Preoperative Clinical Predictors of Lymphovascular Invasion of Bladder Tumors at Transurethral Resection Pathology

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\textbf{Key Words}

Metastasis • Invasive bladder cancer • Adjuvant therapy • Metastasectomy

\textbf{Abstract}

\textbf{Background:} The assessment of lymphovascular invasion (LVI) on the specimens of a transurethral resection of bladder tumors (TURBT) is very important for risk stratification and decision-making on further treatment for bladder cancer. \textbf{Objectives:} The present study aimed to identify clinical predictors associated with the risk of bladder cancer with LVI before a first TURBT. \textbf{Methods:} A total of 291 patients underwent a first TURBT for bladder cancer at Toho University Sakura Medical Center between January 2012 and December 2016. We analyzed predictors of LVI based on data from 217 patients and predictors of high grade and ≥ pT1 tumors based on data from the medical records of 237 patients for comparison with LVI risk factors. \textbf{Results:} Univariate analysis significantly associated LVI with episodes of gross hematuria, positive urinary cytology, and larger, non-papillary and sessile tumors. Multivariate analysis selected larger tumors [odds ratio (OR) 1.39; 95 % confidence interval (CI) 1.08–1.78; \( p = 0.01 \)], and non-papillary [OR 10.05; 95% CI 3.75–26.91; \( p < 0.01 \)] and sessile (OR 2.65; 95% CI 1.18–5.93; \( p = 0.02 \)) tumors as significant predictors of LVI. Some predictors such as tumor size and non-papillary tumors overlapped between high-grade and ≥ pT1 bladder cancer. \textbf{Conclusions:} These predictors can help clinicians to identify patients with, or who are at high-risk for LVI before undergoing a first TURBT and to determine priorities for preoperative evaluation and scheduling consecutive treatments.
sive bladder cancer (NMIBC) into grade G1, G2, and G3 in 1973 [10]. The WHO/International Society of Urological Pathology 2004 that is presently applied mainly classifies NMIBC simply as low- or high-grade [9].

Risk is classified using pathological TURBT specimens, and risk factors slightly differ among various guidelines. One set of guidelines classifies NMIBC according to risk groups based on pathological and clinical factors in order to predict the risk of recurrence and progression in individual patients [11]. For example, the American Urological Association (AUA) guidelines define high-grade and T1 tumors, recurrent high-grade and Ta tumors, high grade Ta and large (> 3 cm) tumors, multifocal high-grade Ta tumors, any carcinoma in situ (CIS), any failure of Bacillus Calmette-Guerin therapy for high-grade tumors, any variant history, high-grade prostatic urethral involvement, and lymphovascular invasion (LVI) as high-risk factors [12].

The recurrence rates of NMIBC are 40–80%, but the prognosis is relatively good. However, NMIBC progresses to muscle invasive bladder cancer in about 15% of patients, and their prognoses are poor [11]. Patients at high, rather than low risk are more likely to progress to muscle invasive bladder cancer and thus, the ability to predict high risk is important. T stage and grade are common high-risk factors in all guidelines and LVI is also included in the AUA guidelines [12].

LVI is the invasion of cancer cells within any arterial, venous, or lymphatic lumen (fig. 1). The diagnosis of LVI is the presence of tumor within endothelium-lined spaces in the AUA guidelines. The evidence strength about the prognostic value of LVI in TURBT is grade C and its recommendation is moderate [12]. When LVI is detected by TURBT and radical cystectomy, it might predict a poor prognosis such as more advanced disease and recurrence. This has also been described as a poor prognostic factor in other types of carcinoma [2, 13–21]. Moreover, a meta-analysis of the impact of LVI at TURBT has shown that it is a robust prognostic factor of disease recurrence and progression in NMIBC with a powerful impact on upstaging when the disease is confined within an organ [22]. Therefore, LVI is an independent high-risk factor in patients with other high-risk factors such as T1 and high-grade bladder cancers. Furthermore, Cho et al. [23] showed that LVI in TURBT predicts disease progression and metastasis in patients with newly diagnosed T1 urothelial carcinoma of the bladder, and LVI is also considered to be an important factor in the first TUR.
The assessment of LVI on TUR specimens and reporting is very important for risk stratification and decision-making for further treatment. Being able to predict LVI before a first TURBT is considered very useful for scheduling further treatments such as a second-look TURBT and radical cystectomy with neoadjuvant chemotherapy in routine clinical practice. In addition, if the urologists predict the presence of LVI, they are consciously going to perform intensified TURBT such as a complete TURBT.

The present study mainly aimed to identify clinical factors that could predict LVI before the first TURBT. We additionally compared predictors with clinical factors that can predict high-grade and ≥pT1 bladder cancer, because these are also characterized by a high progression rate.

### Materials and Methods

This retrospective study was approved by the institutional review board (Approval No. S17108). Among 424 patients who underwent TURBT for bladder cancer at Toho University Sakura Medical Center between January 2012 and December 2016, 291 underwent the first TURBT for bladder cancer. We excluded patients from the present study due to their having tumors of other origin, only bladder CIS lesions, concurrent or recurrent bladder cancer with upper urinary tract urothelial carcinoma, or missing values. We analyzed predictors of LVI based on data from 217 patients whose specimens could be reviewed to confirm if LVI existed. Additionally, predictors of high grade and ≥pT1 tumors were analyzed based on data from the medical records of 231 patients for comparison with LVI risk factors.

Bladder cancer was preoperatively evaluated using abdominal ultrasound, flexible or rigid cystoscopy, computed tomography, magnetic resonance imaging, and urinary cytology.

The following information was collected during a retrospective survey of medical records: age, sex, episodes of urinary symptoms, tumor size, number of tumors, location of the largest tumor (lateral walls, base, posterior wall, dome, and anterior wall), growth type (papillary or not, pedunculated or sessile), hydronephrosis, urinary cytology findings, pathological T stage, grade (low or high), and LVI defined as unequivocal findings of nests of neoplastic cells within a space lined with endothelium without an underlying muscular wall [2]. LVI in specimens was assessed using conventional hematoxylin and eosin staining (Fig. 1). Positive urinary cytology was defined as ≥class IV (strongly suggestive of malignancy) according to Papanicolaou classification. Any 2 of 3 pathologists in a council system at Toho University Sakura Medical Center evaluated pathological findings using the tumor (T), node (N), and metastasis (M) classification system (updated 2009) and the classification for grading non-invasive urothelial bladder carcinomas proposed by the WHO and the International Society of Urological Pathology in 2004 [7–10].

#### Statistical Analysis

Results are presented as medians (range) or as means ± SD, as appropriate. Continuous parametric variables were compared using t-tests. Non-parametric variables were compared using Mann-Whitney U-tests. Categorical variables were compared using χ² or Fisher’s exact tests. Associations between LVI and preoperative variables were initially assessed by univariate analysis. Significant candidate variables that were identified by univariate analysis were then entered into multivariate logistic regression analysis in order to identify clinical predictors associated with LVI. Predictors of high-grade and ≥pT1 bladder tumors were also similarly identified using univariate and multivariate analysis as described above.

All data were statistically analyzed using SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA). Values with p < 0.05 were considered statistically significant.

#### Results

Table 1 summarizes the baseline characteristics of the enrolled 231 patients. The mean age was 71.7 ± 9.2 years, 80.1% were male, and 71.0% had episodes of gross hematuria, n (%) 185 (80.1), Urinary hematuria, n (%) 117 (51.6), Tumor size, cm 7.2 (1.8–8.5), Multiple tumors, n (%) 107 (46.3), Location of the largest tumor, n (%) Lateral walls 107 (46.3), Base 76 (32.9), Posterior 27 (11.7), Dome 15 (6.5), Anterior 6 (2.6), Appearance Non-papillary, n (%) 24 (10.4), Sessile, n (%) 129 (55.8), Hydronephrosis present, n (%) 16 (6.9), Urinary cytology, n (%) Low 43 (18.6), Class I 43 (18.6), Class II 30 (13.0), Class III 98 (42.4), Class IV 2 (0.9), Class V 58 (25.1), Pathological T stage, n (%) Ta 117 (50.7), T1 75 (32.5), ≥T2 39 (16.9), Grade, n (%) Low grade 52 (22.5), CIS, n (%) 24 (10.4), ≥pT1 tumors 137 (60.1), AUA risk classification, n (%) Low 26 (11.3), Intermediate 44 (19.1), High 95 (41.1), Others 66 (28.5).

### Table 1. Baseline characteristics of patients (n = 231)

| Variable                                      | Values                  |
|-----------------------------------------------|-------------------------|
| Age, years                                    | 71.7 ± 9.2              |
| Male, n (%)                                   | 185 (80.1)              |
| Gross hematuria, n (%)                        | 164 (71.0)              |
| Urinary frequency, n (%)                      | 36 (15.6)               |
| Tumor size, cm                                | 2 (0.1–8.5)             |
| Multiple tumors, n (%)                        | 107 (46.3)              |
| Location of the largest tumor, n (%)          |                         |
| Lateral walls                                 | 107 (46.3)              |
| Base                                          | 76 (32.9)               |
| Posterior                                     | 27 (11.7)               |
| Dome                                          | 15 (6.5)                |
| Anterior                                      | 6 (2.6)                 |
| Appearance                                    |                         |
| Non-papillary, n (%)                          | 24 (10.4)               |
| Sessile, n (%)                                | 129 (55.8)              |
| Hydronephrosis present, n (%)                 | 16 (6.9)                |
| Urinary cytology, n (%)                       |                         |
| Class I                                       | 43 (18.6)               |
| Class II                                      | 30 (13.0)               |
| Class III                                     | 98 (42.4)               |
| Class IV                                      | 2 (0.9)                 |
| Class V                                       | 58 (25.1)               |
| Pathological T stage, n (%)                   |                         |
| Ta                                            | 117 (50.7)              |
| T1                                            | 75 (32.5)               |
| ≥T2                                           | 39 (16.9)               |
| Grade, n (%)                                  |                         |
| Low grade                                     | 52 (22.5)               |
| CIS, n (%)                                    | 24 (10.4)               |
| ≥pT1 tumors                                   | 137 (60.1)              |
| AUA risk classification, n (%)                |                         |
| Low                                           | 26 (11.3)               |
| Intermediate                                  | 44 (19.1)               |
| High                                          | 95 (41.1)               |
| Others                                        | 66 (28.5)               |
maturia. The median tumor size was 2.0 cm (range 0.1–8.5 cm). Multiple, non-papillary, and sessile tumors were found in 107 (46.3%), 24 (10.4%), and 129 (55.8%) patients, respectively. Urinary cytology was positive (class ≥ IV) in 60 (26.0%) patients, 179 (77.5%) had pathologically diagnosed high-grade bladder cancer, 10.4% had concomitant CIS, and 21.6% were positive for LVI. LVI was significantly higher in patients with high-grade and ≥ pT1 bladder cancer (39.8 vs. 2.7%, p < 0.01). In accordance with AUA classification, low, intermediate, high risk, and others were found in 23 (11.3%), 44 (19.1%), 95 (41.1%), and 66 (28.5%) patients, respectively.

Table 2 summarizes the preoperative factors associated with risk of LVI on univariate and multivariate analysis. Among the 217 patients, 50 (23.0%) were positive for LVI. During the follow-up after the first TURBT, 21 (42.0%) patients with LVI and 41 (24.6%) patients without LVI experienced disease recurrence, respectively. Based on log-rank testing, the patients with LVI had a higher risk of a disease recurrence and progression than without LVI (recurrence p = 0.01; progression p = 0.06). Univariate analysis significantly associated LVI at TURBT with episodes of gross hematuria (p = 0.04), larger (p ≤ 0.01), non-papillary (p ≤ 0.01), and sessile (p ≤ 0.01) tumors, and positive urinary cytology (p ≤ 0.01). Multivariate analysis selected larger tumors [odds ratio (OR) 1.39; 95% confidence interval (CI) 1.08–1.78; p = 0.01], non-papillary tumors (OR 10.05; 95% CI 3.75–26.91; p < 0.01), and sessile tumors (OR 2.65; 95% CI 1.18–5.93; p = 0.02) as significant predictors of LVI.

Table 2. Uni- and multi-variate analysis of clinical predictors for LVI before first-time TURBT

| Variable                      | Overall (n = 217) | Univariate | Multivariate |
|-------------------------------|-------------------|------------|--------------|
|                               | With LVI (n = 50) | Without LVI (n = 167) | p   | OR (95% CI) | p   |
| Age, years                    | 72.1 ± 10.3       | 71.1 ± 9.1 | 0.48         |      |      |
| Male, n (%)                   | 40 (80.0)         | 134 (80.2) | 0.97         |      |      |
| Gross hematuria, n (%)        | 42 (84.0)         | 115 (68.9) | 0.04         |      | 0.20 |
| Tumor size, cm                | 2.7 (0.1–7.0)     | 1.7 (0.1–8.5) | < 0.01     | 1.39 (1.08–1.78) | 0.01 |
| Multiple tumors, n (%)        | 23 (46.0)         | 75 (45.0)  | 0.89         |      |      |
| Appearance                    |                   |            |              |      |      |
| Non-papillary, n (%)          | 19 (38.0)         | 7 (4.1)    | < 0.01       | 10.05 (3.75–26.91) | < 0.01 |
| Sessile, n (%)                | 39 (78.0)         | 81 (48.5)  | < 0.01       | 2.65 (1.18–5.93)  | 0.02 |
| Hydronephrosis, n (%)         | 6 (12.0)          | 10 (6.0)   | 0.34         |      |      |
| Positive urinary cytology, n (%) | 21 (42.0)       | 31 (18.6)  | < 0.01       |      |      |

Table 3. Uni- and multi-variate analysis of clinical predictors for high grade and ≥ pT1 bladder cancer before TURBT

| Variable                      | Overall (n = 231) | Univariate | Multivariate |
|-------------------------------|-------------------|------------|--------------|
|                               | High grade and ≥ pT1 (n = 113) | Not high grade and ≥ pT1 (n = 118) | p   | OR (95% CI) | p   |
| Age, years                    | 72.3 ± 9.7        | 71.1 ± 8.7 | 0.24         |      |      |
| Male, n (%)                   | 90 (79.7)         | 95 (80.5)  | 0.87         |      |      |
| Gross hematuria, n (%)        | 92 (81.4)         | 72 (61.0)  | < 0.01       | 2.51 (1.14–5.53) | 0.02 |
| Tumor size, cm                | 2.2 (0.1–8.5)     | 1.5 (0.1–4.3) | < 0.01     | 1.78 (1.28–2.46)  | < 0.01 |
| Multiple tumors, n (%)        | 62 (54.9)         | 47 (39.8)  | 0.02         |      |      |
| Appearance                    |                   |            |              |      |      |
| Non-papillary, n (%)          | 23 (20.4)         | 1 (0.9)    | < 0.01       | 17.58 (2.13–144.89) | < 0.01 |
| Sessile, n (%)                | 74 (65.5)         | 55 (46.6)  | < 0.01       |      |      |
| Hydronephrosis, n (%)         | 10 (8.9)          | 6 (5.1)    | 0.26         |      |      |
| Positive urinary cytology, n (%) | 51 (45.1)       | 8 (6.8)    | < 0.01       | 10.64 (4.33–26.32) | < 0.01 |
Table 3 summarizes preoperative factors associated with high-grade and ≥ pT1 bladder cancer in univariate and multivariate analysis. Univariate analysis significantly associated high-grade and ≥ pT1 bladder cancer with episodes of gross hematuria (p < 0.01), positive urinary cytology (p < 0.01), larger (p < 0.01), multiple (p = 0.02), non-papillary (p < 0.01) and sessile (p < 0.01) tumors, and multivariate analysis significantly associated these types of bladder cancer with episodes of gross hematuria (OR 2.51; 95% CI 1.14–5.53; p = 0.02), larger (OR 1.78; 95% CI 1.28–2.46; p < 0.01) and non-papillary (OR 17.58; 95% CI 2.13–144.89; p < 0.01) tumors, and positive urinary cytology (OR 10.64; 95% CI 4.33–26.32; p < 0.01).

Discussion

Having LVI at TURBT is associated with recurrence, lymph node metastasis, and a poor prognosis [1, 2, 15, 16, 22–29]. Kim et al. [24] evaluated the relationship between LVI at TURBT, and found the risk of pathological upstaging and clinical outcomes in a meta-analysis of 3,905 patients and identified an 18.6% (range 3.0–67.0%) prevalence of LVI. We found that 50/217(23.0%) patients had LVI, which was similar to that in the meta-analysis. Kim et al. [24] associated LVI at TURBT with pathological upstaging (OR 2.21; 95% CI 1.44–3.39). Moreover, they significantly associated LVI at TURBT with recurrence-free (hazard ratio 1.47; 95% CI 1.24–1.74) and progression-free (hazard ratio 2.28; 95% CI 1.45–3.58) survival. Resnick et al. [25] also associated LVI at TURBT with an increasing likelihood of node-positive disease (48.3 vs. 25.0%, p < 0.001).

Mathieu et al. [26] summarized current data about the effect of LVI on disease outcomes in patients with NMIBC. They showed that high-grade pT1 bladder and LVI detected in biopsy specimens were poor prognostic factors for disease recurrence and progression. Furthermore, LVI was significantly associated with disease recurrence, cancer-specific, and overall survival in patients with high-grade pT1 bladder cancer treated by radical cystectomy [29].

It has been shown that LVI is an independent prognostic factor and an important factor in bladder cancer with pT1 and high-grade tumors that are considered to be poor prognostic factors [27–30]. Thus, the presence of LVI is considered to be associated with a poor prognosis, such as recurrence and progression, which was also confirmed in this study.

The ability to visually predict pathological results, such as cancer grade and stage, although intuitive, is regularly used before TURBT in clinical practice. However, whether urologists can accurately predict grade and stage might depend on their experience [31, 32]. There may also be a risk that younger unskilled urologists cannot predict the pathology of bladder cancer, such as LVI, at the time of diagnosis. Clinical factors can help them to predict pathological outcomes before TURBT. Therefore, the present study offers important predictors for LVI before a first TURBT, as far as we can ascertain.

The present multivariate analysis significantly associated LVI with large, non-papillary, and sessile types of tumors (table 2). Furthermore, high-grade and ≥ pT1 bladder cancer was significantly associated with gross hematuria and positive cytology in addition to tumor size and non-papillary tumors (table 3).

Larger and non-papillary tumors comprised common factors in patients on multivariate analysis (table 2, 3). LVI was significantly higher in high-risk patients (with high-grade and ≥ pT1) (p < 0.01). This might be the reason why these predictors overlapped between LVI and high-grade and ≥ pT1. If the patients have sessile tumors in addition to these 2 factors even without gross hematuria and positive cytology, there is a high possibility that they have bladder cancer with LVI. These predictors, such as larger tumor size, non-papillary, and sessile tumors might reflect the nature of invasive bladder cancer. Moreover, if the patients have gross hematuria and positive cytology in addition to these 2 factors, they can be predicted to be at a higher risk of high-grade and ≥ pT1 bladder cancer. Thus, we suggest that clinical combined factors in addition to larger and non-papillary tumors are predictors of LVI or high-grade ≥ pT1 bladder cancer, which means high-risk bladder cancer. Patients with high-risk bladder cancer can be predicted before they undergo a first TURBT.

Predicting LVI before first-time TURBT can offer much information. Urologists can aim to resect tumors widely and deeply for pathological evaluation of LVI. They can also inform pathologists that there is a high possibility that LVI exists in TUR specimens, because LVI is hard to identify and generally is under-reported in the pathological reports of TURBT. Thus, pathologists will be able to consciously review the specimens. These predictors can become good communication tools between urologists and pathologists.

Several limitations of the present study should be considered. The retrospective design includes inherent risks of selection bias, which might weaken the power of this
study. A central pathological review of TURBT specimens was not performed in this study, although many pathologists assess and diagnose specimens in daily clinical practice. Tumor size was determined using several devices (abdominal ultrasound, computed tomography, magnetic resonance imaging, and cystoscopy), although clinicians comprehensively determine the tumor size based on all modalities.

Conclusion

In conclusion, LVI at the time of TURBT was associated with large tumors and different growth types (non-papillary and sessile). Additionally, high-grade and $\geq$ pT1 types of bladder cancer were associated with episodes of gross hematuria, tumor size, non-papillary type tumors, and positive urinary cytology. Although the predictors partially overlapped, clinicians can predict high-risk bladder cancer, such as LVI or high-grade and $\geq$ pT1, based on these factors at initial diagnosis. Bladder cancer with LVI should be prioritized over lower risk patients for more urgent surgery. Being able to detect bladder cancer with LVI using these factors will allow urologists to determine priorities for preoperative evaluation and schedule consecutive treatments more efficiently and confidently. Moreover, it is also useful for urology practitioners to be able to predict LVI in order to know the patients who require sooner surgical intervention.

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