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Evaluation of the Extent of Variant Histology in Urothelial Carcinoma as a Predictive Marker of Clinical Outcomes After Radical Cystectomy

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Abstract. *Background/Aim: This study investigated the impact of the extent of variant histology (VH) on the prognosis of patients with bladder cancer (BC). Patients and Methods: We retrospectively evaluated consecutive patients with muscle-invasive BC who were treated with radical cystectomy (RC) at our institution between 2005 and 2018. Recurrence-free survival (RFS) and overall survival (OS) rates were evaluated using Kaplan–Meier analysis and Cox regression. Results: We identified 103 and 47 patients with pure urothelial carcinoma (UC) and a VH in UC, respectively. At the cutoff of 80%, univariate analysis identified significant differences in RFS (p=0.046) and OS (p=0.038) between patients with ≥80% VH (n=21) and those with <80% VH (n=26). Multivariate analysis revealed that the presence of ≥80% VH was significantly associated with RFS and OS. Conclusion: The presence of ≥80% VH in UC could be an independent predictor of recurrence and mortality after RC.*

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Bladder cancer (BC) is a common malignancy of the genitourinary system. According to Global Cancer Incidence, Mortality and Prevalence estimates, 549,000 new cases of BC and 199,000 deaths occurred worldwide in 2018 (1). Pure urothelial carcinoma (UC) is the predominant histology of BC; however, variant histologies (VHs) in UC are frequently observed in muscle-invasive BC (MIBC). Morphological diversity is common in UC, accounting for approximately 33% of surgical specimens in radical cystectomy (RC) (2). The opportunities for the treatment of VHs in UC are thus relatively increased.

Several studies have suggested that patients with variant histology (VH) have poorer survival outcomes compared with those with pure UC treated with RC (3-6), but others have reported similar survival rates for patients with pure UC and those with VH based on univariate analysis (7-9). Research controlling for the effects of clinicopathologic characteristics has shown that the presence of a VH in UC is not an independent predictor of mortality (10, 11). However, these studies mainly focused on the prognostic value of the presence of VHs and were thus limited by their lack of adjustment for the extent of the VH. In daily practice, the proportion of the extent of the VH varies per case.

Soave *et al*. (12) reported an association between the extent of the VH and survival outcomes in an RC cohort. They did not find a prognostic benefit in stratifying patients by the extent of the VH (<70% or ≥70%). Nevertheless, the effect of the extent of the VH in MIBC has rarely been reported, and its impact on prognosis has yet to be fully elucidated. Evidence of the implication of this parameter's survival prediction currently does not exist (2, 7, 12).

Therefore, this study assessed the impact of the extent of the VH on oncological outcomes after RC.

Patients and Methods

Patient population. We conducted a retrospective review of 172 consecutive patients with MIBC (T2-4aN0M0) who had undergone RC at the University of Occupational and Environmental Health (UOEH; Kitakyushu, Japan) between March 2005 and September 2018. Only patients who had histologically confirmed pure UC or UC with a VH were included. Patients with such pure VHs as squamous cell carcinoma and adenocarcinoma as well as those without residual were excluded from the study, resulting in a total of 150 patients in the analysis. All the intended procedures in the present study were approved by the UOEH Institutional Review Board (approval no. H28-047).

Patient management. Patients underwent a routine precystectomy assessment, including physical examination, laboratory tests, confirmation of muscular invasion by transurethral resection of the bladder tumour, chest-abdominal-pelvic computed tomography (CT) scan and bone scintigraphy. All of them underwent RC, pelvic lymphadenectomy and urinary diversion. Tumour stage and nodal status were assigned according to the tumour, lymph nodes and metastasis (TNM) staging system (13).

The presence of VHs was re-reviewed in RC specimens by a dedicated genitourinary pathologist who was blinded to the clinical outcomes. Patients were classified as demonstrating a VH if they presented with UC combined with any morphological diversity in the RC specimens (14). VH subtypes were classified as per the World Health Organization Classification of Tumors (2). Each section was first scanned at low power for all tumoural fields (original magnification ×40) using conventional UC and VH subtypes to account for the heterogeneity of distribution. The extent of the VH was assessed by a meticulous workup of each slide via measurement of the proportion of the area it occupies in the whole lesion.

Prognostic assessment. Postoperative follow up examinations consisted of physical examinations, laboratory tests and CT scans, which were conducted every 6 months until the fifth year and annually thereafter. When symptoms appeared, the appropriate additional examinations were conducted. Disease recurrence was confirmed when local failure in the pelvic site, the presence of regional lymph nodes or distant metastasis, was detected. The recurrence-free survival (RFS) duration was calculated from the date of RC to the date of the first clinical recurrence or death due to any cause, or to the last follow up if the patient had no known recurrence. The overall survival (OS) duration was calculated from the date of RC to the date of death due to any cause, or to the date of the last follow up if the patient was alive. In addition, follow up information was obtained through the medical records of our institute or local hospitals. For patients whose medical records did not include follow up data, information was obtained through telephone contact.

Statistical analysis. All statistical analyses were performed using EZR ver.1.40 (Easy R, Vienna, Austria), which is a graphical user interface for R (The R Foundation for Statistical Computing). The Fisher exact test and χ^2 test were used to examine associations between categorical variables, whereas the Mann–Whitney *U*-test was used to compare continuous variables. RFS and OS were estimated using the Kaplan–Meier method and the log-rank test. Univariable and multivariable Cox proportional hazards models assessed time to recurrence and mortality. *p*-Value <0.05 was considered statistically significant.

Table I. *Histologies identified in the study patients*.

Histologic type	Number of patients (%)
Pure UC	103 (68.7)
Variant histology	47 (31.3)
Squamous differentiation	25 (16.7)
Glandular differentiation	7 (4.7)
Micropapillary variant	6 (4.0)
Sarcomatoid variant	3 (2.0)
Neuroendocrine differentiation	3 (2.0)
Plasmacytoid variant	1 (0.6)
Trophoblastic differentiation	1 (0.6)
Giant cell variant	1 (0.6)

UC: Urothelial carcinoma.

Results

Clinicopathologic characteristics of histologic subtypes. Of the 150 patients, 103 (68.7%) had pure UC and 47 (31.3%) had a VH in UC. Squamous differentiation (16.7%) was the most common variant element, followed by glandular differentiation (4.7%) and micropapillary variant (4.0%) (Table I). The clinicopathologic characteristics of the patients stratified by pure UC and the presence of a VH are shown in Table II. The differences between the groups in terms of age, sex, age-adjusted Charlson comorbidity index score, and administration of neoadjuvant or adjuvant chemotherapy were not statistically significant. The presence of a VH was significantly associated with an advanced tumour stage and a higher rate of pathologic lymph node positive status.

Association of the extent of the VH with disease recurrence and mortality. The median follow-up time was 45 months [interquartile range (IQR)=23-96], during which 62 (41.3%) patients experienced recurrence and 55 (36.7%) died. The patients with a VH had poorer RFS and OS values compared with those with pure UC (Figure 1). The 3-year RFS rates of the pure UC and VH groups were 65.6% (median RFS, not reached) and 41.9% (median RFS, 14 months) (p=0.018), respectively; their corresponding 3-year OS rates were 74.9% (median OS, not reached) and 49.1% (median OS, 36 months) (p=0.012).

In the patients with a VH, the median extent of histologic subtypes in the whole lesion was 60% (IQR=20-80). The VH

Table II. *Patient characteristics*.

	Pure UC n=103	Variant histology n=47	*p*-Value
Age, median (IQR)	69 (63-76)	68 (61-74)	0.244
Gender, n (%)			0.519
Male	79 (76.7)	33 (70.2)	
Female	24 (23.3)	14 (29.8)	
Age adjusted CCI score, median (IQR)	4 (3-5)	4 (3-5)	0.899
Clinical tumor stage, n (%)			0.030
T2	71 (68.9)	23 (48.9)	
≥T3	32 (31.1)	24 (51.1)	
Neoadjuvant chemotherapy, n (%)			0.608
Not administered	78 (75.7)	33 (70.2)	
Administered	25 (24.3)	14 (29.8)	
Pathologic tumor stage, n (%)			<0.001
≤T2	78 (75.7)	18 (38.3)	
≥T3	25 (24.3)	29 (61.7)	
Pathologic lymph node stage, n (%)			0.034
Negative	82 (79.6)	29 (61.7)	
Positive	21 (20.4)	18 (38.3)	
No. of lymph node removed, median (IQR)	9 (6-13)	9 (6-12)	0.918
Soft tissue surgical margin status, n (%)			0.287
Negative	98 (95.1)	42 (89.4)	
Positive	5 (4.9)	5 (10.6)	
Adjuvant chemotherapy, n (%)			0.360
Not administered	81 (78.6)	33 (70.2)	
Administered	22 (21.4)	14 (29.8)	

UC: Urothelial carcinoma; IQR: interquartile range; CCI: Charlson comorbidity index.

group was divided into two groups according to the proportion of histologic subtypes using the cut-off values of 20%, 40%, 60% and 80%. The RFS and OS rates of the groups, as estimated using univariate analysis, are presented in Table III. Comparisons of patients with ≥20% VH (n=37) *vs*. <20% VH (n=10), ≥40% VH (n=26) *vs*. <40% VH (n=21) and ≥60% VH (n=24) *vs*. <60% VH (n=23) revealed that the groups did not significantly differ in survival; the cut-off value of 80%, however, distinguished patients with a VH [≥80% (n=21) *vs*. <80% (n=26)] in terms of disease recurrence [hazard ratio (HR)=2.00; 95% confidence interval (CI)=1.09-4.18; p=0.046] and mortality (HR=2.28; 95%CI=1.07-5.33; p=0.038).

Kaplan–Meier curves assessed RFS and OS according to the following three categories: pure UC, <80% VH, and ≥80% VH (Figure 2). The outcomes between patients with pure UC and those with <80% VH did not exhibit any statistically significant difference. On the other hand, the patients with ≥80% VH had poorer RFS and OS compared with those with pure UC and those with <80% VH. The 3-year RFS rates of the <80% VH and ≥80% VH groups were 49.2% (median RFS, 37 months) and 32.7% (median RFS, 7 months) (p=0.047), respectively; their corresponding 3-year OS rates were 60.9% (median OS, not reached) and 34.6% (median OS, 19 months) (p=0.041).

The results of multivariate Cox proportional hazards regression analysis predicting RFS and OS after factors were adjusted for clinicopathologic characteristics are shown in Table IV. With regard to the extent of histologic subtypes in UC, ≥80% VH was identified as a significant independent predictor of disease recurrence (HR=2.08; 95%CI=1.08-3.99; p=0.028) and mortality (HR=2.27; 95%CI=1.15-4.49; p=0.019). In addition, advanced tumour stage and pathologic lymph node metastases were significantly associated with both survival outcomes.

Discussion

To assess the influence of the extent of the VH on oncological outcomes, we conducted a pathologic re-review of RC specimens as well as a clinical investigation of patients treated with RC for pure UC or a VH in UC. The patients with ≥80% VH had poorer RFS and OS compared with those with pure UC and those with <80% VH. Moreover, the presence of ≥80% VH was significantly associated with worse oncological outcomes in multivariate analyses. The widespread presence of the VH was identified to reveal its survival value as a prognostic factor.

In general, UC is known to be associated with a variety of histologic differentiation markers (15). The increasing

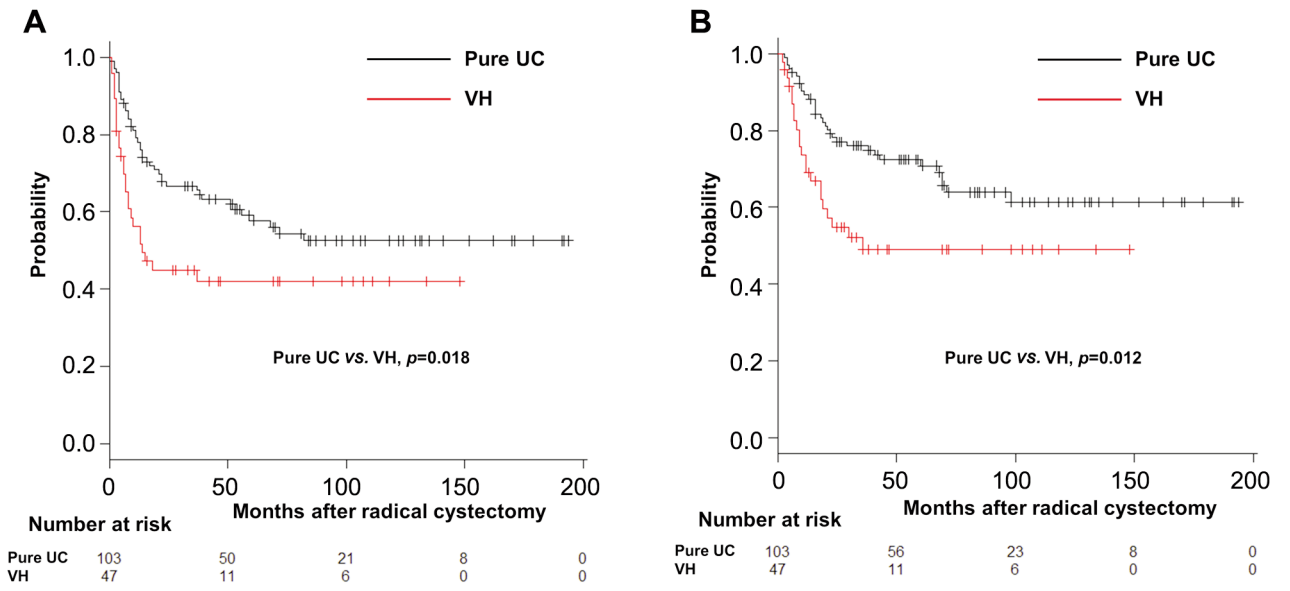

Figure 1. *Kaplan–Meier curves for the study patients stratified by pure urothelial carcinoma and variant histology in urothelial carcinoma after radical cystectomy. (A) Recurrence-free survival. (B) Overall survival. UC: Urothelial carcinoma; VH: variant histology.*

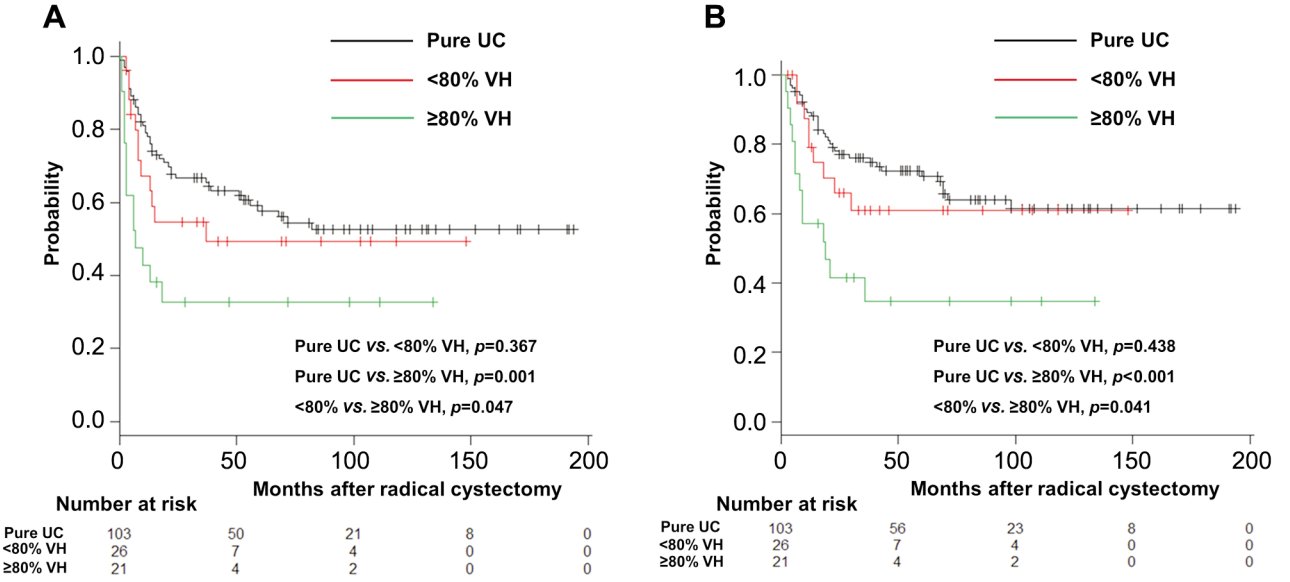

Figure 2. *Kaplan–Meier curves for the study patients stratified by pure urothelial carcinoma, the presence of <80% variant histology, and the presence of ≥80% variant histology. (A) Recurrence-free survival. (B) Overall survival. UC: Urothelial carcinoma; VH: variant histology.*

prevalence of VHs is largely due to improved pathologic recognition (16). In this study, we found that 31.3% of patients had a VH, with squamous differentiation, glandular differentiation, and micropapillary variant being common. The incidence rate of VHs in this study is similar to previously reported rates in patients treated with RC (2). In addition, the association between the presence of a VH and a higher rate of extravesical and lymph node positive disease is consistent with previous results (11, 17).

We also found differences in survival between patients with pure UC and those with a VH. Although several studies previously assessed the impact of VHs at the time of RC, the results on survival outcomes are controversial (3-6, 8-11). The dissension can be attributed to the studies' lack of detailed

Table III. *Results of univariate analysis of disease recurrence and survival in the study patients.*

Variable	Disease recurrence			Mortality		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Presence of variant histology *vs*. pure UC	1.78	1.09-2.91	0.020	1.97	1.14-3.34	0.015
≥20% variant histology *vs*. <20% variant histology	1.71	0.58-4.96	0.323	1.74	0.52-5.89	0.323
≥40% variant histology *vs*. <40% variant histology	1.57	0.72-3.41	0.259	1.71	0.59-4.97	0.372
≥60% variant histology *vs*. <60% variant histology	1.93	0.89-4.49	0.094	1.89	0.79-4.50	0.152
≥80% variant histology *vs*. <80% variant histology	2.00	1.09-4.18	0.046	2.28	1.07-5.33	0.038

HR: Hazard ratio; CI: confidence interval; UC: urothelial carcinoma.

Table IV. *Results of multivariate analysis of clinicopathologic factors predicting risk of disease recurrence and mortality after radical cystectomy in the study patients.*

Variable	Disease recurrence			Mortality		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (continuous)	0.99	0.96-1.02	0.589	1.03	0.99-1.07	0.092
Gender (female *vs*. male)	0.97	0.50-1.88	0.931	1.06	0.52-2.17	0.870
Pathologic tumor stage (≥T3 *vs*. ≤T2)	3.35	1.78-6.32	<0.001	3.67	1.83-7.38	<0.001
Pathologic lymph node status (positive *vs*. negative)	3.50	1.88-6.48	<0.001	2.86	1.49-5.49	0.002
Neoadjuvant chemotherapy (yes *vs*. no)	0.99	0.58-1.72	0.984	1.29	0.72-2.31	0.399
Adjuvant chemotherapy (yes *vs*. no)	0.50	0.26-0.97	0.043	0.77	0.38-1.56	0.463
Histologic type						
<80% variant histology *vs*. pure UC	0.83	0.41-1.65	0.589	0.73	0.34-1.60	0.438
≥80% variant histology *vs*. pure UC	2.08	1.08-3.99	0.028	2.27	1.15-4.49	0.019

HR: Hazard ratio; CI: confidence interval; UC: urothelial carcinoma.

pathologic features, including the percentage of the VH in the RC specimens. Many investigators have described the importance of assessing the influence of the extent of the VH on prognosis after RC (6,11, 17-19). Although the recent meta-analysis by Mori *et al*. (18) showed that the presence of a VH was associated with worse RFS (pooled HR=1.32; 95%CI=1.20-1.45) and OS (pooled HR=1.44; 95%CI=1.26-1.65), it demonstrated that the extent of the VH had not been assessed by most studies. Therefore, a cut-off value for the extent of the VH that is associated with survival has yet to be established. Soave *et al*. (12) did not detect any difference in survival between tumours with <70% VH and those with ≥70% VH. In addition, a standard technique to help quantify the level of the VH within tumour lesions is currently not available (20). Although we assessed the extent of the VH subjectively, the results of our study suggest that its presence is a good prognostic factor by stratifying patients at the cut-off value of 80%.

In terms of each subtype of VH, Monn *et al*. (17) reported that the micropapillary and plasmacytoid variants were independently associated with the risk of mortality compared with pure UC, after adjusting for pathologic features. Moreover, we have previously demonstrated that squamous differentiation predicted poor OS after RC in multivariate analysis (21, 22). However, we failed to identify the significance of ≥50% squamous differentiation in prognosis (22), which can be attributed to the extremely small sample size we used. By contrast, Mitra *et al*. (23) reported that ≥50% squamous differentiation was associated with significantly decreased rates of OS in univariate analysis. Another study on squamous differentiation and glandular differentiation by Kim *et al*. (7) indicated that the percentage categories of <30% *vs*. ≥30% did not differ in cancer-specific survival (CSS). Similarly, Wang *et al*. (24) did not detect any difference in CSS between the percentage categories of the micropapillary variant (10%, 10%-50% and ≥50%). To date, few studies have evaluated the impact of the extent of each variant, which renders the results thereof inconclusive. Although the impact of VHs on clinical outcomes may vary depending on the subtype, we considered all subtypes as one entity in analysing our study cohort. The limited number of patients with VH subtypes did not allow for a separate outcome analysis.

At the molecular level, MIBC is a heterogeneous disease that is characterised by genomic instability and a high mutation rate (25). Some investigators have demonstrated the importance of molecular subtype identification (26). Recently, Kamoun *et al*. (27) identified a consensus set of six molecular classes:

luminal papillary, luminal nonspecified, luminal unstable, stroma-rich, basal/squamous, and neuroendocrine-like. VH subtypes are approximately represented within each consensus class; however, a discrepancy exists between each subtype of VH and these molecular classes. Warrick *et al*. (28) indicated that 39% of cases with a VH demonstrated intratumoural molecular heterogeneity in BC. Therefore, the concomitant presence of several mutational patterns may affect survival. Although we still cannot use molecular classification in the clinical setting, information on genomic alterations will change the biological recognition of UC with a VH in the future.

This study has several limitations, including its retrospective nonrandomised single-institutional design and small sample size. In addition, the treatment was not uniform, as some patients received RC alone, whereas others received RC with perioperative chemotherapy. The effects of neoadjuvant and adjuvant chemotherapy on outcomes in patients with a VH are currently unclear for MIBC (29-31) and require further exploration. However, despite these limitations, our results suggest that patients with ≥80% VH are at high risk of disease recurrence and short-term survival. Thus, the widespread presence of the VH may play a role in the aggressive behaviour of UC with MIBC treated with RC.

VHs are not always available in pathologic reports. Pathologists should report the proportion of the VH in UC lesions, which might help physicians predict poor survival outcomes after RC. We believe that our study provides a better understanding of the significance of VHs in terms of the biological behaviour of UC. Multi-institutional studies with larger cohorts and preferably using a prospective study design are warranted to further validate our results regarding the ideal threshold for VHs. In conclusion, the presence of ≥80% VH in UC could be an independent predictor of recurrence and mortality after RC.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AM: conceptualisation, investigation, data curation, formal analysis and writing of the original manuscript. HN: pathologic assessment. RM, KH and GY: investigation. RK and YH: data curation. IT and NF: supervision. All Authors discussed, verified and approved the final version of the manuscript.

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