Impact of variant histology in the prognosis of non-muscle invasive bladder cancer with low-tumor burden: A propensity score-matched analysis with conventional urothelial carcinoma

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Abstract. Bladder cancer (BCa) with variant histology (VH) is associated with an increased risk of recurrence and progression, as well as worse survival. However, the available literature does not provide the prognostic value of VH based on its tumor burden in non-muscle invasive BCa (NMIBC). The purpose of the present study was to investigate the prognosis of VH in NMIBC with low-tumor volume compared with conventional urothelial carcinoma (UC) with a similar tumor burden. The present single-center study analyzed patients diagnosed with NMIBC and retrospectively characterized them based on their VH status. Propensity scores for VH status were calculated to match patients with VH with those with conventional UC (1:3). The VH group was further divided into two subgroups based on pathological aggressiveness: Aggressive and highly aggressive variants. Oncological outcomes were compared among the three groups. Among the 494 patients with NMIBC, 60 (12.1%) had VH. Patients with VH had a higher tumor stage and grade and more multiple tumors (all P<0.05). In the matched cohort, >80% had tumors <3 cm, and >65% had solitary tumors. During a median follow-up of 42.5 months (range, 4.0-122.0 months), 35.1% (85/240) experienced recurrence and 5.4% (13/240) progressed to muscle-invasive disease. Prognosis did not differ between patients with aggressive or highly aggressive variants and those with conventional UC, including 5-year recurrence-free and pathologic progression-free survival (log-rank, P=0.510 and 0.257, respectively). Intravesical Bacillus Galmette-Guerin was the only factor associated with reduced recurrence (P<0.001). In conclusion, NMIBC with low-tumor burden and VH have similar oncologic outcomes to conventional UC with a similar tumor burden, indicating that bladder-sparing methods currently used for high-risk conventional NMIBC may be effective for managing low-tumor burden NMIBC with VH.

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Introduction

Bladder cancer (BCa) is the 10th most common form of cancer worldwide and the 2nd most common urologic malignancy (1). Of these, non-muscle invasive BCa (NMIBC) accounts for 70-75% of patients with bladder urothelial carcinoma (UC) at the time of initial diagnosis (2,3). Histologically, BCa with variant histology (VH) represents 15-25% of all patients who have undergone transurethral resection of bladder tumor (TURBT) or radical cystectomy (RC) (4,5). Prior to the 2016 World Health Organisation (WHO) histological classification (6), there was a notable scarcity of reports and analyses concerning VH. The 2016 classification has heightened the interest in the precise morphological characterization of histological variants, introducing the category of 'invasive UC with divergent differentiation' for tumors exhibiting a combination of 'usual type' UC and other morphologies. Although individual variants are relatively rare, they collectively constitute a significant subset of the disease. Consequently, studies have been conducted on patients undergoing RC to evaluate the clinical significance of VH, particularly in muscle invasive BCa (MIBC). Most studies have reported that VH is associated with an increased risk of recurrence and progression, as well as worse cancer-specific survival (7-9).

Despite the increasing interest in the management of VH in BCa, a limited number of studies have reported on the management and prognosis of VH in NMIBC, and some of the findings are controversial (10-16). Most studies comparing the efficacy of RC with a bladder-sparing approach in NMIBC with VH have mainly focused on micropapillary variants (17-20). Unfortunately, there is a lack of adequate information on other types of VH. Furthermore, studies comparing the oncologic outcomes of VH and conventional UC in NMIBC managed with a bladder-sparing approach have concluded that VH is associated with worse survival outcomes without considering other high-risk features, such as carcinoma *in situ*, extensive stromal invasion and significant tumor burden (11,21,22).

Even with this limited evidence, the American Urological Association (AUA) risk stratification for NMIBC includes any VH as high risk, and the National Comprehensive Cancer Network (NCCN) guidelines recommend aggressive therapy, including RC, for NMIBC with VH (23,24). However, there is a more recent view that VH can be divided into aggressive variants (glandular, squamous, microcystic, giant cell, nested) and highly aggressive variants (micropapillary, plasmacytoid, sarcomatoid), based on their pathologic aggressiveness, to determine whether a bladder-sparing approach or aggressive treatment is appropriate (25). In addition, the prompt consideration of early RC in NMIBC with VH without considering the tumor burden in each patient is controversial and may lead to overtreatment. In this context, a propensity score matching (PSM) analysis was performed to assess the prognostic value of VH in NMIBC compared with conventional UC with a similar tumor burden.

Materials and methods

Patients. The present study is based on a review of the database of Busan Paik Hospital (Busan South Korea), which contains information on 1,068 consecutive patients who underwent TURBT between February 2010 and December 2020. The database consisted of 698 men and 370 women between the ages of 23 and 94. The inclusion criteria for the study were as follows: i) Pathological diagnosis of UC in the bladder; ii) pathological tumor stage a-1 with no clinical evidence of lymph node or distant metastasis; and iii) complete resection, meaning no visible tumor left behind and bladder muscle clearly identifiable by the pathologist and free of disease. The exclusion criteria were as follows: i) Patients with previous or sequential second primary cancers, including NMIBC or upper tract UC; ii) those with incomplete clinical data; and iii) patients with nonurothelial variants, such as pure adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma. Ultimately, a total 494 newly diagnosed patients with NMIBC were included in the final analysis. The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki and received prior approval (approval no. BPIRB 2023-23-030) from the Institutional Review Board of Inje University Busan Paik Hospital (Busan, South Korea). The collected data included age, sex, tumor size and multifocality, pathological tumor staging and grading, the presence of VH, and disease recurrence status.

Patients with VH were matched with patients with conventional UC on a 1:3 ratio. For this purpose, a PSM analysis was performed based on the propensity of patients with VH. A nearest neighbor PSM without replacement generated by logistic regression was used to adjust for confounding factors between the two groups (26,27). Pathologic stage and grade, tumor size, tumor number and postoperative Bacillus Galmette-Guerin (BCG) instillation were selected as covariates. After matching, all standardized mean differences were found to be <0.1 for the covariates and <0.15 for squares and two-way interactions between covariates, indicating an adequate balance between the two groups.

Pathologic evaluation. Tumor size was measured based on the largest dimension determined by macroscopic examination at cystoscopy, which was conducted no more than one month before the TURBT. The diameter described by the operator before TURBT was also taken into account. In the cases of multifocality, the largest tumor diameter was used for analysis. All specimens were histologically confirmed by a genitourinary pathologist with >20 years of experience at the institution. Tumor staging was assessed according to the tumor, node and metastasis classification systems of the 7th and 8th American Joint Committee on Cancer, and grading was performed according to the 2004 and 2016 WHO systems and the International Society of Urological Pathology consensus classification (6,28-30). VH was considered based on previous reports that are widely accepted by the uropathological community and WHO classifications (6,28,31). The extent of VH was semiquantitatively assessed by visually estimating the VH percentage in the initial TURBT specimens. VH components of <25, 25-50%, and >50% of the total tumor architecture were classified as focal, moderate, and extensive, respectively. Carcinoma *in situ* and lymphovascular invasion status were also evaluated. The histologic variants of NMIBC were stratified into two groups based on to their pathologic aggressiveness (25): Aggressive variants (glandular differentiation, squamous differentiation, microcystic variant, giant cell variant and nested variant) and highly aggressive variants (micropapillary variant, plasmacytoid variant and sarcomatoid variant).

Management and follow-up. Patients with high-risk features of AUA risk stratification or VH were recommended to repeat TURBT and receive intravesical BCG instillation (23). However, if the patient was unwilling, these procedures were not performed according to protocol after the first TURBT. BCG TICE (OncoTICE®; MSD; Merck & Co., Inc.) instillation was typically initiated 2-4 weeks after the last TURBT. According to the European Association of Urology (EAU) guidelines, patients would undergo a 6-week course of intravesical BCG induction followed by a standard maintenance regimen (32). Patients were generally followed up every 3 months for the first 2 years after TURBT, every 6 months for the 3rd to 5th year, and annually thereafter. Follow-up examinations included cystoscopy, serum laboratory tests and periodic thoracoabdominal computed tomography scans or magnetic resonance imaging. Recurrence was defined as the detection of new NMIBC at 3 months after complete resection or 1.5 months after the induction course with BCG. Pathologic progression was defined as the recurrence of a tumor with features of MIBC after the first TURBT. Distant metastasis was defined as the detection of a new extravesical lesion in the lymph node or other organs on imaging or pathological examination at 3 months after the last TURBT.

Statistical analysis. Continuous variables were presented as either the mean and standard deviation or the median and interquartile range (IQR), while categorical variables were presented as frequencies and percentages. The distribution of clinicopathological characteristics according to the VH status before and after PSM (Table I), as well as patient characteristics and oncologic outcomes stratified by pathologic aggressiveness of VH (Table II, Fig. 1), were evaluated using Pearson's chi-squared test, Fisher's exact test, and linear-by-linear

Table I. Clinicopathological characteristics according to the variant histology status before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
Clinicopathological characteristics	Conventional UC n=434	Variant UC n=60	P-value	Conventional UC n=180	Variant UC n=60	P-value
Median age at surgery, years (IQR)	68.0 (40-93)	71 (49-86)	0.032	70 (43-92)	71 (49-86)	0.288
Sex, n (%)						
Male	345 (79.5)	50 (83.3)	0.486	144 (80.0)	50 (83.3)	0.570
Female	89 (20.5)	10 (16.7)		36 (20.0)	10 (16.7)	
T stage						
Ta	168 (38.7)	3 (5.0)	<0.001	10 (5.6)	3 (5.0)	1.000
T1	266 (61.3)	57 (95.0)		170 (94.4)	57 (95.0)	
WHO grade 2004/2016						
Low grade	179 (41.2)	4 (6.7)	<0.001	11 (6.1)	4 (6.7)	1.000
High grade	255 (58.8)	56 (93.3)		169 (93.9)	56 (93.3)	
Concomitant CIS						
No	366 (84.3)	45 (75.0)	0.070	145 (80.6)	45 (75.0)	0.359
Yes	68 (15.7)	15 (25.)		35 (19.4)	15 (25.)	
Median tumor size, cm (IQR)	1.5 (0.5-4.0)	1.45 (0.5-4.8)	0.223	1.75 (0.5-4.8)	1.45 (0.5-4.8)	0.695
Tumor size						
<3 cm	387 (89.2)	48 (80.0)	0.091	147 (81.7)	48 (80.0)	0.775
≥3 cm	47 (10.8)	12 (20.0)		33 (18.3)	12 (20.0)	
Median tumor number, n (IQR)	1 (1-2)	1.0 (1-3)	0.489	1.0 (1-3)	1.0 (1-3)	0.604
No. of tumors						
Single	341 (78.6)	39 (65.0)	0.019	132 (73.3)	39 (65.0)	0.217
Multiple	93 (21.4)	21 (35.0)		48 (26.7)	21 (35.0)	
Repeat TURBT						
No	350 (80.6)	38 (63.3)	0.002	123 (68.3)	38 (63.3)	0.475
Yes	84 (19.4)	22 (36.7)		57 (31.7)	22 (36.7)	
Postoperative BCG instillation						
No	296 (68.2)	33 (55.0)	0.128	102 (56.7)	33 (55.0)	0.822
Yes	138 (31.8)	27 (45.0)		78 (43.3)	27 (45.0)	
Postoperative BCG duration						
No	296 (68.2)	33 (55.0)	0.105	102 (56.7)	33 (55.0)	0.751
<1 year	64 (14.7)	11 (18.3)		38 (21.1)	11 (18.3)	
≥1 year	74 (17.1)	10 (16.7)		40 (22.2)	10 (16.7)	
AUA risk						
Low risk	106 (24.4)	2 (3.3)	<0.001	5 (2.8)	2 (3.3)	0.922
Intermediate risk	89 (20.5)	2 (3.3)		7 (3.9)	2 (3.3)	
High risk	239 (55.1)	56 (93.3)		168 (93.3)	56 (93.3)	
[a]Markedly high-risk features	0 (0)	60 (100)		0 (0)	60 (100)	

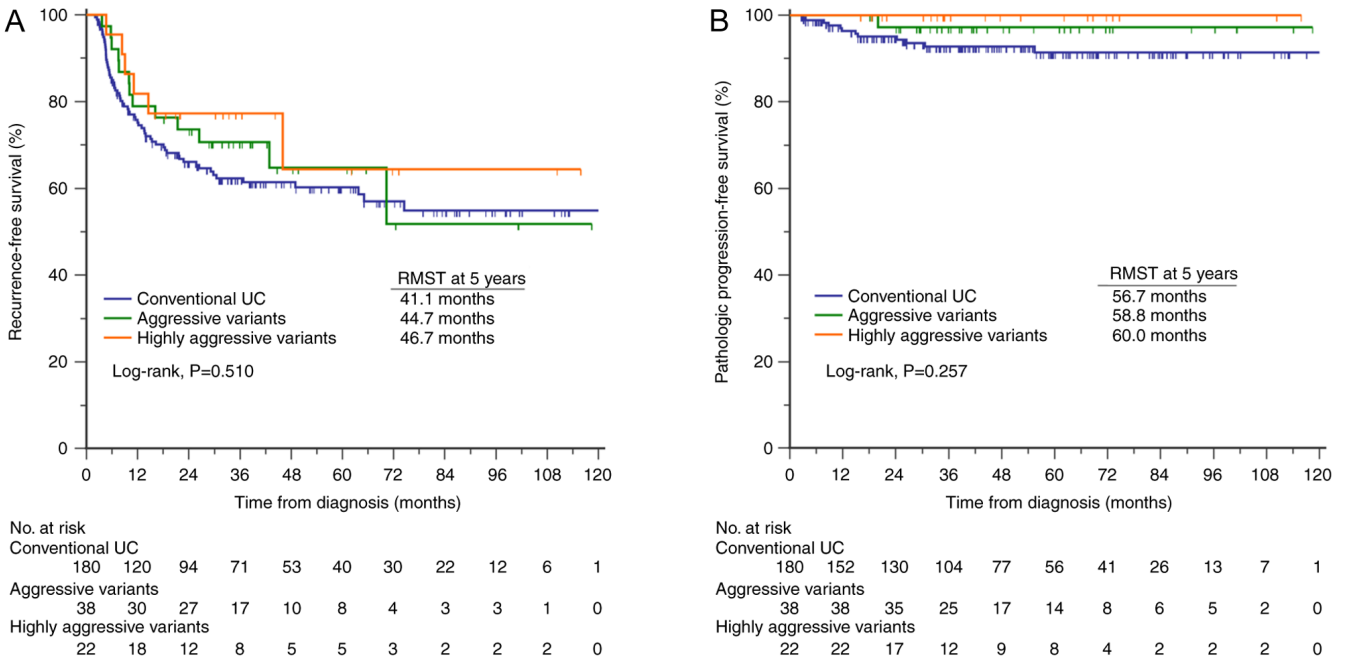
[a]Markedly high-risk features (any): BCG unresponsive, variant histologies, lymphovascular invasion and prostatic urethral invasion. IQR, interquartile range; No., number; CIS, carcinoma *in situ*; TURBT, transurethral resection of bladder tumor; BCG, Bacillus Galmette-Guerin; AUA, American Urological Association.

association for categorical variables, and Student's t-test and one-way analysis of variance with Tukey's post hoc tests for continuous variables. Recurrence-free survival (RFS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method, and log-rank testing was used to assess statistical differences. The restricted mean survival time (RMST) analysis was used to compare the average survival from baseline to a specific time point between study groups. A univariate logistic regression model was employed to identify any clinicopathologic factors that may have influenced RFS, with risk expressed as odds ratios (ORs) and 95% confidence intervals (CIs) determined using reference groups. Statistical

Table II. Characteristics of patients with variant histology stratified by pathologic aggressiveness of variant histology in bladder cancer.

Patient characteristics	Aggressive variants[a] n=38 (63.3%)	Highly aggressive variants[b] n=22 (36.7%)	P-value
Median age at surgery, years (IQR)	70 (49-81)	76 (54-83)	0.133
Males (%)	31 (81.6)	19 (86.4)	0.732
T stage a/1 (%)	3/35 (8.6)	0/22 (0)	0.292
High grade (%)	34 (89.5)	22 (100)	0.286
Concomitant CIS (%)	12 (31.6)	3 (13.6)	0.122
Median tumor size, cm (IQR)	1.4 (0.5-4.1)	1.65 (0.5-4.8)	0.281
Tumor size, ≥3 cm (%)	6 (15.8)	6 (27.3)	0.327
Median tumor no. (IQR)	1 (1-3)	1 (1-3)	0.965
Multifocal tumor (%)	14 (36.8)	7 (31.8)	0.694
Repeat TURBT (%)	24 (63.2)	14 (63.6)	0.970
Variant extent			0.738
Focal (<25%)	30 (81.1)	20 (87.0)	
Moderate (25-50%)	6 (16.2)	2 (8.7)	
Extensive (>50%)	1 (2.7)	1 (4.3)	
Postoperative BCG instillation (%)	17 (44.7)	10 (45.5)	0.957
Postoperative BCG duration ≥1 year (%)	11 (28.9)	5 (22.7)	0.600
AUA high risk (%)	34 (89.5)	22 (100)	0.140

[a]Indicates the following: Glandular differentiation, 28 (46.7%); squamous differentiation, 4 (6.7%); microcystic variant, 4 (6.7%); giant cell variant, 1 (1.7%); and nested variant, 1 (1.7%). [b]Indicates the following: Micropapillary variant, 17 (28.3%); plasmacytoid variant, 3 (5.0%); and sarcomatoid variant, 2 (3.3%). IQR, interquartile range; CIS, carcinoma *in situ*; TURBT, transurethral resection of bladder tumor; BCG, Bacillus Galmette-Guerin; AUA, American Urological Association.



	Conventional UC	Aggressive variants	Highly aggressive variants	P-value
Disease recurrence (%)	66 (36.7)	13 (34.2)	6 (27.3)	0.394
Pathologic progression* (%)	12 (6.7)	1 (2.6)	0 (0)	0.125
Distant metastasis (%)	2 (1.1)	1 (2.6)	0 (0)	0.982

Figure 1. Kaplan-Meier curves comparing variant tumors with conventional UC. (A) Recurrence-free survival and (B) pathologic progression-free survival. *Recurrence of a tumor with features of MIBC after initial TURBT. UC, urothelial carcinoma; RMST, restricted mean survival time; No., number.

analysis was performed using the SPSS v.27.0 (IBM Corp.) and MedCalc v.22.0 (MedCalc Software Ltd.). PSM was performed using R v.4.1.0 (R Foundation for Statistical Computing) with the 'MatchIt' package (26). For all tests, a two-sided P-value of <0.05 was considered to indicate a statistically significant difference.

Results

During the 10-year period, a total of 494 patients were newly diagnosed with NMIBC, of whom 60 (12.1%) presented with VH. The median age of the patients at the time of surgery was 68 years (IQR, 40-93 years). The study included 395 men (79.9%) and 99 women (20.1%). Patients with VH were found to have an older age at the time of surgery (P=0.032), a higher tumor stage (P<0.001), a higher tumor grade (P<0.001), and a higher prevalence of multiple tumors (P=0.019) compared with patients diagnosed with conventional UC. According to the AUA risk stratification for NMIBC, a higher proportion of patients with VH were classified as high-risk compared with patients with conventional UC [56 (93.3%) vs. 239 (55.1%); P<0.001]. In the analyses with the 1:3 propensity-matched groups, there were no significant differences in baseline clinicopathological characteristics between the VH and conventional UC groups (Table I). After matching, it was found that 195 (81.3%) patients had tumor sizes <3 cm, and 171 (71.3%) patients had solitary tumors. These findings indicated that most of the patients included in the analysis had a lower tumor burden. Overall, 105 patients (43.8%) received postoperative BCG instillation.

Among the 60 patients with VH, the different types of VH identified were as follows: Glandular differentiation (n=28, 46.7%), micropapillary variant (n=17, 28.3%), squamous differentiation (n=4, 6.7%), microcystic variant (n=4, 6.7%), plasmacytoid variant (n=3, 5.0%), sarcomatoid variants (n=2, 3.3%), giant cell variant (n=1, 1.7%) and nested variant (n=1, 1.7%). The extent of VH was focal (<25%) in 50 patients (83.3%), moderate (25-50%) in 8 patients (13.3%), and extensive (>50%) in 2 patients (3.3%). When the VH group was stratified based on its pathological aggressive nature, there were no significant differences in clinicopathological characteristics between the aggressive and highly aggressive variants (Table II).

Among the 240 propensity score-matched patients, 85 (35.1%) experienced disease recurrence and 13 (5.4%) progressed to MIBC during a median follow-up period of 42.5 months (IQR, 4.0-122.0 months). Distant metastasis occurred in 2 out of 180 patients with conventional UC (1.1%) and 1 out of 60 patients with VH (1.7%). All these patients developed pathologic progression and then distant metastasis. The median RFS and PFS were not reached in any of the groups (Fig. 1). There was no significant difference in RFS (log-rank, P=0.510). The RMST for RFS at 5 years was 41.1 months (95% CI, 37.4-44.8) for conventional UC, 44.7 months (95% CI, 37.6-51.9) for aggressive variants, and 46.7 months (95% CI, 37.7-55.7) for highly aggressive variants. The difference in RMST for RFS was 3.6 months (95% CI, -1.4-11.6; P=0.377) between conventional UC and aggressive variants and 5.6 months (95% CI, 4.1-15.2; P=0.260) between conventional UC and highly aggressive variants (Fig. 1A). Similarly, there was no significant difference in PFS (log-rank, P=0.257). The RMST for PFS at 5 years was 56.7 months (95% CI, 54.8-58.5), 58.8 months (95% CI, 56.7-61.0) and 60.0 months (95% CI, 60.0-60.0) for conventional UC, aggressive variants and highly aggressive variants, respectively. The difference in RMST for PFS was 2.1 months (95% CI, -0.6-4.9; P=0.129) between conventional UC and aggressive variants and 3.3 months (95% CI, 1.4-5.1; P<0.001) between conventional UC and highly aggressive variants (Fig. 1B). Univariate analysis revealed that intravesical BCG treatment was the only factor associated with a reduced risk of recurrence (OR, 8.20; 95% CI, 1.94-34.75; P<0.001; Table III). The results allowed a risk-adapted management of NMIBC with VH based on tumor burden (Fig. 2).

Discussion

The aim of the present study was to evaluate the prognostic value of VH in NMIBC compared with conventional UC with a similar tumor burden. Over the last two decades, the importance of VH in BCa has increased. Several studies have examined the prognostic role of VH in MIBC, particularly in patients treated with RC, and most have revealed that VH in NMIBC is associated with worse survival outcomes (7-9). However, the prognostic role of VH in NMIBC has been less studied. Understanding the impact of VH in NMIBC is crucial, especially when deciding between bladder preservation or RC based on the presence and type of VH (33). Current guidelines recommend an aggressive approach when VH is detected on pathology (24,32). Therefore, initial RC is generally favored for NMIBC with VH, as it is considered as a significantly high-risk category for NMIBC according to both the EAU and AUA guidelines (23,32). However, relying solely on the presence of VH as an indication for RC without considering the tumor burden and extent of VH in each patient may lead to overtreatment and is not aligned with the current trend of personalized medicine.

Similar to studies on MIBC series, several studies have identified the presence of VH as a poor prognostic factor for recurrence and disease progression in NMIBC. The reported progression rates can be as high as 40% (10,17,34,35). However, upon close examination of these studies, no balance was observed between the VH with conventional UC (Table IV) (10-16,18-22,36-38). The significant differences of this study compared with previous studies are as follows. First, numerous previous studies did not clearly present tumor size and multifocality (10,11,16,18,19,21,22). In the present study, the prognosis and treatment outcomes of NMIBC with conventional UC were compared based on a tumor size of 3 cm and multifocality, which are representative criteria for tumor burden. Additionally, the extent of VH, which is known to significantly impact VH prognosis, was clearly presented. Furthermore, most previous studies only compared a single variant with conventional UC (14-16,18-21,36,37). By contrast, the present study classified VH according to its aggressiveness and performed a comprehensive analysis that included most VH. In addition to tumor characteristics, treatment management is also an important factor affecting prognosis. Numerous previous studies did not evidently present whether and how often repeat TURBT and intravesical treatment were performed (12-16,36). However, the present study provided

Table III. Univariate logistic regression analysis of factors influencing recurrence after diagnosis of non-muscle invasive bladder cancer.

	Univariate analysis		
Characteristics	OR	95% CI	P-value
Age (years)	1.01	0.98-1.03	0.426
Sex (male vs. female)	0.96	0.49-1.89	0.920
T stage (Ta vs. T1)	1.24	0.37-4.18	0.719
WHO grade 2004/2016 (low vs. high)	1.54	0.47-5.01	0.467
Concomitant CIS (no vs. yes)	0.82	0.42-1.60	0.570
Tumor size	0.85	0.67-1.08	0.209
No. of tumors	1.02	0.78-1.33	0.852
Mutlifocal tumor (no vs. yes)	1.05	0.58-1.88	0.866
Types of variant histology			
Conventional UC	1.00	-	
Aggressive variants	0.89	0.43-1.87	0.774
Highly aggressive variants	0.64	0.24-1.73	0.388
Repeat TURBT (yes vs. no)	0.84	0.48-1.48	0.561
AUA risk (low and intermediate vs. high)	1.30	0.72-2.33	0.371
Intravesical BCG (yes vs. no)	8.20	1.94-34.75	<0.001

CIS, carcinoma *in situ*; No., number; UC, urothelial carcinoma; TURBT, transurethral resection of bladder tumor; AUA, American Urological Association; BCG, Bacillus Galmette-Guerin.

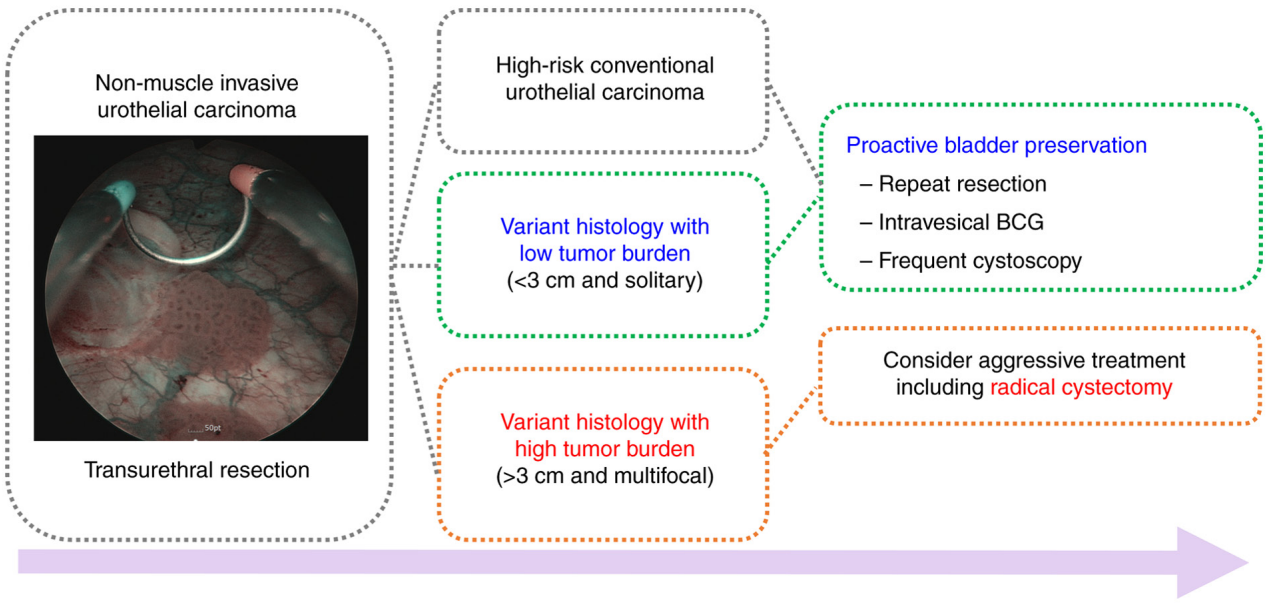


Figure 2. Risk-adapted management of non-muscle invasive bladder cancer with variant histology based on tumor burden. BCG, Bacillus Galmette-Guerin.

clear information on these aspects. Therefore, without considering these various factors, it is not appropriate to simply conclude that the presence of VH indicates a poor prognosis in NMIBC. To the best of our knowledge, the present study is the first to investigate the prognostic role of VH in NMIBC using PSM to ensure baseline characteristics, including tumor burden, are balanced between VH and conventional UC.

The present study found no difference in the disease recurrence rate between conventional UC and VH in NMIBC, and intravesical treatment was the only factor that prevented recurrence. Similarly, there was no difference in pathologic progression or distant metastasis rates between conventional UC and VH. Reviewing the treatment records of all patients with progression revealed that all had multifocal tumors, and half did not receive intravesical BCG or chemotherapy. These findings have important implications for managing NMIBC with VH. In high-risk NMIBC cases managed with intensive bladder preservation, the presence of VH does not significantly

Table IV. Clinical outcomes of VH in NMIBC according to selected studies.

First author, year	Study design	Cases, n	Stage	VH, n (%)	Subtype, %	Treatment, %	Presentation of tumor burden	Clinical significance	(Refs.)
Present study	Single center, retrospective comparison with conventional UC	494	Ta/T1	60 (12.1)	GD 46.7; MV 28.3; SD 6.7; MC 6.8; PV 5.0; SV 3.3; GV 1.7; NV 1.7	All patients: Repeat TUR, 21.4; IVS BCG, 43.8; IVS CTx, N/A; RC, N/A	No.: Solitary, 86.2%; size: <3 cm, 88.0%; extent of VH: <25%, 83.3%; 25-50%, 13.3%; >50%, 3.3%	No difference in RFS or pathologic PFS in VH with low-tumor burden compared with conventional UC	-
Xu *et al*, 2017	Single center, retrospective comparison with conventional UC	869	Ta/T1	232 (26.7)	SD/GD, 100	All patients: Repeat TUR, N/A; IVS BCG, none; IVS CTx, 100; RC, N/A	No.: Solitary, 59.6%; size: <3 cm, 67.4%; extent of VH: N/A	Higher recurrence rate and shorter RFS compared with conventional UC	(13)
Li *et al*, 2018	Single center, retrospective comparison with conventional UC	426	T1	213 (50)	SD, 100	All patients: Repeat TUR, N/A; IVS BCG, none; IVS CTx, 100; RC, N/A	No.: Solitary, 70.4%; size: <3 cm, 67.4%; extent of VH: N/A	Prognostic factor for poor recurrence and progression rate	(14)
Zhao *et al*, 2019	Single center, retrospective comparison with conventional UC	248	T1	82 (33.0)	GD, 100	All patients: Repeat TUR, N/A; IVS BCG, none; IVS CTx, 100; RC, N/A	No.: Solitary 64.5%; size: <3 cm, 71.3%; extent of VH: N/A; LVI^+, 15.3%	Higher recurrence and progression rates and poorer OS compared with conventional pT1 UC	(15)
Li *et al*, 2016	Single center, retrospective SD only	206	T1	206 (100)	SD, 100	All patients: Repeat TUR, N/A; IVS BCG, N/A; IVS CTx, 100; Management after recurrence (n=65): TUR, 42; RC, 58	No.: Solitary, 50.8%; size: <3 cm, 70.4%; extent of VH, N/A; LVI^+: 27.6%	-Shorter CSS rate in LVI^+ cases-Shorter median CSS after TURBT than after RC in recurrent patients	(36)
Gofrit *et al*, 2016	Single center, retrospective comparison with conventional UC	181	Ta/T1	41 (22.6)	MV, 34; SD, 32; GD, 22; NV, 17	VH only: Repeat TUR, 100; IVS BCG, 100; IVS CTx, N/A; RC, none	No.: N/A; size: N/A; extent of VH: N/A	Shorter 5-year RFS, PFS, DSS and OS compared with conventional high-grade UC	(11)
Shapur *et al*, 2011	Single center, retrospective comparison with conventional UC	166	Ta/T1	22 (13.2)	SD, 32; NV, 27; GD, 18; MV, 18; SV, 5	VH only: Repeat TUR, 100; IVS BCG, 100; IVS CTx, 0; RC, 22.7	No.: N/A; size: Non-bulky (<4 cm), 100%; extent of VH: N/A	-Worse 2- and 5-year PFS and shorter median time to progression compared with conventional UC -No differences in RFS and DSS	(10)

Table IV. Continued.

First author, year	Study design	Cases, n	Stage	VH, n (%)	Subtype, %	Treatment, %	Presentation of tumor burden	Clinical significance	(Refs.)
Fujii *et al*, 2017	Single center, retrospective comparison with conventional UC	148	T1	17 (11.5)	GD, 59; SD, 29; SD + GD, 12	All patients: Repeat TUR, N/A; IVS BCG, 33.1; IVS CTx, 46.6; RC, N/A	No.: Solitary, 42.6%; size: <3 cm, 75%; extent of VH: <25%, 58.8%; 25-50%, 29.4%; >50%, 11.7%	Shorter RFS and PFS rates compared with conventional UC	(12)
Mally *et al*, 2017	Single center, retrospective comparison with conventional UC	120	T1	30 (25)	NV, 100	VH only: Repeat TUR, 100; IVS therapy, 53.3; Early RC, 43.3	No.: Solitary, 40%; size: N/A; extent of VH: N/A	No difference in metastasis-free survival and CSS compared with conventional UC	(21)
Lopez-Beltran *et al*, 2022	Single center, retrospective comparison with conventional UC	92	T1	34 (36.9)	NV, 23.5; MV, 20.5; GD, 5.8; SD, 4.7; MC, 2.9; inverted, 23.5; basaloid, 2.9; VL, 2.9; LL, 2.9	All patients: Repeat TUR, N/A; IVS BCG, 92.4; IVS CTx, 7.6; RC, N/A	No.: N/A; size: N/A; extent of VH: N/A	Worse cumulative PFS and DSS in VH compared to conventional UC Conventional UC, MV, NV, GD, Basaloid are high-risk of aggressive disease	(22)
Willis *et al*, 2015	Single center, retrospective MV only	72	T1	72 (100)	MV, 100	VH only: Repeat TUR, 100; IVS BCG, 55; IVS CTx, N/A; early RC, 36	No.: N/A; size: N/A; extent of VH: <25%, 65%; >25%, 26%; unknown, 8%; LVI^+, 17%	Higher 5-year DSS in RC group compared with BCG or RC after recurrence	(20)
Suh *et al*, 2019	Single center, retrospective SD/GD only	62	Ta/T1	62 (100)	SD/GD, 100	All patients: Repeat TUR, 56.4; IVS BCG, 48.3; IVS CTx, N/A; RC, 24.2	No.: Solitary, 45.2%; size: <3 cm, 62.9%; Extent of VH: N/A	Similar 5-year OS and CSS in both BCG and RC groups	(38)
Yorozuya *et al*, 2018	Multicenter, retrospective SD/GD only	47	Ta/T1	47 (100)	GD, 80.9; SD, 19.1	VH only: Repeat TUR, 49; IVS BCG, 42.5; IVS CTx, 12.7; early RC, 12.8	No.: Solitary, 57.4%; size: <3 cm, 83.0%; extent of VH: <50%, 19.1%; ≥50%, 36.2%; unknown, 44.7%	Improved RFS, PFS, and CSS after BCG compared with other treatments or no additional treatment	(37)
Spaliviero *et al*, 2014	Single center, retrospective MV only	36	T1	36 (100)	MV, 100	VH only: Repeat TUR, 100; IVS BCG, 44.4; IVS CTx, N/A; early RC, 41.6	No.: Solitary, 60.7%; size: N/A; extent of VH: <10%, 6.2%; 10-50%, 68.7%; >50% 25%	No difference in outcome between early RC and conservative management	(19)
Sangoi *et al*, 2020	Single center, retrospective MV only	20	Ta	20 (100)	MV, 100	VH only: Repeat TUR, N/A; IVS BCG, 10; IVS CTx, 5; early RC, 5	No.: N/A; size: N/A; extent of VH: <25%, 50%; 25-50%, 25%; >50%, 25%	No difference in PFS rates compared with conventional pTa high grade UC	(16)

Table IV. Continued.

First author, year	Study design	Cases, n	Stage	VH, n (%)	Subtype, %	Treatment, %	Presentation of tumor burden	Clinical significance	(Refs.)
Ghoneim *et al*, 2011	Single center, retrospective MV only	10	Ta/T1	10 (100)	MV, 100	VH only: Repeat TUR, N/A; IVS BCG, 70; IVS CTx, N/A; RC, 30	No.: N/A; size: N/A; extent of VH: N/A	All patients with cTa/T1 who had undergone initial bladder-sparing therapy with BCG had pathologically advanced disease at cystectomy	(18)

determine progression or distant metastasis. In other words, in low-volume NMIBC cases, regardless of the presence of VH, proactive bladder preservation treatment, including intravesical BCG, effectively prevents recurrence and progression, avoiding more aggressive treatments such as RC. These findings are consistent with a recent review showing that VH does not significantly worsen survival compared with conventional UC at the same disease stage (39).

In the present study, 80% of patients with VH had tumors <3 cm, and 65% had solitary tumors. No significant differences were observed in disease recurrence and progression rates between VH and conventional UC. These findings support the efficacy of a bladder preservation approach for low tumor burden NMIBC with VH. Management of VH can be stratified by tumor burden, defined by size and multifocality. For low tumor burden VH (≤3 cm and solitary), a proactive bladder preservation approach, including repeat resection, intravesical therapy, and frequent surveillance, is viable. For high tumor burden VH (>3 cm and multifocal), an aggressive treatment approach, including RC, is recommended to prevent progression. The risk-adapted management protocol of the authors aims to prevent overtreatment of low tumor burden VH in real clinical practice.

In the present study, patients were categorized into two groups: Aggressive VH and highly aggressive VH, based on the clinical and pathologic aggressiveness of VH, as suggested by a previous recommendation (25). According to the current NCCN guidelines, immediate RC is recommended for highly aggressive VH, such as micropapillary, plasmacytoid and sarcomatoid (24). However, the findings of the present study showed no significant difference in survival between the two groups. This suggested that the current recommendation to divide patients into these two groups for deciding between bladder preservation and RC may not be useful in low-volume NMIBC with VH. The discrepancy between the recommendation and the study findings may be attributed to the nature of the landmark studies used as references. For instance, a retrospective study at MD Anderson Cancer Center focused on patients with T1 NMIBC with a micropapillary variant and treated with BCG, and found that the majority did not respond to BCG (89%) and experienced disease progression (67%), including metastatic disease (22%) (17). However, this study cohort did not provide information on tumor burden, such as tumor size and number, despite indicating the extent of the micropapillary variant. On the other hand, a retrospective study from Memorial Sloan Kettering Cancer Center revealed no statistically significant difference in disease-specific survival at 5 years between initial RC and bladder sparing with repeat TURBT and intravesical BCG in T1 NMIBC with micropapillary variant (19). Therefore, considering the findings of these studies and the current study, the treatment recommendations for highly aggressive variants should take into account evidence-based considerations regarding tumor burden.

The present study suggested that bladder preservation may be a viable treatment option for low-burden NMIBC with VH. However, it is important to recognize that VH in BCa is an aggressive disease that requires intensive surveillance. While the study design of the following studies was retrospective and lacked correction for baseline characteristics such as tumor

burden, several studies have reported lower response rates to intravesical BCG in patients with VH, leading to higher recurrence and progression rates than conventional UC (10,11,38). Therefore, close follow-up with frequent cystoscopy and pelvic imaging is crucial in managing NMIBC with VH to reduce morbidity and mortality from missed recurrence and progression.

Although the present study makes several important contributions, it is important to acknowledge some limitations, including its small sample size, single-institution setting and retrospective design. There were also differences in baseline characteristics between the VH and conventional UC groups, as VH is often associated with unfavorable pathological features, including T stage, high-grade tumors and large tumor burdens. In addition, although postoperative intravesical therapy is the only method to reduce the recurrence or progression of NMIBC regardless of VH, the number of patients treated in the present study was relatively limited. To minimize the impact of unbalanced baseline characteristics on tumor burden and the effect of intravesical treatment between the two groups, the PSM method was used. Finally, although the present study showed no difference in oncological outcomes in NMIBC regardless of VH status in cases of low tumor burden, only a limited number of cases with VH were included for analysis. In fact, including the current study there are limited multicenter large cohort studies evaluating the oncologic outcome of VH in NMIBC. Further studies based on multicenter larger cohorts are required.

In conclusion, the prognostic significance of VH in NMIBC with low-tumor burden has been evaluated. Despite the adverse pathologic features often associated with NMIBC with VH at diagnosis, the findings revealed no significant difference in RFS or pathologic PFS compared with conventional UC with a similar tumor burden. This suggests that careful bladder preservation methods, such as intravesical BCG instillation, currently used for high-risk conventional NMIBC, may also be effective for treating low-tumor burden NMIBC with VH.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author in reasonable request.

Authors' contributions

HSL and CHL contributed to the concept and design of the study. Clinical data on patients who underwent TURBT were collected by KSM, WIS, SJS and CHL. SJJ provided the pathological data. SJJ and JIC confirm the authenticity of all raw data. CHL, KSM, WIS, SJS and CHL analyzed and interpreted the clinicopathological data, and JIC assisted with all statistical analyses. The first draft of the manuscript was written by HSL, and all authors commented on earlier versions of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board of Inje University Busan Paik Hospital (BPIRB 2023-23-030). For this type of retrospective and/or observational study formal consent is not required. Pursuant to the provisions of the ethics committee and the ethic guideline in Korea, written consent was not required in exchange for public disclosure of study information in the case of retrospective and/or observational study using a material such as the existing documentation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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