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Original Article
Clinical Investigation

Biological and prognostic implications of biopsy upgrading for high-grade upper tract urothelial carcinoma at nephroureterectomy

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Abbreviations & Acronyms
CI = confidence interval
CSS = cancer-specific survival
HR = hazard ratio
KSS = kidney sparing surgery
LN = lymph node
LVI = lymphovascular invasion
OS = overall survival
RFS = recurrence-free survival
RNU = radical nephroureterectomy
URS = ureteroscopy
UTUC = upper tract urothelial carcinoma

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Objectives: Technical limitations of ureteroscopic (URS) biopsy has been considered responsible for substantial upgrading rate in upper tract urothelial carcinoma (UTUC). However, the impact of tumor specific factors for upgrading remain uninvestigated.

Methods: Patients who underwent URS biopsy were included between 2005 and 2020 at 13 institutions. We assessed the prognostic impact of upgrading (low-grade on URS biopsy) versus same grade (high-grade on URS biopsy) for high-grade UTUC tumors on radical nephroureterectomy (RNU) specimens.

Results: This study included 371 patients, of whom 112 (30%) and 259 (70%) were biopsy-based low- and high-grade tumors, respectively. Median follow-up was 27.3 months. Patients with high-grade biopsy were more likely to harbor unfavorable pathologic features, such as lymphovascular invasion ($p < 0.001$) and positive lymph nodes (LNs; $p < 0.001$). On multivariable analyses adjusting for the established risk factors, high-grade biopsy was significantly associated with worse overall (hazard ratio [HR] 1.74; 95% confidence interval [CI], 1.10–2.75; $p = 0.018$), cancer-specific (HR 1.94; 95% CI, 1.07–3.52; $p = 0.03$), and recurrence-free survival (HR 1.80; 95% CI, 1.13–2.87; $p = 0.013$). In subgroup analyses of patients with pT2-T4 and/or positive LN, its significant association retained. Furthermore, high-grade biopsy in clinically non-muscle invasive disease significantly predicted upstaging to final pathologically advanced disease (≥pT2) compared to low-grade biopsy.

Conclusions: High tumor grade on URS biopsy is associated with features of biologically and clinically aggressive UTUC tumors. URS low-grade UTUC that becomes upgraded to high-grade might carry a better prognosis than high-grade UTUC on URS. Tumor specific factors are likely to be responsible for upgrading to high-grade on RNU.

Key words: biopsy grade, intratumor heterogeneity, survival, upgrading, upper tract urothelial carcinoma.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease with heterogeneous biology and clinical behaviors.[1,2] Tumor grade based on ureteroscopy (URS) biopsy is an important factor for accurate risk stratification.[3] A previous study revealed that cancer-specific (CSS) and overall survival (OS) estimates at 2 years for patients with low-grade UTUC tumors on initial URS biopsy are significantly better than those with high-grade (98% vs. 65% and 95% vs. 64%, respectively).[4] Despite the importance of URS grade on clinical decision-making regarding kidney sparing surgery (KSS), studies have reported considerable upgrading rates (33%–51%) between the biopsy tissue and final radical nephroureterectomy (RNU) specimen, posing significant challenges for the choice of KSS.[5,6] Uncertainty over the biopsy grade has been assumed due to inadequate specimen size and quality resulting from tumor morphology, anatomical difficulties, and/or instrumental limitations.[7] This suboptimal assessment of tumor grade partly hinders the widespread adoption of KSS for patients with localized UTUC. However, previous studies failed to show the significance of specimen size on URS biopsy for ensuring accurate diagnosis.[8,9] Moreover, studies in urothelial carcinoma of the bladder have demonstrated that heterogeneity in histological grades within the same tumor/lesion may influence prognosis with better outcomes compared to pure high-grade lesions.[10,11] Taken together, we hypothesized that not only intraoperative technical limitations but also tumor specific factors including intratumor grade heterogeneity, could be partially responsible for the suboptimal biopsy grading in UTUC tumors as well.[5] Therefore, to test the clinical significance of our hypothesis, we assessed the differential prognostic impact of low versus high tumor grade based on URS biopsy in patients with pathologically confirmed high-grade UTUC at final RNU pathology.

PATIENTS AND METHODS

Patients

We relied on an international multi-institutional UTUC collaboration that included data from 13 institutions; eight from Europe, three from North America, and two from Asia. Data were collected after approval of institutional review board at all participating institutions. All data were collected retrospectively on patients who had URS biopsies followed by RNU in a timely fashion (less than 3 months). After collection in each individual site, the data were combined for analysis. The database was frozen, quality assurance performed with continuous communication, and finally the current analysis was performed after external data quality audit by independent experts. Patients who underwent preoperative URS with biopsy followed by RNU for high-grade UTUC between 2005 and 2020 were included. Exclusion criteria were undetermined grade on biopsy, low- or no grade reported on the final RNU specimen, and missing oncological outcomes data.

Surgical technique

Tumor biopsy was performed using either endoscopic or percutaneous image-guided technique.[12] Endoscopic access to obtain tumor tissues was achieved using a retrograde URS. Ureteroscopic biopsies were performed using a semi-rigid and/or flexible ureteroscope via either a cup biopsy forceps or a stainless-steel flat wire basket at the treating urologist's discretion. RNU, including bladder cuff excision, was performed via either open, laparoscopic, or robotic approach. Lymphadenectomy was performed at the surgeon's discretion. Perioperative chemotherapy was administered according to the potential tumor aggressiveness and patient comorbidities after local multidisciplinary tumor board approval.

Data collection and variable evaluation

Clinical tumor grade was defined on pathological biopsy results. All surgical specimens were examined according to standard pathologic procedures at each participating institution. Tumor grading was evaluated using the 2004 World Health Organization/International Society of Urologic Pathologists consensus classification and tumor staging was based on the 2002 American Joint Committee on Cancer-International Union Against Cancer system. According to the selective urinary cytology findings, tumors were classified as positive versus negative; cases of atypical cytology were included into negative group. In case selective cytology findings were not available, bladder cytology findings were used. Hydronephrosis and tumor size were evaluated based on preoperative imaging. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls. All pathologic evaluations were performed by each institutional pathologist and all specimens were histologically confirmed as urothelial carcinomas.

Follow-up

Due to the retrospective nature of the study, follow-up schedule was not standardized. However, it generally relied on the patients' risk according to the national and international guidelines[3] or institutional standards. Follow-up regimens consisted in general of laboratory assessment, urinary cytology, cystoscopy, and cross-sectional imaging. Disease recurrence was defined as tumor relapse at the operative site, regional lymph nodes (LNs), and/or distant metastasis. Intravesical recurrence was not considered as recurrence. Cause of death was determined by treating physicians, chart review corroborated by death certificates or death certificates alone. Patients identified as having died of UTUC had progressive, widely disseminated metastasis at the time of death.

Statistical analysis

The chi-square test and the Mann–Whitney *U* test were used to assess the differences in categorical and continuous variables, respectively. The Kaplan–Meier method was applied to estimate survival probabilities after RNU and log-rank tests were used for pairwise comparisons. Multivariable analyses using Cox proportional hazards models were performed to assess the association between biopsy-based tumor grade and other established factors with OS, CSS, and recurrence-free

survival (RFS). Subgroup analyses of pT2-T4 patients were performed to determine the discriminative ability of adjuvant treatment strategies after RNU. Multivariable analyses using logistic regression were performed to explore risk factors of upstaging from clinical non-muscle invasive (≤cT1) to advanced pathological stage (≥pT2) disease on RNU specimen. Statistical analyses were performed using STATA version 14.0 (Stata Corp.). Two-sided $p < 0.05$ was defined as statistically significant.

RESULTS

After applying our inclusion and exclusion criteria, a total of 371 patients were eligible for this study (Figure S1). Table 1 summarizes the descriptive patients' characteristics, stratified by tumor grade at biopsy. Patients had low- and high-grade tumors, determined by URS biopsy, in 112 (30%) and 259 (70%) cases, respectively. There was no significant difference in urinary cytology, tumor size and hydronephrosis between low- and high-grade tumors ($p = 0.85$, 0.13 and 0.37, respectively). Pathologic stage distribution was comparable between UTUC with low- and high-grade biopsy ($p = 0.77$). On final pathological RNU specimen examination, patients with high-grade URS biopsy were more likely to harbor adverse pathologic features, such as LVI ($p < 0.001$), and positive LN ($p < 0.001$) compared to those with low-grade URS biopsy. Furthermore, patients with high-grade URS biopsy were more likely to undergo lymphadenectomy ($p < 0.001$) and neoadjuvant chemotherapy ($p = 0.008$).

TABLE 1 Distribution of clinical and histopathological variables in RNU confirmed high-grade UTUC patients stratified by biopsy grade

	Total	Low-grade biopsy	High-grade biopsy	*p*
Total, *n* (%)	371 (100)	112 (30)	259 (70)	
Gender, *n* (%)				0.25
Male	252 (68)	81 (72)	171 (66)	
Female	118 (32)	31 (28)	87 (34)	
Missing	1 (0)	0 (0)	1 (0)	
Age, median (IQR)	73 (66–79)	73 (65–80)	73 (67–79)	0.68
Urinary cytology, *n* (%)				0.85
Negative	120 (32)	37 (33)	83 (32)	
Positive	251 (68)	75 (67)	176 (68)	
Tumor size, *n* (%)				0.13
≤1 cm	270 (72)	84 (75)	186 (72)	
>1 cm	51 (14)	14 (12.5)	37 (14)	
Unspecified	50 (14)	14 (12.5)	36 (14)	
Hydronephrosis, *n* (%)				0.37
Absence	229 (62)	73 (65)	156 (60)	
Presence	142 (38)	39 (35)	103 (40)	
Multifocality				0.83
Absence	309 (83)	94 (84)	215 (83)	
Presence	62 (17)	18 (16)	44 (17)	
Pathological stage, *n* (%)				0.31
≤pT1	160 (43)	47 (42)	113 (44)	
pT2	57 (15)	22 (20)	35 (13)	
≥pT3	154 (42)	43 (38)	111 (43)	
Histological variant, *n* (%)				0.29
Absence	343 (92)	106 (95)	237 (92)	
Presence	28 (8)	6 (5)	22 (8)	
Lymphovascular invasion, *n* (%)				**<0.001**
Absence	284 (77)	100 (89)	184 (71)	
Presence	68 (18)	8 (7)	60 (23)	
Missing	19 (5)	4 (4)	15 (6)	
LN status, *n* (%)				**<0.001**
No lymphadenectomy	200 (54)	76 (68)	124 (48)	
Negative	121 (33)	30 (26)	91 (35)	
Positive	47 (13)	5 (4)	42 (16)	
Missing	3 (1)	2 (2)	2 (1)	
Neoadjuvant chemotherapy, *n* (%)				**0.008**
No	329 (89)	107 (96)	222 (86)	
Yes	41 (11)	5 (4)	36 (14)	
Missing	1 (0)	0 (0)	1 (0)	

Note: Bold *p* values are considered statistically significant. Abbreviations: LN, lymph node; RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma.

Association with OS, CSS, and RFS

During a median follow-up of 27.3 (IQR 10.4–48.7) months, 123 (33%) patients experienced disease recurrence and 118 (32%) died from any cause, and 74 (20%) died from UTUC. OS estimates at 1- 2-, and 3-year were 92.1%, 84.5%, and 79.5% in patients with low-grade URS biopsy tumors versus 87.4%, 75.4%, and 64.3% in patients *w*ith high-grade URS biopsy tumors, respectively. The Kaplan–Meier curves showed that patients with low-grade URS biopsy tumors were at a significantly lower risk of OS, CSS, and RFS compared to those with high-grade URS biopsy tumors (hazard ratio [HR] 1.94; 95% confidence interval [CI], 1.27–2.95; $p = 0.002$, HR 2.30; 95% CI, 1.31–4.02; $p = 0.004$, HR 1.91; 95% CI, 1.26–2.98; $p = 0.002$, respectively) (Figure 1). On multivariable analyses that adjusted for the effects of established risk factors, URS biopsy tumor grade retained an independent prognostic role for OS, CSS and RFS (HR 1.74; 95% CI, 1.10–2.75; $p = 0.018$, HR 1.94; 95% CI, 1.07–3.52; $p = 0.03$, and HR 1.80; 95% CI 1.13–2.87; $p = 0.013$, respectively) (Table 2). When multivariable analyses that adjusted for postoperative prognostic factors only were performed, URS biopsy grade remained an independent prognostic factor for RFS (HR 1.65; 95% CI, 1.03–2.66; $p = 0.039$) but not for OS and CSS (HR 1.58; $p = 0.06$ and HR 1.57; $p = 0.15$, respectively) (Table S1). Of the entire cohort, 217 patients had high-grade pT2-T4 or LN positive UTUC diseases at RNU pathology. Among these, URS biopsy-based tumor grade remained associated with OS, CSS, and RFS on multivariable analyses (HR 1.88; 95% CI, 1.03–3.41; $p = 0.038$, HR 2.68; 95% CI, 1.23–5.80; $p = 0.013$, and HR 2.75; 95% CI, 1.45–5.20; $p = 0.002$, respectively) (Table 3).

Association with upstaging

Upstaging to muscle invasive disease (≥pT2) at the time of RNU occurred in 79 patients (45%) with clinically non-muscle invasive disease. On multivariable logistic regression exploring risk factors of upstaging, URS-based tumor grade was significantly associated with increased odds of upstaging (OR 2.29; 95% CI, 1.08–4.84; $p = 0.031$) for RNU confirmed high-grade disease (Table 4).

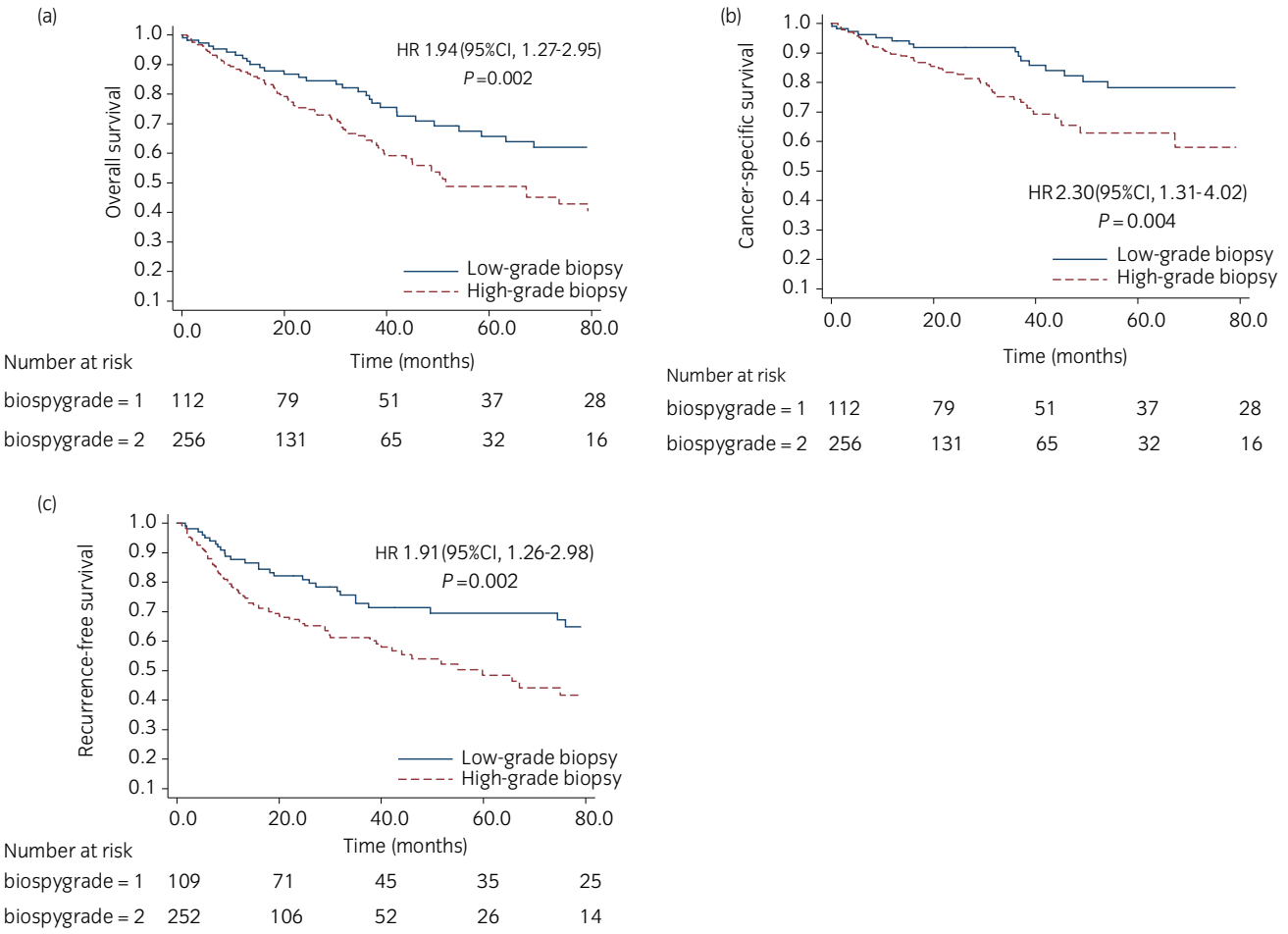

FIGURE 1 Kaplan–Meier analysis for overall survival (a), cancer-specific survival (b), and recurrence-free survival (c), in upper tract urothelial carcinoma patients treated by radical nephroureteretectomy after ureteroscopic biopsy

TABLE 2 Multivariable Cox regression analyses adjusted for risk factors predicting OS, CSS, and RFS in 371 patients treated with RNU following ureteroscopic biopsy for RNU confirmed high-grade UTUC

	OS			CSS			RFS		
	Multivariable			Multivariable			Multivariable		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age	1.03	1.00–1.05	**0.03**	1.01	0.98–1.04	0.43	1.00	0.98–1.02	0.93
Sex	0.99	0.67–1.47	0.96	1.34	0.83–2.15	0.23	0.88	0.58–1.33	0.53
Urinary cytology	1.42	0.92–2.19	0.11	1.61	0.92–2.82	0.10	1.06	0.760–1.62	0.77
Hydronephrosis	1.06	0.71–1.58	0.78	—			1.29	0.87–1.91	0.20
Tumor size	0.65	0.43–1.00	0.05	—			0.62	0.41–0.95	**0.03**
Pathologic stage (ref. pT0/pTa/Tis/T1)									
pT2	0.98	0.52–1.85	0.96	—			1.53	0.84–2.81	0.17
≥pT3	1.84	1.20–2.82	**0.005**	—			2.39	1.52–3.77	**<0.001**
≥pT2	—			1.99	1.15–3.46	**0.014**	—		
Multifocality	1.00	0.61–1.64	1.0	—			1.30	0.81–2.08	0.28
LN positive (ref. N0/Nx)	2.45	1.49–4.02	**<0.001**	2.64	1.47–4.72	**0.001**	2.48	1.50–4.12	**<0.001**
Neoadjuvant chemotherapy	1.35	0.72–2.52	0.35	1.77	0.92–3.41	0.09	1.36	0.77–2.42	0.29
Biopsy grade (ref. biopsy low-grade)	1.74	1.10–2.75	**0.018**	1.94	1.07–3.52	**0.030**	1.80	1.13–2.87	**0.013**

Note: Bold *p* values are considered statistically significant. Abbreviations: CSS, cancer-specific survival; OS, overall survival; LN, lymph node; RFS, recurrence-free survival; RNU, radical nephroureterectomy, UTUC, upper tract urothelial carcinoma.

TABLE 3 Multivariable Cox regression analyses predicting OS, CSS, and RFS in 217 patients with pT2-pT4 or LN positive treated with RNU following ureteroscopic biopsy for RNU confirmed high-grade UTUC

	OS			CSS			RFS		
	Multivariable			Multivariable			Multivariable		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age	1.03	1.00–1.07	**0.026**	1.01	0.98–1.04	0.61	1.01	0.98–1.04	0.57
Sex	1.16	0.72–1.86	0.55	1.51	0.87–2.60	0.14	1.13	0.70–1.82	0.62
Histological variant	1.61	0.83–3.12	0.16	1.69	0.79–3.62	0.18	1.23	0.61–2.48	0.56
Lymphovascular invasion	1.83	1.08–3.12	**0.026**	1.81	0.97–3.35	0.06	1.60	0.94–2.74	0.09
LN positive (ref. N0/Nx)	2.18	1.27–3.73	**0.004**	2.31	1.27–4.20	**0.006**	1.89	1.09–3.27	**0.023**
Biopsy grade (ref. biopsy low-grade)	1.88	1.03–3.41	**0.038**	2.68	1.23–5.80	**0.013**	2.75	1.45–5.20	**0.002**

Note: Bold P values are considered statistically significant. Abbreviations: CSS, cancer-specific survival; LN, lymph node; OS, overall survival; RFS, recurrence-free survival; RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma.

TABLE 4 Multivariable logistic regression analyses predicting upgrading to pathologically advanced (≥pT2) disease at final RNU in 174 patients with clinically non-muscle invasive UTUC (≤cT1)

	Upstaging					
	Univariable			Multivariable		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Age	1.01	0.98–1.05	0.34	1.01	0.98–1.04	0.55
Sex	1.60	0.85–3.01	0.14	1.73	0.88–3.37	0.11
Urinary cytology	1.28	0.68–2.42	0.45	0.96	0.48–1.92	0.91
Hydronephrosis	0.81	0.42–1.54	0.52	0.88	0.44–1.75	0.72
Tumor size	1.26	0.61–2.59	0.53	1.22	0.56–2.65	0.61
Multifocality	2.33	1.00–5.44	0.05	2.22	0.90–5.47	0.08
Biopsy grade (ref. biopsy low-grade)	2.14	1.04–4.41	**0.038**	2.29	1.08–4.84	**0.031**

Note: Bold *p* values are considered statistically significant. Abbreviations: CSS, cancer-specific survival; LN, lymph node; OS, overall survival; RFS, recurrence-free survival; RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma.

DISCUSSION

In this study, we investigated the differential oncological and survival impact of tumor grade on URS biopsy (low- vs. high-grade) in patients with definitely high-grade UTUC diseases on final RNU specimen. We found that patients with high-grade biopsy had a significantly higher risk of harboring pathologic features of biologically aggressive disease, such as LVI and positive LN compared to those with low-grade URS biopsy despite both having definitive high-grade tumor on final RNU specimen. Moreover, we revealed that URS detected high-grade tumors were significantly associated with an increased risk of worse OS, CSS and RFS on multivariable analyses adjusted for the effects of established risk factors. This association was also confirmed in patients with pT2-T4 or LN positive UTUC diseases. In addition, we revealed that high-grade URS biopsy significantly predicted upstaging to advanced pathological stage (≥pT2).

KSS for UTUC patients at low risk is a reasonable option with the benefit of preserving the renal function. Biopsy-based high URS tumor grade has been shown to predict advanced pathologic stage.[6] CSS of patients with high-grade UTUC on the RNU specimen at 10 years was 38% compared to 89% for those with low-grade.[4] Thus, the accurate preoperative identification of tumor grade on URS biopsy is essential to distinguish patients who could be candidates for KSS compared to those needing RNU with or without perioperative systemic treatment.

Given the importance of URS tumor grade in our clinical decision-making,[13] upgrading is a major clinical concern for patients with UTUC who are considered at low-risk in the preoperative work-up. Despite a relatively good concordance between tumor grade on biopsy material and the final specimen pathology, a recent meta-analysis revealed that upgrading is more likely to occur than downgrading (34% vs. 5%); approximately one-third of patients presumed to have clinical low-grade diseases were upgraded in the final specimens.[5,14] Classically, inadequate acquisition of biopsy tissue and crush artifact resulting from morphology, or anatomical and instrumental limitations have been considered responsible for this high rate of upgrading,[15] which limits the dissemination of KSS. Recent studies, however, have reported that the pathologic evaluation of tumor grade was independent of the biopsy volume.[6,8,9] Interestingly, these previous studies failed to identify any predictors of upgrading on multivariable analyses, which may imply the presence of uncaptured factors for

upgrading.[6,8] Therefore, we hypothesized that tumor grade determined by URS biopsy may reflect the inherent distribution of intratumor grade heterogeneity; in other words, detecting low-grade URS biopsy in pathological high-grade UTUC tumors, is not only due to a technical error, but may reflect tumor behavior leading to clinical oncologic/prognostic information that could be harnessed for guiding our postoperative management. We found that low-grade tumors on URS biopsy represented an independent predictor of longer OS, CSS and RFS on multivariable analyses after adjusting for the effects of other risk factors. These findings were also confirmed by subgroup analyses of high-grade UTUC patients with pT2-T4 and/or positive LN. In addition to survival outcomes, URS high-grade tumors with seemingly non-muscle invasion on imaging significantly harbored advanced stage disease compared to URS low-grade tumors. Although adjuvant chemotherapy provides a significant improvement in survival for UTUC patients with pT2-T4 and/or positive LN,[16] a large heterogeneity of these patients in the risk of recurrence and progression and postoperative decreased renal function confound clinicians to offer this treatment. According to our findings, biopsy-based tumor grade may help identify best candidates who benefit from adjuvant intensified treatments. Furthermore, given that URS high-grade cases had a higher risk of harboring adverse pathologic features and occult advanced diseases (≥pT2), neoadjuvant chemotherapy might confer survival benefits for clinically high-grade UTUC patients determined by URS biopsy. However, since the significant association of differential biopsy grade disappeared on multivariable analyses controlling for postoperative confounders only, its ability to predict prognosis may be limited compared to the abilities of other established prognostic factors (pathologic stage, LVI, or LN status etc.).

Data have demonstrated that heterogeneity in tumor grade is not uncommon in bladder cancer.[10] These patients with low- and high-grade tumors in their tumors were more favorable prognosis rather than those with pure high-grade tumors.[10,11] These data suggest that in UTUC tumors also biopsy grade may reflect intratumor heterogeneity. In support of this, recent studies investigating UTUC according to computed tomography texture analysis supported this hypothesis by demonstrating that pathological high-grade tumors were subjectively and quantitatively more heterogeneous than low-grade tumors.[17,18] However, as their evaluation of heterogeneity is only from the radiologic experimental point of view, future validation based on high quality thorough pathologic evaluation is warranted to confirm/reject our hypothesis.

In terms of pathologic assessments of tumor grade, European Association of Urology guidelines have advocated the use of 2004/2016 classification to improve its variability and reproducibility, but 1973 classification remains recommended.[3] High-grade tumors adopted in this study include both G2 and G3 tumors, which may represent the variabilities in recurrence and progression. Although it remains controversial, high-grade tumors are likely to have better survival compared with G3 tumors.[19,20] Therefore, the wide spectrum of high-grade UTUC tumors defined by 2004/2016 WHO classification may have contributed to our study findings. The suboptimal survival prediction of 2004/2016 classification may hint at the need not for a simple three-tier grading system, but for the subclassification of high-grade diseases.

The main limitations of this study that may have affected our findings are inherent to its retrospective and multicentric nature. First, the lack of central pathologic review and institutional variabilities in pathologic evaluations, surgical techniques and treatment strategies may have limited the robustness of our findings. In this context, interobserver heterogeneity might affect our study's results. Second, the exclusion of patients who have missing data and those who received KSS treatments may have influenced our study findings. Third, we could not capture several important variables such as the number of cores, tumor biopsy site or tumor architecture. Despite these limitations, our findings may stretch the importance of diagnostic URS and offer clinical and biological rationale to further studies with pathologic assessment investigating intratumor heterogeneity in UTUC tumors to help understand the wide spectrum of clinical behavior of seemingly similar UTUC tumors. While upgrading to high-grade tumor on final pathology has classically represented a barrier to the implementation of KSS, our study suggests that upgrading carries the additional important implications likely to be associated with the probability of survival outcomes. Additionally, understanding of intratumor structure in UTUC tumors may help develop the detailed classification according to the occupied proportion of low-grade component for the accurate prognostic predictive decision-making.

In conclusion, our study suggests that tumor grade determined by URS biopsy provides additional prognostic information for patients with pathological high-grade UTUC on RNU. Diagnostic URS with concomitant biopsy is an important step for decision-making regarding KSS. Based on our data, URS grade biopsy also helps for prognostication and upstaging. Further research, combined with thorough pathologic and radiologic assessments of UTUC tumors are warranted to validate the findings of this study and prove the nature and clinical/biological value of tumor grade heterogeneity in UTUC.

AUTHOR CONTRIBUTIONS

Satoshi Katayama: Conceptualization; methodology; formal analysis; writing – original draft; data curation. **Benjamin Pradere:** Methodology; project administration; resources. **Nico C. Grossman:** Methodology. **Aaron M. Potretzke:** Validation. **Stephen A. Boorjian:** Validation. **Alireza Ghoreifi:** Methodology. **Sia Daneshmand:** Validation. **Hooman Djaladat:** Validation. **John P. Sfakianos:** Validation. **Andrea Mari:** Methodology. **Zine-Eddine Khene:** Validation. **David D'Andrea:** Validation. **Nozomi Hayakawa:** Methodology; Validation. **Alberto Breda:** Validation. **Matteo Fontana:** Methodology; Validation. **Kazutoshi Fujita:** Validation. **Alessandro Antonelli:** Validation. **Thomas van Doeveren:** Validation. **Christina Steinbach:** Validation. **Keiichiro Mori:** Investigation; Methodology. **Ekaterina Laukhtina:** Visualization. **Morgan Rouprêt:** Validation; Supervision. **Vitaly Margulis:** Validation. **Pierre I. Karakiewicz:** Validation. **Motoo Araki:** Supervision. **Eva Compérat:** Validation. **Yasutomo Nasu:** Methodology.

Shahrokh F. Shariat: Writing – review & editing; supervision; project administration.

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CONFLICT OF INTEREST

None declared.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by each institutional review board at all participating institutions.

INFORMED CONSENT

N/A.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1.
Table S1.