RESEARCH ARTICLE

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Tumor Morphology as a Risk Factor for Muscle Invasiveness in Newly Diagnosed Bladder Cancer: A Stratified Analysis

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Abstract

Objective: To investigate the association between tumor morphology and muscle-invasive bladder cancer (MIBC) in patients with newly diagnosed bladder cancer (BC). **Methods:** This retrospective study included 416 patients who underwent transurethral resection of a bladder tumor for newly diagnosed BC between January 2018 and December 2023 at a tertiary hospital in Vietnam. Multivariable logistic regression analysis was applied to assess the adjusted association between the sessile morphology of BC on cystoscopy and the risk of muscle invasion. Age, sex, tumor size, number of tumors, and pathological grade were considered confounders. Stratified analysis by tumor size and number of tumors was performed to clarify the effect modification. **Results:** Patients with MIBC had a significantly higher prevalence of sessile morphology (68.8% vs. 28.4%, p<0.001). After controlling for confounders, patients with sessile tumors were three times more likely to have MIBC than those with papillary tumors (OR = 3.1, 95% CI = [1.8–5.3], p < 0.001). The association of sessile tumor with MIBC was higher in patients with tumor ≤3 cm (about 25%, OR = 3.9, 95% CI = [1.9–7.8]) and having >3 tumors (about 64%, OR = 5.1, 95% CI = [2.1–12.4]). **Conclusions:** Sessile morphology is associated with the risk of MIBC in patients newly diagnosed with BC. This association was more pronounced in patients with tumor ≤3 cm and >3 tumors.

Keywords: muscle invasive- risk factor- tumor morphology- urinary bladder neoplasms

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Introduction

Bladder cancer (BC) is one of the most common urological cancers, with approximately 573,000 new cases and over 200,000 deaths annually [1]. The incidence of BC in Vietnam is lower than that in Western countries, with national estimates ranging from 2.3 to 3.7 per 100,000 men and 0.85 to 1.2 per 100,000 women [2]. At initial diagnosis, approximately 75% of BC cases are non-muscle invasive (stages Ta, T1, or carcinoma in situ), while the remaining 25% have already invaded the detrusor muscle (stage T2 or higher) [3]. This distinction is crucial, as muscle-invasive bladder cancer (MIBC) has a substantially worse prognosis and requires more aggressive treatment approaches, including radical cystectomy, chemotherapy, or multimodal therapy.

Early identification of patients at high risk of muscle-invasive disease is essential for optimal clinical management. Currently, several clinicopathological parameters are used to predict the risk of muscle invasion, including tumor size, multiplicity, grade, and the presence of carcinoma in situ [4]. However, these factors alone have limited predictive accuracy, and significant variability in outcomes remains among patients with similar risk profiles. Tumor morphology, specifically the distinction between papillary and sessile (solid) growth patterns, has emerged as a potentially important but understudied predictor of muscle invasion.

While some studies have suggested an association between sessile morphology and aggressive disease features [5, 6], the independent predictive value of tumor morphology for muscle invasion at the initial diagnosis has not been thoroughly investigated. Furthermore, the potential interaction between morphology and other established risk factors, such as tumor size and multiplicity, remains largely unexplored. Understanding these relationships could significantly enhance our ability to identify patients at the highest risk of muscle-invasive diseases. This study aimed to investigate the association between tumor morphology and muscle invasion in newly diagnosed BC, with a particular focus on sessile morphology as an independent predictor. Additionally, we sought to investigate the potential effect of modification by other clinicopathological variables, including tumor size and multiplicity. By leveraging data from a high-volume tertiary referral center in Vietnam, we hope to contribute regional data to the global literature and inform clinical decision making in resource-limited settings.

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Materials and Methods

Study Design

This retrospective observational study was conducted at the Urology and Andrology Center of a tertiary hospital in Vietnam. The study was performed in accordance with the Helsinki Declaration and was approved by the Institutional Review Board (IRB) of the current institution. Informed consent was obtained from all study participants and their guardians before enrollment.

Patient Selection

The medical records of all patients who underwent transurethral resection of bladder tumors (TURBT) between January 2018 and December 2023 were reviewed. Patients were eligible if they had a first-time diagnosis of primary BC confirmed by histopathology, with detrusor muscle present in the TURBT specimen. Exclusion criteria were as follows: (1) tumors metastatic to the bladder from other sites, (2) low malignant potential lesions (e.g., papillary urothelial neoplasm of low malignant potential), or (3) incomplete medical records.

Surgical Procedure and Pathological Evaluation

TURBT was performed under general or spinal anesthesia using monopolar or bipolar resection techniques. An effort was made to completely resect the tumor and include detrusor muscle in the specimen. The histopathological examination was performed by experienced uropathologists. Tumor grade was categorized as low or high according to the WHO 2016 classification [7]. Tumor morphology was recorded as papillary or sessile, based on cystoscopic appearance.

Variables and Definitions

The primary outcome was the presence or absence of muscle invasion on histopathology. The variables included age, sex, clinical presentation, tumor size, number of tumors, morphology (papillary vs. sessile), and grade (low vs. high). Tumor morphology was recorded intraoperatively by two senior urologists. Sessile morphology was defined as a solid, broad-based lesion lacking a stalk and long braches while papillary morphology was difined as a lesion with exophytic fronds attached to the bladder wall by a stalk according to EAU guidelines [1] and previous study [6]. Any ambiguous morphology was resolved by the two senior urologists with consensus. The tumor size was measured using either preoperative CT or MRI. In cases of multiple tumors, the size of the largest tumor was recorded. Tumor size was classified as ≤3 cm or >3 cm, according to the EORTC risk model [4]. The number of tumors was counted using intraoperative cystoscopy, and the number was classified as ≤3 and >3 according to the CUETO risk model (2008) [8].

Statistical Analysis

Descriptive statistics were used to summarize continuous variables as means with standard deviations, and categorical variables as frequencies with percentages. Differences in characteristics between MIBC and NMIBC were compared using bivariate analyses, such as the T-test for continuous variables and the chi-square test for categorical variables. Multivariate logistic regression was conducted to identify independent predictors of muscle invasion, and the results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Age, sex, tumor size, number of tumors, and pathological grade were considered as confounders. The Variance Inflation Factor (VIF) analysis showed very low multicollinearity (correlation) among the independent variables (Supplementary Table). Statistical significance was set at $P < 0.05$. The effect of the modification of tumor size and number of tumors was explored using stratified analysis. All analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Of 684 patients who underwent TURBT during the study period, 416 were eligible (Figure 1). Mean age was 66.3 ± 12.4 years (range 16–92). The majority were

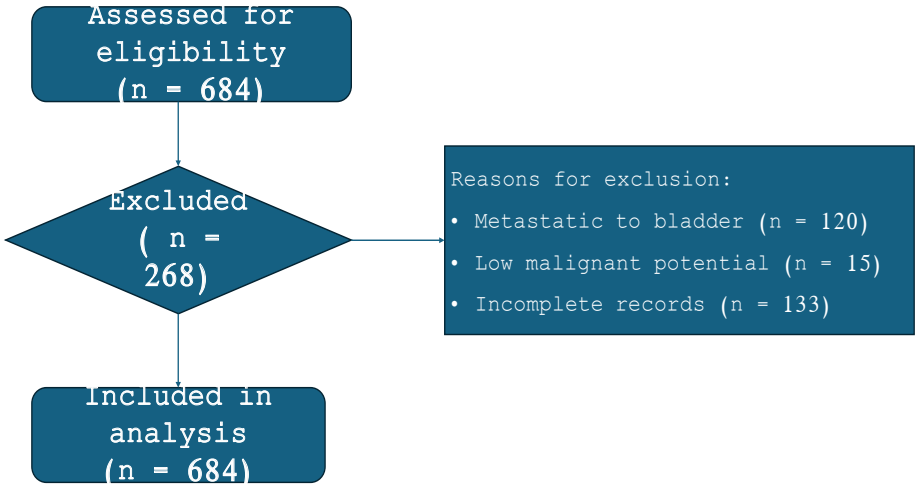

Figure 1. Patient Flow Diagram. A total of 684 patients were assessed for eligibility. Of these, 268 patients were excluded for the following reasons: tumors metastatic to the bladder from other sites (n = 120), low malignant potential lesions (n = 15), or incomplete medical records (n = 133). Finally, 416 patients were included in the analysis.

Table 1. Characteristics of Patients by Muscle Invasion status (n = 416)

		Muscle invasion status		
Variable	n	NMIBC (n = 320)	MIBC (n = 96)	P-value
Size of tumor (mm)*	416	22.4 ± 11.9	35.3 ± 15.3	< 0.001
Age (year)	416	65.5 ± 13.1	68.8 ± 9.6	0.026
Sex				
Male	369	284 (88.8)	85 (88.5)	1.0
Female	47	36 (11.2)	11 (11.5)	
Morphology†				
Papillary	259	229 (71.6)	30 (31.3)	< 0.001
Sessile	157	91 (28.4)	66 (68.8)	
Pathological Grade				
Low	97	90 (28.1)	7 (5.4)	< 0.001
High	319	230 (71.9)	89 (92.6)	
Tumor size‡				
≤ 3 cm	303	258 (80.6)	45 (46.9)	0.01
> 3 cm	113	62 (19.4)	51 (53.1)	
Number of tumors#				
≤ 3	287	231 (72.2)	56 (58.3)	0.01
> 3	129	89 (27.8)	40 (41.7)	

Data are presented as numbers (raw percentage) for categorical variables and mean ± standard deviation for continuous variables. NMIBC, Non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; P-values were obtained by Chi-square test for categorical variables and T-test for continuous variables; *Size of tumor was measured on CT/MRI images by a senior radiologist; †Morphology of tumor was determined according to EORTC risk model (2006) [4]. ‡Size of tumor was classified according to EORTC risk model (2006) [4]. #Number of tumors was classified according to CUETO risk model (2008) [8].

male (88.7%), with a male-to-female ratio of 7.8:1. Gross hematuria was the most common presenting symptom (77.9%), followed by incidental findings during ultrasound (13.7%), and lower urinary tract symptoms (8.4%).

Table 2. Adjusted association of Tumor's Morphology with Muscle Invasion (n = 416)

Variable	OR (95% Confidence Interval)	P-value
Morphology†		
Papillary	1	
Sessile	3.1 (1.8 – 5.3)	<0.001
Tumor size*		
≤ 3 cm	1	
> 3 cm	2.7 (1.6 – 4.6)	<0.001
Pathological grade		
Low-grade	1	
High-grade	4.1 (1.5 – 11.0)	0.005
Age	1.0 (0.9 – 1.0)	0.7
Sex		
Male	1	
Female	1.0 (0.4 – 2.3)	1.0
Number of tumors#		
≤ 3 tumors	1	
> 3 tumors	1.5 (0.9 – 2.6)	0.1

p-values were obtained by logistic regression adjusted for Tumor size, Pathological grade, Age, Sex, and Number of tumors; †Morphology of tumor was determined according to EORTC risk model (2006) [4]; *Size of tumor was measured on CT/MRI images by a senior radiologist. Size of tumor was classified according to EORTC risk model (2006) [4]; #Number of tumors was classified according to CUETO risk model (2008) [8].

The tumor morphology was papillary in 62.3% (259/416) and sessile in 37.7% (157/416) of the cases. In terms of tumor burden, 69% (287/416) of patients had three or less tumors, whereas 31.0% (129/416) had four or more tumors. The mean tumor size was 25.3 ± 13.8 mm (range, 5–74 mm), with 27.2% having tumors >3 cm. Histologically, 99.04% were urothelial carcinomas, 76.7% (319/416) of which were high-grade (Table 1).

Muscle invasion was found in 23.1% (96/416) of the patients. Patients with MIBC had a significantly higher prevalence of sessile morphology (68.8% vs. 28.4%, p<0.001), tumor size >3 cm (53.1% vs. 19.4%, p<0.001), and high-grade histology (94.6% vs. 71.9%, p<0.001) than those with NMIBC. There were no significant differences in age or sex between the two groups (Table 1).

The multivariale logistic regression model identified that sessile tumor morphology was associated with a threefold increased risk of muscle invasion compared to papillary tumors (OR = 3.1, 95% CI = [1.8–5.3], p < 0.001). Tumor size greater than 3 cm also significantly increased the odds of invasion (OR = 2.7, 95% CI = [1.6–4.6], p < 0.001). High-grade tumors had a four-fold higher risk of muscle invasion than low-grade tumors (OR = 4.1, 95% CI = [1.5–11.0], p = 0.005) (Table 2).

In ROC curve analysis, the baseline model including age, sex, tumor size, number of tumors, and pathological grade achieved an AUC of 0.74 (95% CI: [0.68-0.80]). Addition of sessile morphology increased the AUC to 0.78 (95% CI: [0.72-0.83]). Stratified analyses by tumor size

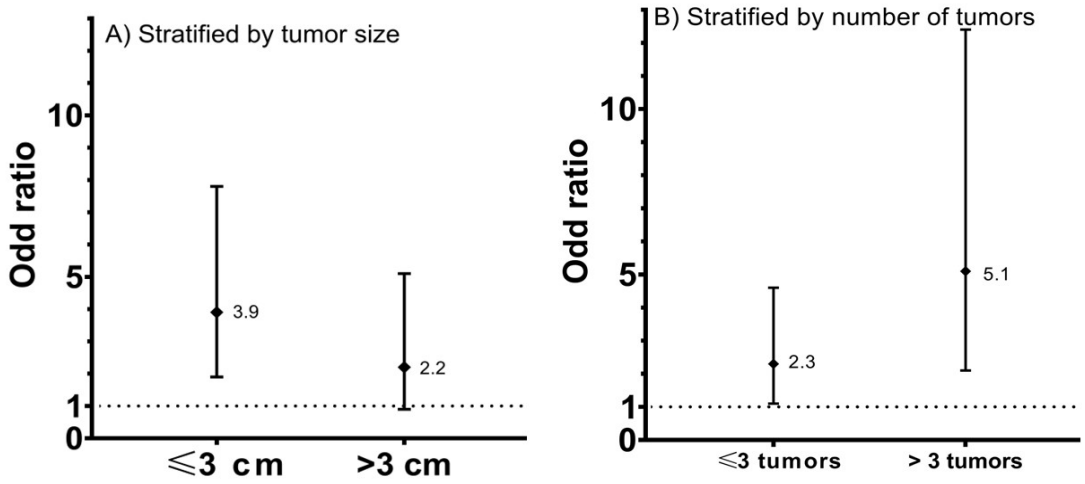

Figure. 2. Tumor size- and number of tumors-stratified association of tumor morphology (sessile vs papilliary) with muscle invasive status (n = 416). A) Tumor size stratified: ≤3 cm (Odds ratio OR = 3.9, Confident interval (CI) = [1.9–7.8], P <0.001); >3 cm (OR = 2.2, CI = [0.9–5.1], p = 0.08); B) Number of tumors stratified: ≤3 tumors (OR = 2.3, CI = [1.1–4.6], p = 0.02); > 3 tumors (OR = 5.1, CI = [2.1–12.4], p <0.001). OR were adjusted for age, sex, tumor size, number of tumors and pathological grade except for stratified variable in the multivariable logistic regression model. The diamond indicates the OR, and a bar indicates 95% CI. The horizontal dotted line is the references as the null of association indicating the OR = 1.

and number of tumors showed that the association between sessile morphology and MIBC was modified in patients with tumor ≤ 3 cm and > 3 tumors (Figure 2). In patients with tumor ≤ 3 cm, the association of sessile morphology and MIBC changed to OR of 3.9 (CI = 1.9–7.8). In patients with number of tumors > 3, the association of sessile morphology and MIBC changed to OR of 5.1 (CI = 2.1–12.4). The association of sessile morphology with muscle invasion appeared stronger in patients with tumor ≤3 cm and those with >3 tumors.

Discussion

Our study showed that the sessile morphology of BC at initial diagnosis was a strong independent predictor of muscle invasion (OR = 3.1), comparable in magnitude to established risk factors, such as high-grade histology (OR = 4.1) and tumor size >3 cm (OR = 2.7). This association was highly modified in patients with tumor < 3 cm and > 3 tumors. Although the addition of morphology modestly improved the AUC of the baseline model (0.04), it indicates that morphology provides incremental predictive value beyond established risk factors. This finding underscores the importance of incorporating gross morphological assessment into the initial evaluation of bladder tumors on cystoscopy.

The strong association between sessile morphology and muscle invasion likely reflects the fundamental biological differences between sessile and papillary growth patterns. Sessile tumors typically demonstrate a broader base of attachment to the bladder wall, potentially facilitating direct invasion into the deeper tissue layers. Palou et al. [9] previously noted that solid appearance was an independent predictor of progression in T1G3 tumors, with a hazard ratio of 2.8 for progression to muscle-invasive disease. At the molecular level, sessile tumors often contain alterations linked to invasive potential, such as mutations in *TP53*, *RB1*, and *ERBB2* genes [10]. The architectural pattern of sessile tumors may more extensively disrupt normal basement membrane integrity than papillary growth, creating pathways for tumor cell migration into deeper layers. Furthermore, sessile tumors frequently demonstrate reduced E-cadherin and increased N-cadherin expression, molecular changes associated with epithelial-mesenchymal transition, and enhanced invasive capacity [11]. In addition, British researchers [11] found that sessile morphology correlates with altered expression of matrix metalloproteinases, which facilitates the degradation of extracellular matrix components and promotes invasion. These biological characteristics may explain why sessile morphology served as a robust predictor of muscle invasion in our cohort.

Our study also showed that the association between sessile morphology and muscle invasion was stronger in specific patient subgroups. In patients with smaller tumors (≤3 cm), sessile morphology was associated with an odds ratio of 3.9 for muscle invasion higher than the overall cohort. This suggests that morphology may be especially important for risk stratification of lesions that might otherwise be considered a lower risk based on size alone. Similarly, in patients with multiple tumors (>3), the odds ratio increased to 5.1, indicating a potential synergistic relationship between tumor multiplicity and sessile morphology in predicting invasion. These effect modifications highlighted the complex interplay between morphological features and other clinicopathological factors, suggesting that the predictive value of sessile morphology may be context-dependent. A study of Janapense reseachers [12] demonstrated that multifocal tumors often share similar genetic alterations, potentially explaining the synergistic effect of morphology in predicting invasion. The stronger association in smaller

tumors is particularly clinically relevant, as these lesions might otherwise be approached less aggressively based solely on size criteria.

The predictive value of sessile morphology for muscle invasion appears to be independent of, yet complementary to, established risk factors such as tumor grade. Although high-grade histology demonstrated the strongest overall association with muscle invasion in our study (OR = 4.1), the inclusion of morphological assessment provided additional prognostic information. This is consistent with the findings of Sjödahl et al. [13], who identified distinct molecular subtypes of BC with different invasion patterns that do not perfectly align with the traditional grading systems. Robertson et al. [14] similarly described five molecular subtypes with varying invasive potential, suggesting that morphology may capture biological features not fully reflected in conventional histopathological assessment. However, sessile morphology alone does not justify upfront aggressive treatment in NMIBC. Management should remain consistent with current guidelines; nevertheless, the presence of sessile morphology at cystoscopy may reasonably prompt a heightened vigilance pathway, such as ensuring detrusor sampling at TURBT or implementing closer cystoscopic and/or imaging surveillance schedules.

The strengths of this study include its large sample size and robust statistical analyses. Additionally, a stratification analysis was performed to clarify the modification of the association. Moreover, this study added valuable data from a Southeast Asian population, which is underrepresented in the literature on BC. These results may be particularly relevant for clinicians practicing in low-to middle-income countries, where advanced imaging and molecular testing are not always available.

However, this study had several limitations. First, its retrospective design was inherently prone to selection and documentation bias. Second, we could not include other risk factors of BC such as VI-RADS scoring on MRI or molecular markers (e.g., *p53*, *FGFR3*, or *Ki-67*) which are increasingly recognized in modern risk stratification. Third, the assessment of tumor's shape was not done by a single surgeon, leading to the potential interobserver variability. Fourth, we were unable to evaluate the concordance between the initial diagnosis of muscle invasion at TURBT and the final cystectomy pathology due to the absence of follow-up pathological data after radical cystectomy. Another limitation is that pathology reports at our institution did not include variant histologies (e.g., micropapillary, nested, plasmacytoid). As these variants are associated with both sessile morphology and a higher likelihood of muscle invasion, their absence from our analysis may have introduced unmeasured confounding. Finally, our outcome was limited to the presence of muscle invasion, and long-term follow-up data such as recurrence, progression, or cancer-specific survival were not available. Future prospective studies integrating epidemiological, radiological, pathological, and molecular parameters are warranted to develop more accurate and individualized predictive models.

In conclusions, our study establishes sessile tumor morphology as a strong independent predictor of muscle invasion in newly diagnosed BC, with an effect that is particularly pronounced in patients with smaller tumors and those with multiple tumors. These findings highlight the importance of careful morphological assessment during the initial cystoscopy and suggest that sessile morphology should be incorporated into preoperative risk stratification to guide treatment planning and patient counseling.

Author Contribution Statement

MTD participated in the study design, performed the statistical analysis, visualization, and revised the manuscript. NDT participated in the study design, carried out the data collection, performed the statistical analysis, and drafted the manuscript. LNT and DNC participated in the study design, carried out the data collection, performed the statistical analysis and visualization, and drafted the manuscript. All authors read and approved the final manuscript.

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Ethical approval

The study was approved by the Institutional Review Board (IRB) of the 108 Military Central Hospital.

Informed consent

The patient in this study has given consent to be included.

Data availability statement

Data were obtained by requesting the corresponding author via e-mail.

Conflict of interests

The authors declare no conflicts of interest regarding the publication of this article.

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