcome prediction by a significant margin. Integration of various important features in nomograms [26–28] may improve individualized prediction, patients counseling, and evidence-based clinical decision making with regard to follow-up and adjuvant treatment.

The major limitation of our study is its retrospective design. The potential flaws of a retrospective study, however, have been minimized by systematic reevaluation of each specimen by a dedicated genitourinary pathologist at each center, with each blinded to clinical outcomes. Still, relatively thin layers in the upper urinary tract compared to

the bladder increase the difficulty of adequate substaging in UTUC [29]. This might relate to a higher difference in the pT3a to pT3b ratio than between pT2 and pT3a, where layer differentiation may be more obvious. We did not, however, perform central pathology review by a single pathologist. On the other hand, the differences in practice patterns across the institutions are reflective of the real world, making the conclusions of our study more generalizable. We also did not adjust the analysis for variant UTUC histology, which might have an undefined impact. Other limitations include the long study period of over 20 yr with changing practice patterns. For example, indication for RNU, standard diagnostic work-up, and follow-up protocols have changed over time. Another limitation resulting from the retrospective character of the study is the lack of a standardized indication, as well as uniform templates, for lymphadenectomy. This heterogeneity might be responsible for the lacking prognostic impact of node-positive tumors in our study.

5. Conclusions

In this large international cohort of pT3 UC located in the renal pelvicalyceal system, subclassification into pT3a and pT3b UTUC stratified patients into significantly different risk groups, proving pT3b as an independent predictor of worse outcome after RNU when compared with pT3a. pT3 subclassification may be helpful in individual risk-adjusted follow-up management. Moreover, selection of patients for adjuvant treatment trials might be guided on the basis of the proposed pT3 subclassification. These data suggest the consideration of pT3 renal pelvicalyceal UTUC subclassification in future issues of the TNM classification system.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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