

# 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.

## 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).

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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 Calmette-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 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<sup>®</sup>; 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.

| Clinicopathological characteristics      | Before propensity score matching |                    |         | After propensity score matching |                    |         |
|------------------------------------------|----------------------------------|--------------------|---------|---------------------------------|--------------------|---------|
|                                          | Conventional<br>UC n=434         | Variant<br>UC n=60 | P-value | Conventional<br>UC n=180        | Variant<br>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)          |         |
| <sup>a</sup> Markedly high-risk features | 0 (0)                            | 60 (100)           |         | 0 (0)                           | 60 (100)           |         |

<sup>a</sup>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 <sup>a</sup><br>n=38 (63.3%) | Highly aggressive<br>variants <sup>b</sup> 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   |

<sup>a</sup>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%). <sup>b</sup>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 Calmette-Guerin; AUA, American Urological Association.

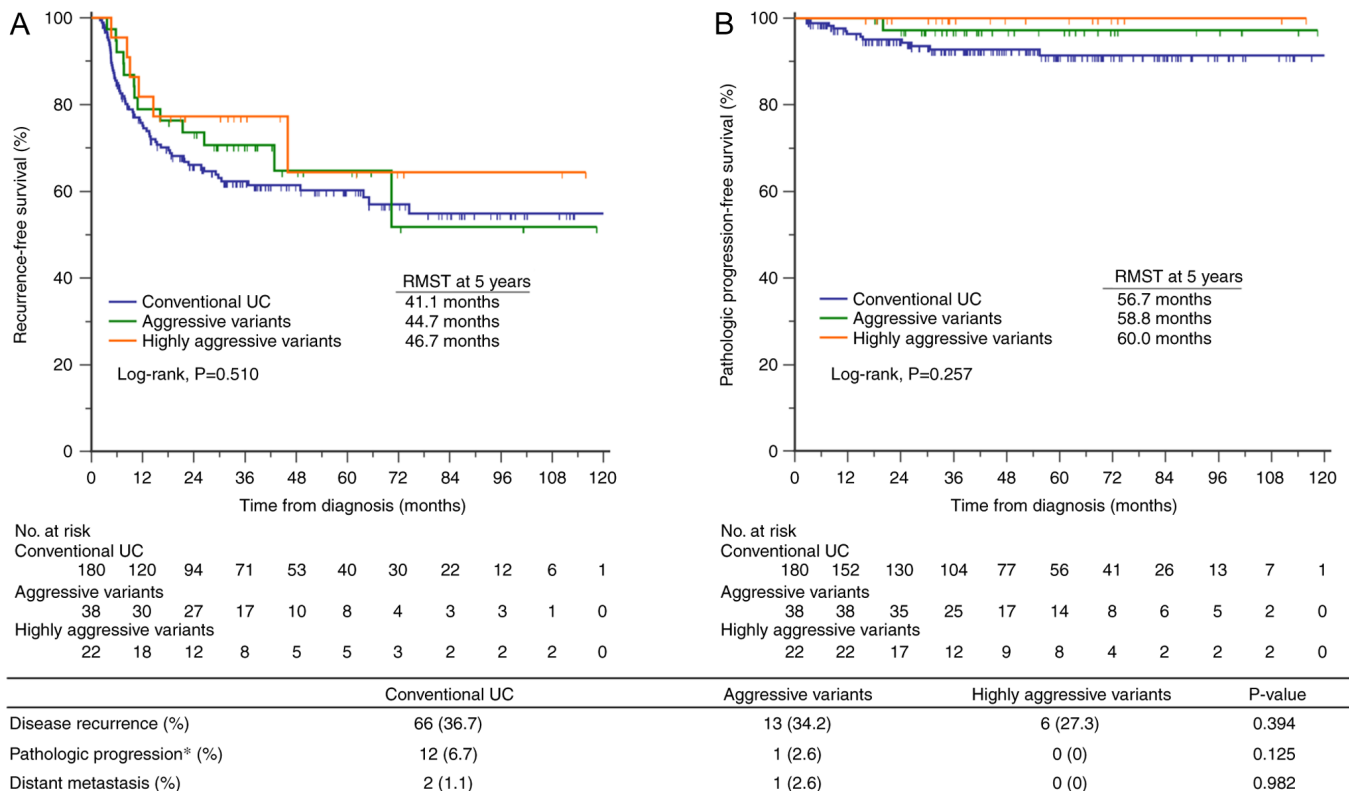


Figure 1. Kaplan-Meier curves comparing variant tumors with conventional UC. (A) Recurrence-free survival and (B) pathologic progression-free survival. \*Recurrence of a tumor with features of MIBC after initial TURBT. UC, urothelial carcinoma; RMST, restricted mean survival time; No., number.

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.

| Characteristics                          | Univariate analysis |            |         |
|------------------------------------------|---------------------|------------|---------|
|                                          | 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   |
| Multifocal 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 Calmette-Guérin.

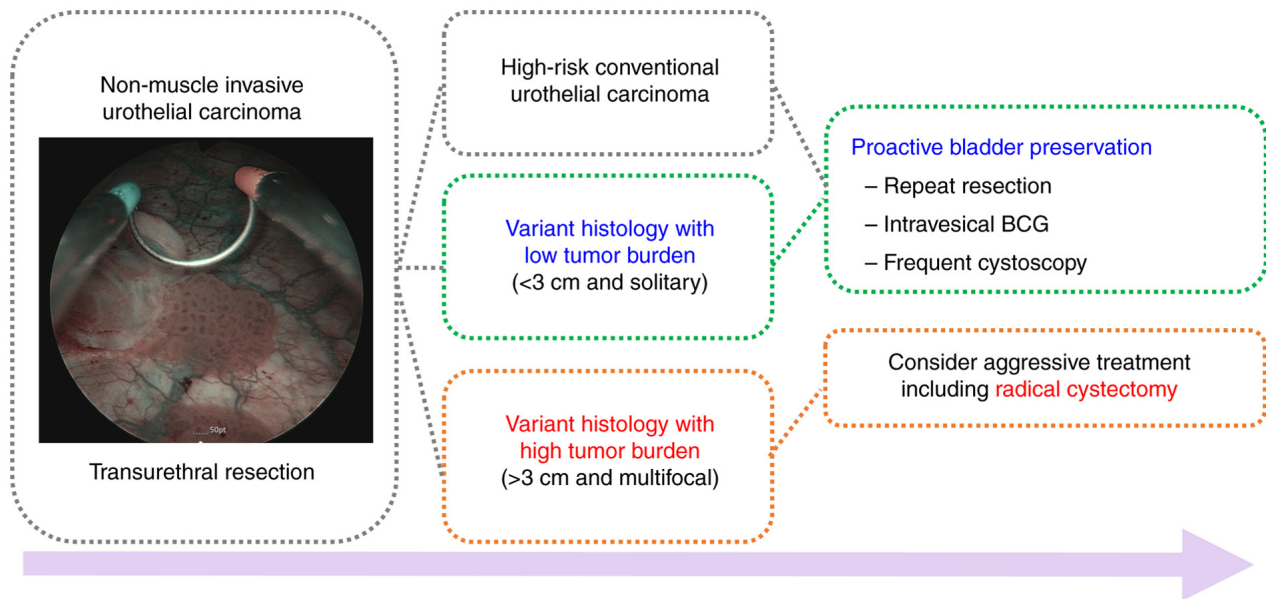


Figure 2. Risk-adapted management of non-muscle invasive bladder cancer with variant histology based on tumor burden. BCG, Bacillus Calmette-Guérin.

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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <sup>+</sup> , 15.3%           | Higher recurrence and progression rates and poorer OS compared with conventional pT1 UC                                      | (15)    |
| Li <i>et al</i> , 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 <sup>+</sup> : 27.6%          | -Shorter CSS rate in LVI <sup>+</sup> cases-Shorter median CSS after TURBT than after RC in recurrent patients               | (36)    |
| Gofrit <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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                                 | (22)    |
| Willis <i>et al</i> , 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 <sup>+</sup> , 17%     | Higher 5-year DSS in RC group compared with BCG or RC after recurrence                         | (20)    |
| Suh <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 2011 | Single center, retrospective<br>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 ( $\leq 3$  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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