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ORIGINAL ARTICLE

Impact of histologic variants on the oncological outcomes of patients with upper urinary tract cancers treated with radical surgery: a multi-institutional retrospective study

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Abstract

Background No definitive evidence exists regarding the clinical significance of histologic variants (HV) in upper urinary tract cancer. We investigated the impact of HV on prognosis in patients with upper urinary tract cancer following radical surgery.

Patients and methods We retrospectively analyzed 451 patients with upper urinary tract cancer who underwent radical nephroureterectomy at six affiliated hospitals from 1990 to 2015. Patients with distant metastatic disease prior to surgery and those who received neoadjuvant chemotherapy were excluded, leaving 441 eligible patients. Patients were classified into two groups: pure urothelial carcinoma (UC) and HV. The clinicopathological variables of each group were examined using Kaplan–Meier plots and proportional Cox hazard ratios (HR) to compare the oncological outcomes between the two groups.

Results HV included 37 patients (8%). Compared with the pure UC patients, HV patients had significantly worse recurrence-free survival (RFS) and cancer-specific survival (CSS; RFS $p = 0.0002$, CSS $p = 0.0001$). Multivariate analysis for RFS revealed HV were independent predictors (HR 1.92; $p = 0.026$), but the association did not remain significant for CSS. There was no significant difference in CSS between the adjuvant chemotherapy (AC) group and the non-AC group for all HV patients, except in patients with ≥ pT3 tumor or positive lymph node status where the AC group had significantly favorable CSS.

Conclusions HV in upper urinary tract cancer are independent predictors for RFS, but not for CSS. AC improved CSS for HV patients with ≥ pT3 tumor or positive lymph node status.

Keywords Histologic variants · Radical nephroureterectomy · Adjuvant chemotherapy · Upper urinary tract cancer · Urothelial carcinoma

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare neoplasm, accounting for approximately 5–10% of all urothelial malignancies [1]. The gold standard treatment for localized UTUC is radical nephroureterectomy (RNU) with ipsilateral bladder excision [2], and the treatment protocol following radical surgery is primarily determined on the basis of histopathological results such as pathological stage, lymph node status, and tumor grade [3]. Due to the low prevalence of UTUC there have been few studies underway examining other established factors [4, 5]. The most common histopathological type of UTUC is urothelial carcinoma (UC), accounting for 90–95% of cases. The remaining cases include those with histologic variants (HV), most commonly UC with squamous cell differentiation, followed by UC with glandular differentiation [6]. Upper urinary tract cancer with pure non-urothelial histology is quite rare, and while there are reports of squamous cell carcinoma and adenocarcinoma, these are primarily reported only in single-center experience or individual cases [7, 8]. The impact of HV in bladder cancer has been evaluated. Several reports revealed that HV in bladder cancer are associated with a pathologically advanced stage and poor prognosis compared to pure UC [9, 10]. However, no definitive conclusion has been reached regarding HV in upper urinary tract cancer, because there are a few published studies available, and only limited data are available regarding the efficacy of postoperative adjuvant chemotherapy (AC) for HV in upper urinary tract cancer. In the present multi-institutional study, we therefore examined the prognostic impact of HV in upper urinary tract cancer following radical surgery.

Patients and methods

Patients and data collection

The medical records of 451 patients with upper urinary tract cancer who underwent RNU at the Department of Urology, Kitasato University Hospital, and five affiliated institutions from 1990 to 2015 were retrospectively analyzed. Eight patients who received neoadjuvant chemotherapy and two patients with distant metastasis at the time of diagnosis were excluded from the study. Consequently, 441 patients were included. The study was approved by the ethical review board of each institution (B15–25) and was conducted in accordance with the Declaration of Helsinki. Age at the time of diagnosis, sex, surgical variables, and pathological variables were recorded. Histopathological examination was performed on the basis of the standardized criteria of each institution. Pathological analysis, including tumor staging, was performed according to the 2002 TNM Classification of Malignant Tumors (TNM), developed by the American Joint Committee on Cancer and the Union for International Cancer Control (UICC) [11]. The histological grade was determined according to the 1998 World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification [12]. Lymphovascular invasion (LVI) was defined as lymphatic and/or vascular invasion, and soft tissue surgical margin was defined as any positive areas in the renal pelvic, or ureteral, and/or exfoliated margin. Based on histology, all patients were divided into two groups: pure UC and HV. HV consisted of pure variant type and mixed type UC with variant pattern.

Surgical procedure and follow-up

RNU was performed laparoscopically in 247 patients [13] and via open surgery in 194 patients. Lymph node dissection was performed at the discretion of each individual surgeon when preoperative lymph node swelling was observed on imaging or when intraoperative lymph node swelling was observed. Postoperative follow-up was performed every 3 months for 2 years, then every 6 months for the subsequent 3 years, and annually thereafter. Physical examination, routine blood sampling, routine urine sampling, urinary cytology, and cystoscopy were performed every 3 months, with computed tomography and chest X-ray imaging performed every 6 months for the initial 2 years, then once every subsequent year. The median follow-up period from RNU was 36.1 months [interquartile range (IQR) 14.9–77.2 months] in the pure UC patients and 15.8 months (IQR 5.7–54.0 months) in the HV patients, respectively.

Recurrence-free survival (RFS) and cancer-specific survival (CSS) were calculated on the basis of medical records. CSS was defined as the length of time from RNU until death due to disease. RFS was defined as the length of time from RNU until local recurrence, evidence of distant metastasis, or death from UTUC or still alive at last follow-up.

Adjuvant chemotherapy

AC was defined as chemotherapy administered within 2 months of RNU [14]. AC was administered to patients diagnosed with pT3 or higher and/or positive for lymph node status, but it was at the discretion of the urologist in charge, considering factors including renal function, performance status, the patient's wishes, and other factors. AC was administered to 100 of 441 patients (22.6%; pure UC: $n=85$; HV: $n=15$). Details regarding the chemotherapy regimen for the pure UC patients included methotrexate, vinblastine,

doxorubicin, and cisplatin (MVAC, $n=38$), gemcitabine and cisplatin (GC, $n=34$), and another regimen ($n=13$). The regimen for HV patients included MVAC ($n=6$), GC ($n=8$), and etoposide and cisplatin (EP, $n=1$). The median number of cycles administered was three cycles for each group (IQR 1–6 cycles).

Statistical analysis

The association between clinicopathological variables was evaluated using the Kruskal–Wallis test, Chi-square test, and Fisher's exact test. Clinicopathological variables are reported as median and IQR. The probabilities following RNU were plotted on a Kaplan–Meier curve and compared between groups using a log-rank test. Univariate and multivariate regression analyses were examined using a Cox proportional hazard model to examine the effect of histopathological factors on RFS and CSS; $p<0.05$ was considered to be statistically significant, and the analyses were performed using Stata ver. 13 for Windows (Stata, Chicago, IL, USA).

Results

Patient characteristics

There were 404 patients with pure UC (92%) and 37 patients (8%) with HV. Among the 37 patients with HV, UC with squamous differentiation was the most common ($n=24$, 5.9%), followed by UC with glandular differentiation ($n=5$, 1.2%), adenocarcinoma ($n=4$, 0.9%), UC with squamous cell carcinoma ($n=1$, 0.2%), and UC with small-cell differentiation ($n=1$, 0.2%). Two patients (0.4%) had multiple differentiations (UC with glandular and squamous differentiation and UC with small-cell differentiation and squamous differentiation). The clinicopathological variables for all 441 patients are shown in Table 1. The patients with HV had significantly higher pT stage ($p<0.0001$), positive lymph node status ($p<0.001$), higher tumor grade ($p=0.002$), and positive sessile tumor architecture ($p=0.033$) than those with the pure UC.

Table 1 Clinicopathological characteristics of the total study cohort and comparative results between pure urothelial carcinoma and histologic variants

Characteristics	Pure UC ($N=404$)	HV ($N=37$)	P value
Age, years			
Median (IQR)	69 (62–75)	71 (60–74)	0.531
Sex			
Male	290 (71.7)	29 (78.4)	0.391
Female	114 (28.2)	8 (21.6)	
Surgery			
Open	223 (55.1)	22 (59.5)	0.618
Laparoscopy	181 (44.8)	15 (40.5)	
pT stage			
pTa	67 (16.6)	1 (2.7)	<0.0001
pTis	17 (4.2)	1 (2.7)	
pT1	90 (22.2)	2 (5.4)	
pT2	76 (18.8)	5 (13.5)	
pT3	136 (33.7)	22 (59.5)	
pT4	18 (4.5)	6 (16.2)	
LN status			
pN0	205 (50.7)	18 (48.6)	<0.0001
pN+	24 (5.9)	7 (18.9)	
pNx	175 (43.3)	12 (32.4)	
Grade[a]			
G1/2	289 (72.1)	16 (47.1)	0.002
G3	112 (27.9)	18 (52.9)	
LVI[b]			
Absent	134 (35.1)	22 (61.1)	0.002
Present	248 (64.9)	14 (38.9)	
CIS[c]			
Absent	332 (82.6)	31 (83.8)	0.854
Present	70 (17.4)	6 (16.2)	
Architecture[d]			
Papillary	279 (72.8)	17 (54.9)	0.033
Sessile	104 (27.2)	14 (45.1)	
STSM			
Positive	377 (93.3)	33 (89.2)	0.347
Negative	27 (6.7)	4 (10.8)	
Follow-up			
Median (IQR)	36.1 (14.9–77.2)	15.8 (5.7–54.0)	0.013

UC urothelial carcinoma, *HV* histologic variants, *LN* lymph node, *IQR* interquartile range, *CIS* carcinoma in situ, *LVI* lymphovascular invasion, *STSM* soft tissue surgical margin

[a]Six patients with unknown tumor grade

[b]Twenty-three patients had no lymphovascular invasion status

[c]Two patients with unknown CIS

[d]Twenty-seven patients with unknown tumor architecture

Survival outcomes

Of the 441 patients, the 5-year RFS rates in the pure UC and HV patients were 63.0% and 45.1%, and the 5-year CSS rates were 74.3% and 51.7%, respectively. Patients with HV showed significantly worse RFS ($p=0.002$) and CSS ($p=0.001$) than those with pure UC (Fig. 1).

In patients with HV, there was no significant difference in the 5-year CSS rates between patients with AC and those without AC (50.0% vs 51.9%, $p=0.734$; Fig. 2a), but in HV patients with ≥ pT3 tumor or positive lymph node status, the AC group had significantly better CSS than the non-AC group (56.0% vs 15.4%, $p=0.039$; Fig. 2b). HV patients with AC were significantly more treated with laparoscopic surgery (60.0% vs 18.1%, $p=0.009$) and shown positive LVI

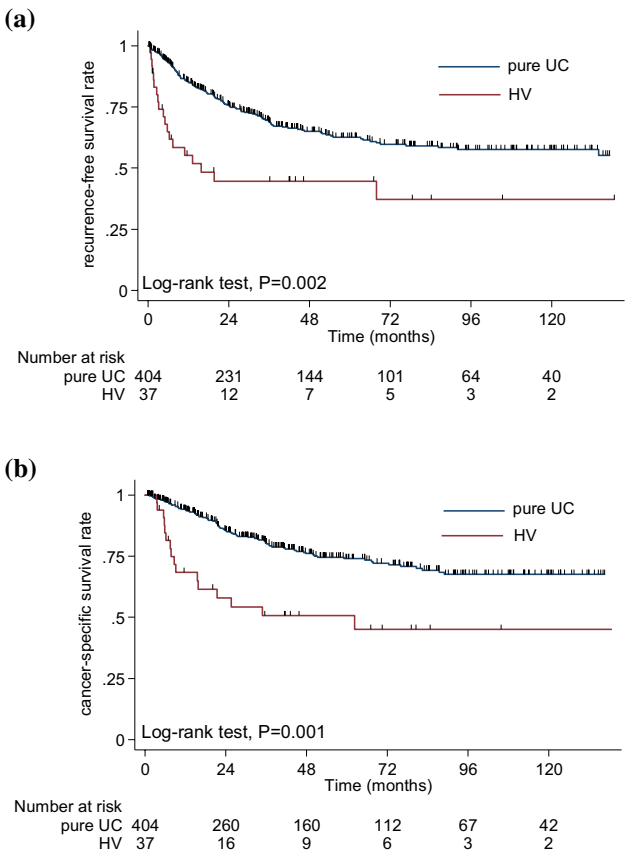

Fig. 1 Kaplan–Meier curves for **a** recurrence-free survival and **b** cancer-specific survival in the 441 patients treated with radical nephroureterectomy for upper urinary tract cancer stratified by pure urothelial carcinoma vs histologic variants

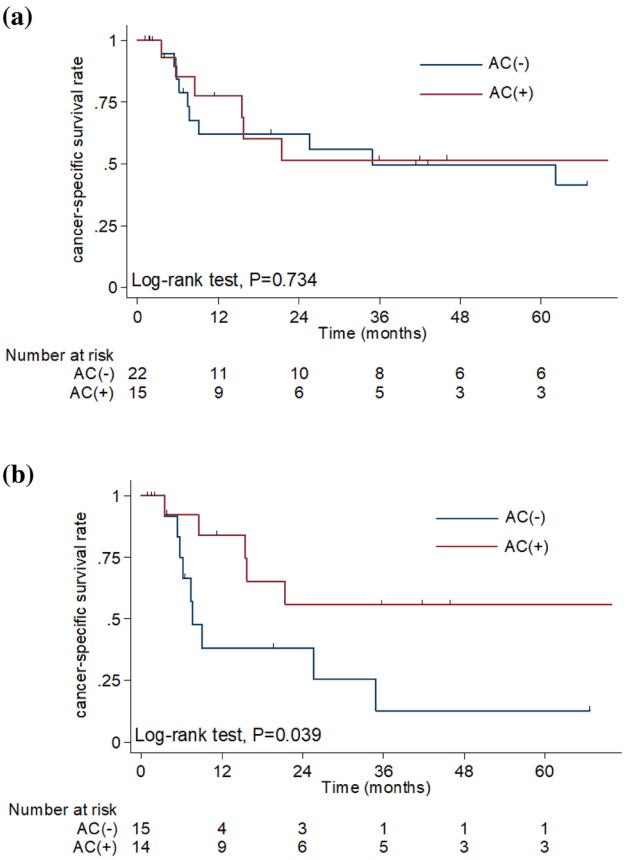

Fig. 2 Kaplan–Meier curves for cancer-specific survival in the histologic variant patients treated with radical nephroureterectomy for upper urinary tract cancer stratified by adjuvant chemotherapy status (**a**) all histologic variants patients (**b**) histologic variants patients with ≥ pT3 tumor or positive lymph node status

(85.7% vs 45.4%, $p = 0.016$) than those without AC. In terms of remaining clinicopathological variables, there were no significant differences between the two groups. Univariate and multivariate analyses using pathological variables on RFS revealed that HV were independent predictors [hazard ratio (HR) 1.92; 95% confidence interval (CI) 1.08–3.42; $p = 0.026$], along with advanced pT stage (≥ pT3), high tumor grade (G3), present LVI and positive lymph node status and soft tissue surgical margin (STSM; see Table 2). In terms of CSS, HV were independent predictors in univariate analysis. In multivariate analysis, advanced pT stage, high tumor grade, present LVI and positive lymph node status and STSM were independent predictors, but HV did not remain significantly variable.

Discussion

In the present study, we found that HV in patients were associated with adverse pathological features, such as positive lymph node status and higher stage and tumor grade. These findings of more aggressive tumor-specific characteristics for patients with HV in upper urinary tract cancer are congruent with previous studies. In addition, HV patients with ≥ pT3 tumor or positive lymph node status showed a significant effect for AC compared to those without AC.

Yan et al. reported that HV were significantly associated with advanced pathological stage and high tumor grade, tumor diameter, lymphovascular invasion, lymph node metastasis, positive surgical margin, and tumor architecture compared with pure UC by analyzing 417 UTUC patients who underwent radical surgery [15]. In 687 patients with surgically treated UTUC, Tang et al. demonstrated that UC with squamous differentiation and/or glandular differentiation significantly correlated with aggressive histopathological features, including larger percentage of sessile tumor architecture, higher tumor stage, and lymph node metastasis [16]. Furthermore, these two studies demonstrated that HV showed significantly poorer oncological outcomes than pure UC. However, it remains controversial whether HV are independent predictive factors. Most previous studies showed no

Table 2 (a) Univariate and multivariate Cox proportional hazards analysis for the prediction of progression-free survival and (b) cancer-specific survival

	Recurrence-free survival					
	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
(a)						
HV (reference: pure UC)	2.4	1.51–4.07	< 0.001	1.92	1.08–3.24	0.026
pT3-4 (reference: ≤ pT2)	4.16	2.91–5.93	< 0.001	1.91	1.2–3.07	0.006
pN+ (reference: pNo/pNx)	4.95	3.02–8.09	< 0.001	2.44	1.32–4.5	0.004
Grade 3 (reference: G1/G2)	3.47	2.47–4.88	< 0.001	1.92	1.27–2.91	0.002
LVI present (reference: absent)	5.11	3.53–7.38	< 0.001	2.4	1.49–3.85	< 0.001
CIS present (reference: absent)	1.06	0.68–1.64	0.784	0.87	0.52–1.45	0.599
Sessile (reference: papillary)	2.28	1.6–3.25	< 0.001	1.19	0.79–1.8	0.381
STSM positive (reference: negative)	8.09	5.23–12.5	< 0.001	3.85	2.3–6.45	< 0.001
	Cancer-specific survival					
	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
(b)						
HV (reference: pureUC)	2.8	1.64–4.79	< 0.001	1.52	0.81–2.84	0.19
pT3-4 (reference: ≤ pT2)	5.62	3.63–8.70	< 0.001	2.43	1.38–4.29	0.002
pN+ (reference: pNo/pNx)	5.14	3.07–8.6	< 0.001	1.91	0.98–3.71	0.054
Grade 3 (reference: G1/G2)	3.57	2.4–5.29	< 0.001	1.87	1.18–2.98	0.008
LVI present (reference: absent)	8.07	5.05–12.8	< 0.001	3.21	1.8–5.7	< 0.001
CIS present (reference: absent)	0.84	0.48–1.46	0.554	0.84	0.45–1.55	0.586
Sessile (reference: papillary)	2.35	1.57–3.57	< 0.001	1.12	0.70–1.79	0.614
STSM positive (reference: negative)	8.42	5.23–13.5	< 0.001	3.14	1.79–5.51	< 0.001

HR hazard ratio, *CI* confidence interval, *HV* histologic variants, *CIS* carcinoma in situ, *LVI* lymphovascular invasion, *STSM* soft tissue surgical margin, *AC* adjuvant chemotherapy

statistical significance in the multivariate analysis for predictors of survival, though HV showed worse cancer-specific outcomes. For example, in the largest recent study, which included 1648 UTUC patients, Rink et al. showed that HV were associated with worse survival outcomes in univariate analysis, but the effect did not remain significant in multivariate analysis [17]. Meanwhile, the study by Yan et al. is the only report that showed HV were independent predictors of CSS in both univariate and multivariate analysis. Our study is in agreement with the most previous studies. In the present study, HV were independent predictors of RFS, but not for CSS. This discrepancy implies that salvage treatments, such as chemotherapy or radiation, may affect clinical outcomes. However, it is difficult to confirm their clinical effects and to answer their association with HV. Since there was no recommended salvage regimen for HV and was a variety of modalities depended on each institution in this retrospective multi-institutional study. In addition, one explanation for this disappearance of effect in multivariate analysis is the different rate of aggressive histological subtypes among the study population. The study by Yan et al. had 10 sarcomatoid and small-cell differentiation out of 90 HV patients, whereas the present study had no sarcomatoid differentiation and only 2 small-cell differentiation cases. As sarcomatoid and small-cell variant are reported to be extremely aggressive [18], the proportion of each aggressive HV may have influenced the survival outcomes. Analysis of each histological subtype could confirm the specific outcomes, but previous studies did not conduct such subgroup analysis due to a small sample size. Further studies with statistical power will verify the biological aggressiveness of HV on survival.

HV are characteristically aggressive tumors with potentially poor prognosis, it has therefore been discussed whether AC can improve the prognosis [19]. The efficacy of AC in patients with UTUC after RNU remains a controversial issue, because no prospective randomized study yet exists. Some researchers report that there is no association between survival mortality and AC [20, 21], but some retrospective analyses revealed survival benefits in high-risk populations with tumors ≥ pT3 or positive lymph node status [22, 23]. Recent meta-analysis of nine retrospective cohort studies also revealed that AC was significantly associated with an

overall survival (OS) benefit for locally advanced and/or positive regional lymph node disease [24]. Our previous report using the same cohort as the current study identified five factors (≥ pT3, pN+, G3, lymphovascular invasion, and positive surgical margin) independently predictive of poorer survival, and AC was associated with improved CSS in high-risk UTUC, when having more than three risk factors defined in the high-risk group [14].

Regarding AC for upper tract urinary cancer patients with HV, there are a limited number of reports available. Kim et al. examined the effectiveness of AC for patients with pure UTUC and UTUC with HV [19]. They revealed that UTUC with HV had significantly poorer CSS and OS than pure UTUC, but their study did not compare outcomes with or without AC among UTUC patients with HV. It is therefore difficult to determine whether AC is effective for HV from their study. Previous reports also chose chemotherapy regimens according to standard pure UTUC management protocol, while there is no consensus on regimens for HV. In the current study, subgroup analysis demonstrated that there was no significant difference on CSS between the AC group and non-AC group in all HV patients. However, the AC group had significantly favorable CSS in HV patients with ≥ pT3 tumor or positive lymph node status. Our results are the first study to identify upper tract urinary cancer patients with HV who benefit from AC using existing standard regimens. Based on these findings, pT stage and pN factors are important for selecting qualified patients for AC in upper tract urinary cancer patients with HV.

Since AC may be effective for a limited population, it is necessary to consider other modalities. Recently, immuno-oncology drugs such as check point inhibitors, which demonstrated a survival benefit for advanced and metastatic urothelial cancer, have the potential to improve the prognosis of HV patients [25, 26]. The data of KEYNOTE-045 comparing pembrolizumab to chemotherapy showed an oncological advantage for check point inhibitors for UC in all subgroups, including the mixed histology type [27]. Of particular note, mixed histology types are more likely to benefit from pembrolizumab compared to pure UC (pure UC: HR 0.80; 95% CI 0.62–1.04 vs mixed type: HR 0.58; 95% CI 0.37–0.89). The potential for these immunotherapies in neoadjuvant and adjuvant settings is the subject of several ongoing clinical trials [28, 29]. Further investigation to compare the effects of other postoperative modalities besides AC for HV in upper urinary tract cancer is warranted.

There are limitations to the present study. First, it is a retrospective investigation with no randomization, which may have introduced bias in the patient selection process. The extent of lymph node dissection, timing of AC, and number of cycles administered depended on the attending physician. In fact, lymphadenectomy were not performed in 43.3% of patients with pure UC and 32.4% with HV. Second, not all histopathology assessments included pathological review, and the cutoff value for the diagnosis of HV in UC was not defined, since this is a multi-institutional study conducted over a 20-year period. However, histopathological processing was conducted at all institutions based on standard criteria. Therefore, we classified the study patients into the pure UC group and the group of those with any variant histology. Finally, subgroup analysis for each histologic variant histological type was not possible due to the small subgroup size, although oncological characteristics differ according to the type of HV. Despite these limitations, this multi-institutional study with a long observation periods still has relevance for daily clinical practice.

Conclusion

HV in upper urinary tract cancer presented more aggressive oncological characteristics than pure UC, and showed poor RFS and CSS. Multivariate analysis found HV to be independent predictors for RFS, but this did not remain significant for CSS. For CSS, AC improved CSS for HV patients with ≥ pT3 tumor or positive lymph node status in this study. These results suggest AC may be considered for high-risk HV in upper urinary tract cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests to report.

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