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Original Article

Impact of Histologic Variants of Bladder Cancer on Oncology Outcome After Radical Cystectomy

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Purpose: To evaluate the oncological outcome of histologic variants in bladder cancer patients who underwent radical cystectomy.

Materials and Methods: We identified 393 bladder cancer patients who underwent radical cystectomy at single center between January 2007 and August 2014. Patients were divided into 4 groups according to histologic types: pure urothelial cell carcinoma (UC) and squamous, micropapillary, and other variants. Kaplan-Meier analysis was performed to assess recurrence-free (RFS) and overall survivals (OS). The patients were divided into those with pathologic stage and nodal status.

Results: Among 393 bladder cancer patients, squamous, micropapillary histologic variants were observed in 38 (9.7%), 26 (6.6%), respectively, whereas 39 had other variant types. Stage T3 cancer occurred in more patients with histologic variant compared with those with pure UC. Pathologic positive nodal status was also frequently found in the histologic variant groups. Subgroup analysis according to T stage and nodal status showed no significant difference in RFS and OS. On multivariate analysis, pathologic T stage (stage T2: hazard ratio [HR], 2.75; 95% confidence interval [CI], 1.34–5.63; p=0.005; stage ≥T3: HR, 3.20; 95% CI, 1.62–6.30; p=0.001) and nodal status (HR, 1.85; 95% CI, 1.05–2.56; p=0.028) were prognostic factors for RFS.

Conclusions: In patients who underwent radical cystectomy, histologic variants were detected more often at advanced pathologic stage. Although histologic variants have been identified in the radical cystectomy specimen, treatment should be performed according to the pathologic stage. **(Korean J Urol Oncol 2017;15:121-130)**

Key Words: Bladder cancer · Histology · Cystectomy

INTRODUCTION

Bladder cancer is the sixth most common cancer in the United States, with more than 430,000 cases diagnosed worldwide.[1] Morbidity and mortality are high, especially in the case of muscle invasion. Multimodal treatment with radical cystectomy and neoadjuvant chemotherapy is preferred.[2] Urothelial cell carcinoma (UC) is the most common pathologic type, accounting for 90% of all bladder cancers.[3] The 2004 World Health Organization (WHO) classification of UC listed 13 his-

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tologic variants.[4,5] Several reports have noted the oncologic effect of histologic variants, although they vary from institution to institution. Interest in histologic variants has increased considering the various clinicopathological features of bladder cancer.

Some reports have noted that histologic variants affect oncologic outcome,[6,7] whereas others have stated that the inclusion of variants in pathological analysis did not impact survival, and discrepancy regarding this still exists to date.[8-10] Therefore, we aimed to determine the prognostic significance of histologic variants associated with recurrence and progression after radical cystectomy in a single-center cohort of patients with bladder cancer.

MATERIALS AND METHODS

1. Study Design and Patients

In total, 424 patients underwent radical cystectomy between January 2007 and August 2014 at Asan Medical Center. Since 2007, histologic variants have been described according to the WHO classification. Our study included patients with UC bladder cancer who underwent radical cystectomy. We excluded 16 patients with adenocarcinoma, 1 with trauma, and 14 with other malignancy, leaving 393 who were enrolled in this study (290 with pure UC without histologic variants and 103 with histologic variants). All patients underwent lymphadenectomy and urinary diversion. Four groups were compared (a pure UC group and groups with squamous, micropapillary, and other variants) according to the 2004 WHO histologic classification system in the order in which they appear frequently. Recurrence-free survival (RFS) and overall survival (OS) were analyzed according to pathologic T stage using the Kaplan-Meier analysis. The entire cohort was divided into patients with pathologic stage ≤T2 or lower and ≥T3 or higher. All pathologic reports of radical cystectomy were read by pathologists at our institute. In the surgical characteristics, surgical margins included positive urinary tract resection margins with positive soft tissue margins.

2. Statistical Analysis

Categorical variables are presented as frequencies and percentages and continuous variables as mean with standard deviation. The chi-square and analysis of variance tests were used to evaluate the categorical and continuous variables, respectively. All available variables were evaluated using univariate and multivariate Cox proportional hazards regression analysis to assess the association between histologic type and survival outcomes. The significance level was set at $p < 0.05$. Survival rates were compared using Kaplan-Meier analysis with the log rank test. All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Among 393 patients, 103 (26.2%) had bladder cancer with histologic variants: 38 (9.7%) had squamous, 26 (6.6%) had micropapillary, 13 (3.3%) had sarcomatoid, 5 (1.3%) had nested, 4 (1.0%) had plasmacytoid, 3 (0.8%) had glandular differentiation, 2 (0.3%) had giant cell variant, 1 (0.3%) had microcystic, 1 (0.2%) had lymphoepithelioma-like, and 1 (0.2%) had lymphoma-like and plasmacytoid variants. In addition, there were 9 patients (2.3%) in whom more than 2 variants were mixed. Table 1 presents the frequency of histologic variants of UC in radical cystectomy specimens based on the 2004 WHO classification system.

Table 2 presents the clinical and pathological characteristics of all patients (n=393). Patients were divided into 4 groups according to histologic types: pure UC and squamous, micropapillary and other variants. Squamous variant group had the highest mean age (67 years) among the 4 groups. Clinical staging at transurethral resection of the bladder tumor (TURBT) showed the squamous variant group (94.1%) to have a higher

Table 1. Frequency of histologic variants of urothelial carcinoma treated with radical cystectomy (2004 World Health Organization classification system)

Variable	Number of patients (%)
Pure urothelial carcinoma	290 (73.8)
Urothelial carcinoma variant	103 (26.2)
Squamous cell differentiation	38 (9.7)
Micropapillary variant	26 (6.6)
Sarcomatoid differentiation	13 (3.3)
Nested variant	5 (1.3)
Plasmacytoid differentiation	4 (1.0)
Glandular differentiation	3 (0.8)
Giant cell variant	2 (0.3)
Microcystic variant	1 (0.3)
Lymphoepithelioma-like variant	1 (0.3)
Lymphoma-like and plamacytoid variants	1 (0.3)
Multiple mixed variant differentiation	9 (2.3)

Table 2. Clinicopathological characteristics of all patients

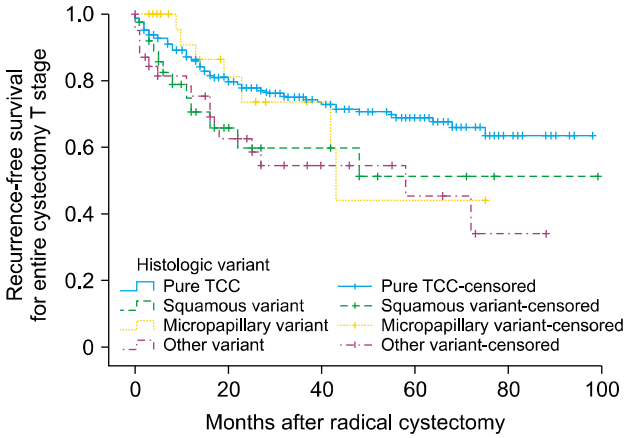
Characteristic	Pure UC	Squamous variant	Micropapillary variant	Other variants	p-value
No. of patients (%)	290 (73.8)	38 (9.7)	26 (6.6)	39 (9.9)	
Age (yr)	63.3±9.7	67.0±8.9	62.0±12.2	59.3±12.3	0.009
Sex					0.531
Male	249 (85.8)	33 (86.8)	24 (92.4)	31 (79.5)	
Female	41 (14.2)	5 (13.2)	2 (7.6)	8 (20.5)	
Body mass index (kg/m^2)	24.2±3.0	23.6±2.5	23.3±2.8	24.0±3.5	0.343
TURBT stage					0.003
Nonmuscle invasive	101 (34.9)	2 (5.3)	9 (34.7)	13 (33.3)	
Muscle invasive	189 (65.1)	36 (94.7)	17 (65.3)	26 (66.7)	
Pathologic T stage					<0.001
≤T1	107 (36.8)	1 (2.6)	2 (7.6)	3 (7.6)	
T2	56 (19.3)	9 (23.7)	5 (19.3)	11 (28.3)	
≥T3	127 (43.7)	28 (73.7)	19 (73.1)	25 (64.1)	
Pathologic nodal status					<0.001
Node negative	224 (77.2)	24 (63.2)	10 (38.5)	25 (64.1)	
Node positive	66 (22.8)	14 (36.8)	16 (61.5)	14 (35.9)	
Surgical margin status					0.240
Margin negative	261 (90.0)	36 (94.7)	21 (80.8)	33 (84.6)	
Margin positive	29 (10.0)	2 (5.3)	5 (19.2)	6 (15.4)	
Pathologic grade					0.203
Low grade	16 (5.5)	1 (2.6)	0 (0)	1 (2.6)	
High grade	254 (87.6)	37 (97.4)	26 (100)	37 (94.8)	
Unknown	20 (6.9)	0 (0)	0 (0)	1 (2.6)	
CIS					0.131
Absent	179 (61.7)	26 (68.4)	12 (46.2)	19 (48.7)	
Present	111 (38.3)	12 (31.6)	14 (53.8)	20 (51.3)	
LVI					<0.001
Absent	172 (59.3)	16 (42.1)	3 (11.5)	16 (41.0)	
Present	118 (40.7)	22 (57.9)	23 (88.5)	23 (59.0)	
Neoadjuvant chemotherapy	27 (9.3)	8 (21.1)	1 (3.8)	8 (20.5)	0.023
Adjuvant chemotherapy	80 (27.6)	14 (36.8)	13 (50.0)	15 (38.5)	0.055

Values are presented as number (%) or mean±standard deviation.
UC: urothelial carcinoma, TURBT: transurethral resection of bladder tumor, CIS: carcinoma *in situ*, LVI: lymphovascular invasion.

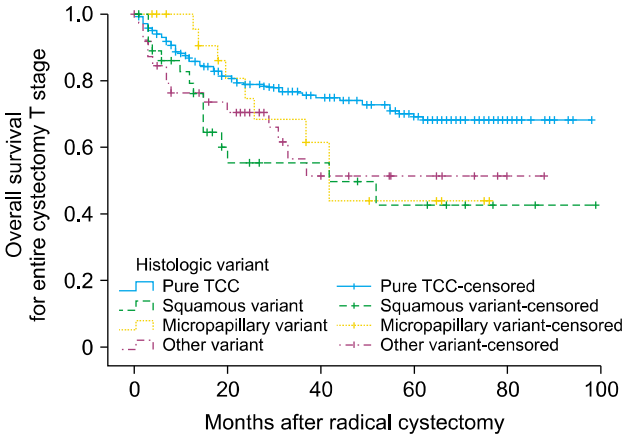
percentage of muscle invasion (pure UC, 65.1%; micropapillary variant, 65.3%; other variants, 66.7%; p=0.003). Pathologic T stage also showed a significant difference. Compared with the pure UC group, variant groups demonstrated more extravesical stage disease (pure UC, 43.7%; squamous variant, 73.7%; micropapillary variant, 73.1%; other variants, 64.1%; p<0.001), a higher number of pathologically positive nodes (22.8%, 36.8%, 61.5%, and 35.9%, respectively; p<0.001), and more frequent lymphovascular invasion (LVI) (40.7%, 57.9%, 88.5%, and 59%, respectively; p<0.001).

Among the study patients, 109 (27.7%) died during a median follow-up of 28 months (interquartile range [IQR], 12–56 months) and 108 (27.5%) had recurrence postoperatively (median follow-up until local recurrence or distant metastasis, 28 months; IQR, 12–56 months). The 5-year RFS rates were 71.2% and 51.3%, 44.2%, and 34.0% for the pure UC and squamous, micropapillary, and other variant groups, respectively. The 5-year OS rates were 87.8% and 42.8%, 44.0%, and 51.4%, respectively. The RFS and OS rates for the pure UC group were statistically superior to those of the squamous (p=0.049 and p=0.005, respectively) and other (p=0.005 and p=0.031, respectively) variant groups (Fig. 1A, B).

Figs. 2 and 3 show the Kaplan-Meier survival analysis of RFS and OS, dividing the entire cohort into patients with pathologic stage ≤T2 and ≥T3 cancer. Patients with pure UC had a better RFS rate than those in the other variants group (p=0.009), but there was no significant difference in OS between each group (Fig. 2). Patients with pathologic stage T3

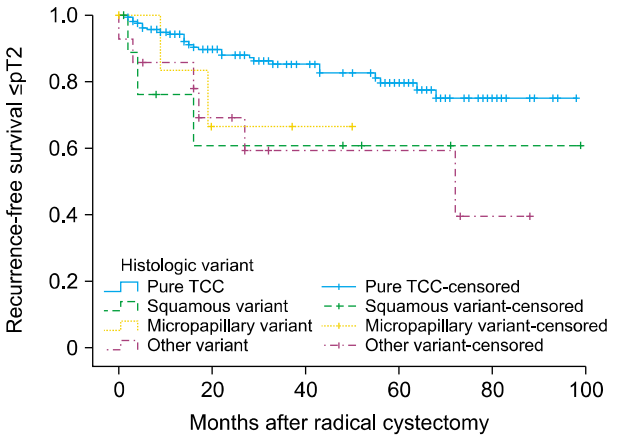


Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.049	0.596	0.005
SQV	0.049		0.382	0.725
MPV	0.596	0.382		0.270
Other	0.005	0.725	0.270	

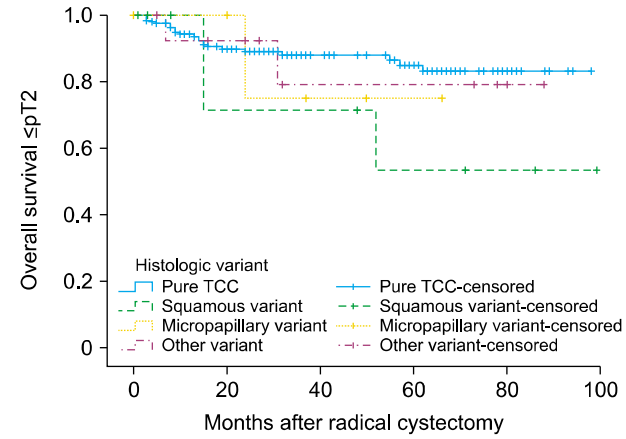


Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.005	0.209	0.031
SQV	0.005		0.329	0.655
MPV	0.209	0.329		0.646
Other	0.031	0.655	0.646	

Fig. 1. Recurrence-free survival and overall survival comparisons of histologic variants (entire cohort). TCC: transitional cell carcinoma, SQV: squamous variant, MPV: micropapillary variant.



Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.101	0.159	0.009
SQV	0.101		0.677	0.931
MPV	0.159	0.677		0.821
Other	0.009	0.931	0.821	



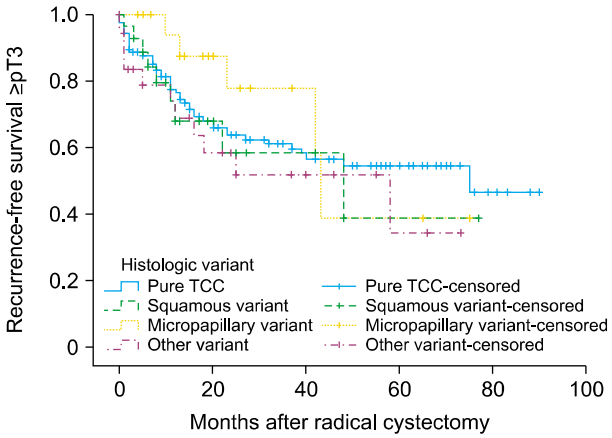
Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.075	0.790	0.793
SQV	0.075		0.541	0.394
MPV	0.790	0.541		0.924
Other	0.793	0.394	0.924	

Fig. 2. Recurrence-free survival and overall survival comparison of histologic variants (≤pT2). TCC: transitional cell carcinoma, SQV: squamous variant, MPV: micropapillary variant.

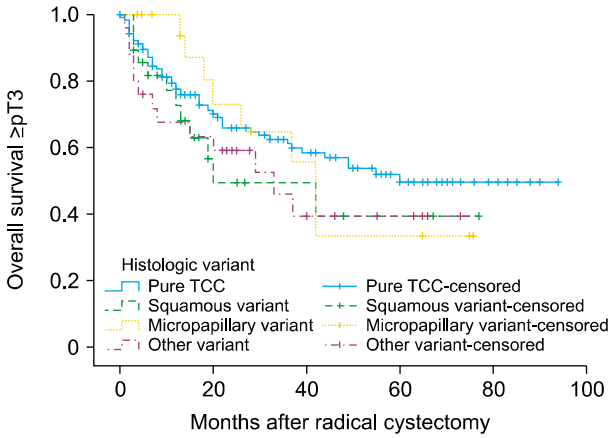
disease demonstrated no significant difference in RFS and OS rates (Fig. 3).

Figs. 4 and 5 show the Kaplan-Meier survival analysis of RFS and OS dividing into node positive and node negative pathology. There was no significant difference in survival between the pure UC group and the variant groups, but only the other variants group showed significantly lower survival result in node negative patients analysis on RFS (p=0.008).

Univariate analysis demonstrated pathologic T stage, nodal status, surgical margin status, body mass index (BMI), LVI, and

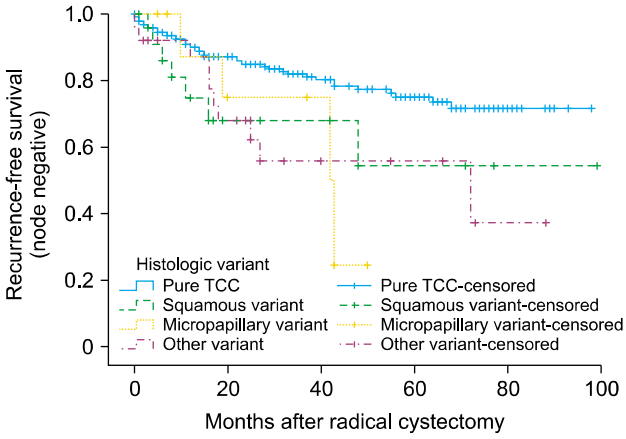


Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.723	0.397	0.354
SQV	0.723		0.305	0.752
MPV	0.397	0.305		0.219
Other	0.354	0.752	0.219	

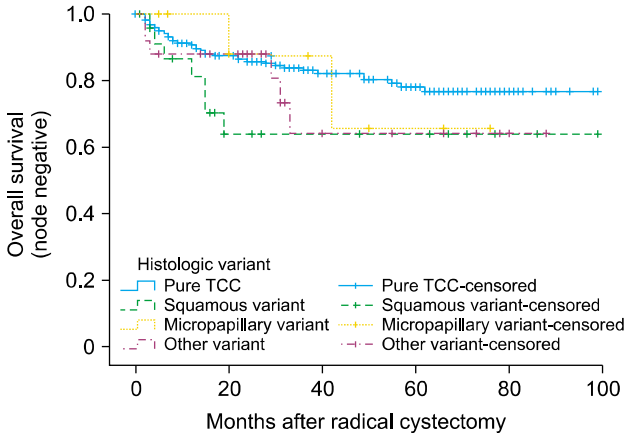


Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.253	0.864	0.199
SQV	0.253		0.356	0.900
MPV	0.864	0.356		0.423
Other	0.199	0.900	0.423	

Fig. 3. Recurrence-free survival and overall survival comparison of histologic variants (≥pT3). TCC: transitional cell carcinoma, SQV: squamous variant, MPV: micropapillary variant.



Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.054	0.054	0.008
SQV	0.054		0.806	0.857
MPV	0.054	0.806		0.931
Other	0.008	0.857	0.931	

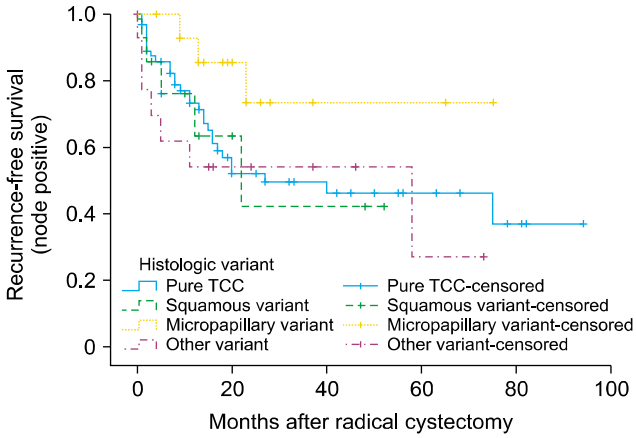


Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.068	0.788	0.312
SQV	0.068		0.391	0.527
MPV	0.788	0.391		0.662
Other	0.312	0.527	0.662	

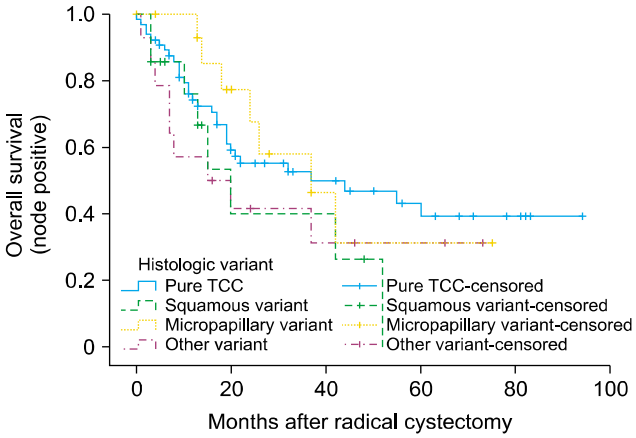
Fig. 4. Recurrence-free survival and overall survival comparison of histologic variant (node negative). TCC: transitional cell carcinoma, SQV: squamous variant, MPV: micropapillary variant.

histologic variant (squamous variant and other variant) to be factors affecting RFS (Table 3). However, on multivariate analysis, significant predictors of RFS were pathologic T stage (stage T2: hazard ratio [HR], 2.75; 95% confidence interval [CI], 1.34–5.63; p=0.005; stage≥T3: HR, 3.20; 95% CI, 1.62–6.30; p=0.001) and nodal status (HR, 1.64; 95% CI, 1.05–2.56; p=0.028). Histologic types (squamous and other variants) were a significant factor for RFS on univariate analysis, but not on multivariate analysis adjusted by T and N stage.

Table 4 presents risk factors affecting OS of the entire



Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.843	0.077	0.480
SQV	0.843		0.095	0.762
MPV	0.077	0.095		0.066
Other	0.480	0.762	0.066	



Pairwise comparison (p-value)				
	Pure	SQV	MPV	Other
Pure		0.159	0.720	0.224
SQV	0.159		0.182	0.918
MPV	0.720	0.182		0.245
Other	0.224	0.916	0.245	

Fig. 5. Recurrence-free survival and overall survival comparison of histologic variant (node positive). TCC: transitional cell carcinoma, SQV: squamous variant, MPV: micropapillary variant.

cohort. Pathologic T stage (stage≥T3: HR, 3.68; 95% CI, 1.89–7.15; p<0.001), nodal status (HR, 2.01; 95% CI, 1.30–3.10; p=0.002) and BMI (HR, 0.92; 95% CI, 0.87–0.98; p=0.021) were significant predictors of OS. Although the squamous variant group showed statistical difference on univariate analysis (HR, 2.20; 95% CI, 1.25–3.84; p=0.006), no difference was noted on multivariate analysis (HR, 1.59; 95% CI, 0.89–2.83; p=0.114) for predicting OS.

DISCUSSION

We aimed to identify the oncological outcome of UC, including histologic variants, in comparison with pure UC. Almost 25%–30% of patients with UC of the bladder show muscle invasion in the cystectomy specimen, for which radical cystectomy is the standard treatment.[11,12] Muscle invasive bladder cancer carries a high risk of death because of disease progression, recurrence, and metastasis.[13] Previous studies have reported approximately 10%–40% of bladder cancers show histologic variants on pathology results.[14] Shah et al.[7] reported that among 101 patients, the squamous variant was the most frequent, followed by glandular and micropapillary variants. In patients who underwent radical cystectomy, the squamous variant accounted for approximately 10%–22% of cancers.[6,10] In our study, the squamous variant also was the most common (9.7%). The micropapillary variant has been reported in approximately 0.7%–6.0% of cases[15,16] and occurred in 6.6% of our patients. Similar to other reports, nested, plasmacytoid differentiation, giant cell, microcystic, lymphoepithelioma-like, lymphoma-like, and plasmacytoid variants were rare in our study.

In several studies, histologic variants were reported to be the contributing factors of poor oncological outcome. One report indicated tumor size and squamous differentiation to be predictors of prognosis and cancer-specific survival.[6] The micropapillary variant has been suggested to be a major factor associated with cancer-related mortality.[10,16] The plasmacytoid variant also has been reported to be associated with mortality with the micropapillary variant.[10] Also, histologic variants in lymph node positive urothelial bladder cancer have been reported to be a significant factor of worse outcome.[17]

In contrast, several studies have indicated that histologic variants were not factors influencing oncological outcome. In a prognostic analysis of squamous and glandular variants, there was no oncologic outcome difference between both variant groups.[18] Indeed, one large study reported that the squamous variant itself did not affect the prognosis.[3] Unlike other reports stating that the micropapillary variant acts as a poor prognostic factor, some studies report no difference compared with pure UC regarding surgical outcome when controlling for pathological factors.[9] Moreover, in a recent study of 303 patients

Table 3. Univariate and multivariate Cox regression analysis for predicting RFS

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (yr)	1.00 (0.98-1.02)	0.785		
Sex				
Male	Reference			
Female	1.49 (0.91-2.43)	0.105		
Body mass index (kg/m^2)	0.93 (0.87-0.99)	0.026	0.95 (0.90-1.01)	0.173
Pathologic T stage				
Nonmuscle invasive (pT0/Ta/T1/CIS)	Reference			
Muscle invasive (T2)	3.41 (1.71-6.80)	<0.001	2.75 (1.34-5.63)	0.005
Extravesical (T3/T4)	4.79 (2.59-8.86)	<0.001	3.20 (1.62-6.30)	0.001
Histologic grade				
Low	Reference			
High	2.09 (0.66-6.61)	0.206		
pT0 or not remarked	0.50 (0.08-3.02)	0.455		
Surgical margin status				
Negative	Reference			
Positive	1.92 (1.15-3.19)	0.011	1.37 (0.80-2.34)	0.244
CIS				
Absent	Reference			
Present	1.16 (0.79-1.71)	0.439		
LVI				
Absent	Reference			
Present	2.32 (1.57-3.43)	<0.001	1.24 (0.78-1.98)	0.353
Pathologic nodal status				
Node negative	Reference			
Node positive	2.43 (1.65-3.57)	<0.001	1.64 (1.05-2.56)	0.028
Histologic type				
Pure UC	Reference			
Squamous variant	1.84 (1.00-3.41)	0.05	1.26 (0.67-2.36)	0.467
Micropapillary variant	1.23 (0.56-2.67)	0.60	0.64 (0.28-1.42)	0.277
Other variants	2.10 (1.13-3.87)	0.01	1.53 (0.82-2.85)	0.175

RFS: recurrence-free survival, HR: hazard ratio, CI: confidence interval, CIS: carcinoma *in situ*, LVI: lymphovascular invasion; UC: urothelial carcinoma.

who underwent trimodal bladder-sparing therapy for muscle invasive bladder cancer, histologic variants of UC did not affect oncologic outcome.[8] Our study also concluded that the effect of histologic variant on oncologic outcome in patients who underwent radical cystectomy was not different from that in patients with pure UC. The OS rate of patients with histologic variants in the cohort seemed to be lower than that of patients with pure UC because histologic variants were more commonly of advanced pathologic stage. Each histologic variant group showed no worse outcome than pure UC according to nodal status except for other variants group of nodal negative patients in RFS. In previous study, variant groups were considered to be factors affecting the survival rate on node positive patients.[17] However, we found that there was no significant difference when the histologic variant types were identified in node positive group analysis.

Consequently, there was no significant difference in the survival rate of patients with variants when controlling for pathologic stage and nodal status, also these findings have been supported by several studies.[6,9,18]

Regarding treatment strategy, Krasnow et al.[8] reported that patients with histologic variants found at TURBT should be advised of the adverse clinical course and cystectomy should be strongly recommended. In this study, we did not investigate the response to chemotherapy, but many studies reported a poor response with neoadjuvant chemotherapy.[19,20] The amount of his-

Table 4. Univariate and multivariate Cox regression analysis for predicting OS

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (yr)	1.01 (0.99-1.03)	0.171		
Sex				
Male	Reference			
Female	1.22 (0.73-2.05)	0.442		
Body mass index (kg/m^2)	0.90 (0.84-0.95)	0.001	0.92 (0.87-0.98)	0.021
Pathologic T stage				
Nonmuscle invasive (pT0/Ta/T1/CIS)	Reference			
Muscle invasive (T2)	2.06 (0.94-4.49)	0.068	1.60 (0.72-3.55)	0.242
Extravesical (T3/T4)	5.53 (2.95-10.39)	<0.001	3.68 (1.89-7.15)	<0.001
Histologic grade				
Low	Reference			
High	1.17 (0.47-2.08)	0.728		
pT0 or not remarked	0.48 (0.11-2.02)	0.319		
Surgical margin status				
Negative	Reference			
Positive	1.98 (1.22-3.22)	0.006	1.35 (0.81-2.25)	0.238
CIS				
Absent	Reference			
Present	1.05 (0.71-1.56)	0.775		
LVI				
Absent	Reference			
Present	2.83 (1.90-4.23)	<0.001	1.34 (0.83-2.17)	0.228
Pathologic nodal status				
Node negative	Reference			
Node positive	2.60 (1.54-4.38)	<0.001	2.01 (1.30-3.10)	0.002
Histologic type				
Pure UC	Reference			
Squamous variant	2.20 (1.25-3.84)	0.006	1.59 (0.89-2.83)	0.114
Micropapillary variant	1.54 (0.77-3.09)	0.218	0.72 (0.35-1.47)	0.370
Other variants	1.82 (0.96-3.45)	0.063	1.15 (0.58-2.25)	0.684

OS: overall survival, HR: hazard ratio, CI: confidence interval, UC: urothelial carcinoma, CIS: carcinoma *in situ*, LVI: lymphovascular invasion.

tologic variants or the mitotic rate has been reported to change significantly after neoadjuvant chemotherapy, and pathologic T stage has been downstaged after neoadjuvant chemotherapy, especially in the case of the squamous variant. The advantage of this study was that we analyzed the recurrence and survival rates according to the pathophysiological characteristics of the histologic variants. According to the stage, histologic variants were identified more often at an advanced stage than pure UC. The reason for this may be because some variant cells exhibit more rapid growth characteristics or the diagnosis is delayed because of atypical symptoms.[21,22]

In our study BMI was a factor affecting OS (HR, 0.92; 95% CI, 0.87-0.98; p=0.021). One article noted that obesity is associated with an increased risk of bladder cancer.[23,24] However, there was no report that obesity is related to the survival rate of bladder cancer. The effect of BMI on OS in our study may need to be confirmed in larger cohort studies.

Our study has several limitations. First, we might have an interobserver reliability problem in terms of variant quantity for interpretation of the same specimen during the study period. Second, survival analysis of pure UC and histologic variants might be affected because of the lack of analysis of the neoadjuvant chemotherapy effect. Third, we did not analyze the histologic variant in TURBT pathology specimens to predict variants in the cystectomy specimens. A few studies have reported the tendency for histologic variants to occur in TURBT

and radical cystectomy specimens. In TURBT pathologic studies, 20%–50% of patients were reported to have a variant component.[7,14] However, according to Abd El-Latif et al.,[14] the sensitivity of initial biopsy or TURBT to detect variants in cystectomy specimens is as low as 39%. Finally, the number of patients in our study was low. Because the 2004 WHO bladder cancer classification has been used to describe the histologic variants from 2007 onwards, we were unable to investigate previous patients, so we were limited only to those studied afterwards.

CONCLUSIONS

In patients who underwent radical cystectomy, histologic variants were detected more often at a locally advanced stage. The outcome for patients with histologic variants appeared to be worse; however, they were more likely to have advanced clinical and pathological stage disease. So we concluded that though histologic variants have been identified in the radical cystectomy specimen, the treatment for the bladder cancer patients should be performed according to the pathologic stage.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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