

Value of Tumor's Depth and Width in Predicting Survival Rate in Non-Muscle-Invasive (pT1) Bladder Cancer

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Abstract

Background: Bladder cancer is classified according to traditional American Joint Committee on Cancer TNM staging. In the absence of nodal (N stage) or distant metastases (M stage), the depth of tumor invasion (T stage) is the most important determination to be made: whether the tumor is invading into or beyond the lamina propria (muscle-invasive bladder cancer) or not (non-muscle-invasive bladder cancer). This study investigated the association between the cutoff value of tumor depth and width and survival rate in non-muscle-invasive (pT1) bladder cancer. **Methods:** This was a retrospective cohort design of randomly selected, single-centered study. The subjects were patients with pT1 urothelial carcinoma who were diagnosed on transurethral resection of bladder specimens at a tertiary hospital in West Java, Indonesia. The research sample was taken by consecutive sampling from 2015 to 2019. **Results:** Sixty-four patients from were included in this study. A tumor depth >2 mm resulted in a hazard ratio (HR) of 1.41 (95% confidence interval [CI], 1.27–3.94;

$p<0.007$), with significant difference. A tumor width >2.4 mm also increased HR significantly (3.27; 95% CI, 1.69–5.87; $p<0.006$). The presence of lymphovascular invasion (LVI) in patients with bladder cancer resulted in an HR of 3.66 (95% CI, 1.5–4.77; $p<0.001$), with statistically significant difference in overall survival (OS). **Conclusion:** Tumor invasion depth, tumor width, and LVI appear to be predictive of poor prognosis in terms of OS in patients with pT1 bladder cancer.

Keywords: Non-muscle-invasive, Bladder cancer, Survival rate

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Introduction

Bladder carcinoma, which has an annual incidence rate of 430,000 cases, is the eleventh most diagnosed cancer worldwide, but it ranks eighth among male populations. In Indonesia, the overall incidence of bladder cancer is estimated to be 7 in 100,000. According to the 2020 GLOBOCAN data, the incidence of bladder cancer in Indonesia ranks 14th worldwide, with 6716 new cases (1.9%), but the precise incidence rate is hard to determine, especially the non-muscle-invasive bladder cancer (NMIBC) type (1). In a previous study from a

tertiary hospital, of 464 patients diagnosed with bladder cancer, 36 (7.76%) had NMIBC. The incidence and mortality rates of bladder cancer vary greatly across different countries because of differences in risk factors, early detection and diagnostic applications, and availability of treatments (2).

At presentation, 90% of bladder cancers are confined to the bladder wall layers, and of all localized bladder cancers ($\leq T2$), 75% are non-muscle-invasive (Tis, Ta, T1) (3, 4). A long-term study of high-risk NMIBC,

including T1 tumors, showed progression and cancer death rates as high as 53% and 34%, respectively (5). This pT1 group has high prognosis variability, and thus, involves the most difficult clinical decisions. Some patients experience no recurrence after initial transurethral resection of the bladder (TURB); meanwhile, some patients show recurrence and stage progression after initial therapy (4). Therefore, prognostication in pT1 group is urgently needed.

T1 tumors represent approximately 25% of NMIBCs. Recognition of early invasion (stage pT1) in urothelial neoplasia is one of the most challenging areas in bladder pathology. Many studies have attempted to stratify T1 tumors by depth of invasion into the lamina propria, but they have had variable success. Invasion of the lamina propria, tumor grade, and carcinoma in situ (CIS) represent significant risk factors for the progression of NMIBC. Owing to its heterogeneity, numerous efforts have been made to identify the subset of T1 carcinomas that carries a high risk of disease recurrence and progression (6).

In a previous study, human papillomavirus status in patients with pT1 bladder cancer had no significant effect on in disease progression (7). However, tumor invasion beyond the lamina propria has shown higher recurrence and progression rates than more superficial invasions. In addition, some investigators have shown that the millimetric depth of invasion measured by a micrometer can be an accurate predictive factor with a significant cutoff invasion depth of 1.5 mm. Lymphovascular invasion (LVI) is also a determining factor in the progression and mortality of bladder cancer (8). The parameters used to predict the prognosis of pT1 patients, i.e., early stages, tumor grade, quantity of tumors, and presence of carcinoma in situ (CIS), cannot accurately predict the patients' prognosis, especially in patients with pT1 tumors (9).

In the present study, we aimed to evaluate the pathologic parameters of tumor correlated with overall survival (OS) rate in pT1 bladder cancer.

Materials and Methods

Patients

The study was conducted in 2022 using a retrospective cohort design of randomly selected, single-centered cohort design involving 64 patients registered at the urology department in a tertiary hospital in West Java, Indonesia, between 2015 and 2019. Inclusion criteria were patients with pT1 urothelial carcinoma diagnosed on transurethral resection of bladder (TURB) specimens. The specimen/preparation is assessed for their depth and width, along with the presence of LVI.

Pathologic evaluation

All specimens from TURB were independently reviewed by one professional pathologist. The pathologist was blinded to the clinical records. Slides were graded according to World Health Organization (WHO) 2004 classification. The recorded demographic characteristics of the patients were age, sex, tumor count, depth of tumor invasion, tumor diameter, and LVI. The invasion depth of the tumor was measured, in millimeters, from the basement membrane of the overlying urothelium to the deepest invasive tumor cell. The tumor diameter, representing the vertical width of the invasive focus rather than its depth, was measured, in millimeters, by measuring the largest tumor width of one tumor focus in the lamina propria. LVI was determined by the presence of tumor invasion in blood vessels by histopathologic examinations.

Statistical analysis

Survival time was defined as the period between the time of diagnosis and the time of death from any cause. The primary endpoint was OS. Chi square test was used to analyze the relationship between microscopic growth pattern and clinicopathologic features. Survival curves were generated by Kaplan–Meier estimator, and log-rank test univariate analysis was utilized to examine the parameters that are significantly associated with OS. Multivariate Cox proportional hazards model was built to verify the independent role of prognostic factors. Two-sided $p < 0.05$ was considered statistically significant. Confidence intervals (CIs) were set at 95% confidence. All statistical analyses were performed with SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Ethical approval

This study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung with ethical approval no. LB.01.02/X.6.5/11/2022. The study protocol was designed according to the standards of the Helsinki Declaration. Written informed consent was obtained from the patients.

Results

Table 1 presents the demographic and clinical characteristics of the patients. Sixty-four patients diagnosed with pT1 bladder cancer were included (mean age, 51.22±4.30 years; male, 78.1%). Multiple tumors were discovered in 85.9% of cases. The mean tumor invasion depth was 1.57±1.70 mm. The mean tumor width was 2.77±1.39 mm. LVI was found in 62.5% of all cases. All invasive tumors had high-grade nuclear features.

Table 1. Demographic characteristics of patients (n=64)

Age (years)	51.22±4.30
Sex	
Male	50 (78.13)
Female	14 (21.88)
Tumor count	
Single	9 (14.06)
Multiple	55 (85.94)
Depth of invasion (mm)	1.57±1.70
Mean tumor diameter (mm)	2.77±2.14
LVI	
No invasion	24 (37.50)
Invasion of blood vessels	40 (62.50)

Categorical data are presented as the count/frequency and percentage, whereas numerical data were displayed as mean±standard deviation.

Univariate analysis showed that tumor depth, tumor width, and LVI were significantly associated with OS (Table 2). On multivariate analysis, depth of invasion, diameter of invasive focus, and LVI were significantly associated with OS. However, the presence of LVI was

associated with OS. A depth of invasion ≥2 mm was significantly associated with OS, achieving a sensitivity of 80%, specificity of 92%, and positive predictive value (PPV) of 85%. In comparison, the cutoff value for the diameter of invasive carcinoma that correlated best with OS was ≥2.4 mm for progression (sensitivity, 80%; specificity, 85%; PPV, 86%).

In the Kaplan–Meier analysis, a tumor depth >2 mm resulted in an HR of 1.41 (95% CI, 1.27–3.94; $p<0.007$), with significant difference (Figure 1). A tumor width >2.4 mm also increased HR significantly (3.27; 95% CI, 1.69–5.87; $p<0.006$). The presence of LVI resulted in an HR of 3.66 (95% CI, 1.5–4.77; $p<0.001$), with statistically significant difference in OS of bladder cancer patients.

Table 2. Univariate analysis of pathologic features affecting patient's survival

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	<i>P</i>	Hazard ratio	95% CI	<i>P</i>
Tumor depth (>2.00 mm)	1.54	1.23–3.26	0.005	1.41	1.27–3.94	0.007
Tumor diameter (>2.4 mm)	2.94	1.3–6.51	0.008	3.27	1.69–5.87	0.006
Lympho vascular invasion	2.37	1.10–5.2	0.028	3.66	1.5–4.77	0.01

The 5-year OS rate was 60% for patients with tumor depth >2.00 mm, and the overall 5-year survival rate was 82% for patients with tumor depth <2.00 mm. All differences in the OS rate were statistically significant between the two groups. The 5-year OS rate was 46% for patients with tumor width >2.40 mm, and the overall 5-year survival rate was 81% for patients with tumor depth <2.40 mm. All differences in the OS rate were statistically significant between the two groups. The 5-year OS rate was 42% for patients with positive LVI, and the overall 5-year survival rate was 76% for patients

with negative LVI. All differences in the OS rate were statistically significant between the two groups.

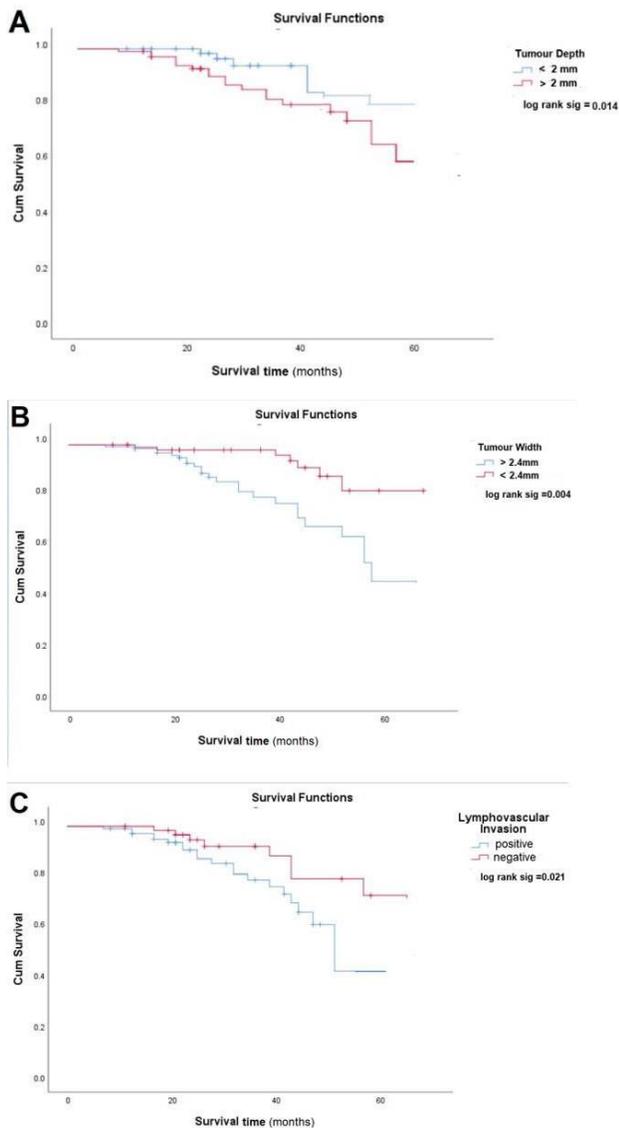


Figure 1. Kaplan–Meier curves of overall survival. Kaplan–Meier survival plot of patient outcome dependent on (A) maximum tumor depth (cutoff, 2.0 mm), (B) maximum tumor diameter (cutoff, 2.4 mm), and (C) lymphovascular invasion.

Discussion

Most cases of newly diagnosed bladder cancer are NMIBC. Once bladder cancer invades the muscle, the 5-year risk of death due to bladder cancer is approximately 50%. High-risk NMIBC accounts for approximately 25% of all newly diagnosed NMIBC, with prior reports of 33% progressing to muscle invasion in 10 years (10). Patients with NMIBC have a high risk

for disease recurrence (i.e., tumors of the same stage and grade as primary tumor), or disease progression (i.e., a higher stage with muscle invasion or metastasis throughout the clinical course of treatment), even in those treated with TURB and existing intravesical therapies. The depth of invasion within the subepithelial connective tissue in the initial transurethral resection specimen has a prognostic value with respect to the risk of tumor progression. A distinctive prognosis can be expected for tumors with different levels of invasion (11).

According to the American Cancer Society in 2020, the 5-, 10-, and 15-year survival rates at all stages of bladder cancer are 77%, 70%, and 65%, respectively (12). Survival estimates for T1 patients vary considerably in the literature, reflecting differences in study populations and methods from modeling survival. Blindheim et al. reported that the 5-year survival rates for all T1 bladder cancer patients were 84% (cause-specific survival) and 65% (OS) (13).

Although NMIBC is a non-muscle-invasive tumor, it is well known for its high risk of recurrence and progression. Multiple tumors, lung cancer, hematuria, and a >60 pack-year smoking history are considered as risk factors for tumor recurrence and worsening progression (14). In this study, the diameter of invasive carcinoma, depth of invasion, and LVI were the pathologic variables that mostly correlated with OS. LVI, depth of tumor, and diameter of tumor were prognostically correlative with OS in the multivariate analysis.

Substaging T1 urothelial carcinoma based on the depth of invasion measured by a micrometer has been advocated by some investigators as being an objective, reproducible, and prognostically significant histologic method of substaging, with cases showing an invasion ≥ 1.5 mm having a high risk of harboring muscle-invasive or higher-stage disease (8). Our study showed that a depth of invasion ≥ 2.00 mm was correlative with poorer OS (60%), confirming the prognostic importance of this pathologic parameter (15). This is supported by the findings of Nishiyama et al. (19), which clarified the prognostic value of the 2004 WHO classification system

of NMIBC. One of the predictor components of OS is the size of the tumor and the depth of tumor invasion. We also believe the maximum diameter of the invasive focus to be a histologic variable that is reproducible, objective, and easy to obtain. Findings from the current study support the incorporation of this variable in the pathologic reporting of T1 urothelial carcinoma. Our results confirm that tumor diameter correlate with OS. The proposed cutoff of 3.0 mm can serve as a practical tool to guide clinicians in their treatment and decision planning. However, we found that a cutoff >2.4 mm in tumor diameter is associated with poorer OS. The second Kaplan–Meier chart shows that the larger diameter group (>2.4 mm) has a lower 5-year OS rate of 46%. This result is in accordance with three previously published studies that used the diameter of the invasive carcinoma for substaging (8, 11, 16). In these studies, the extent of invasion was strongly associated with progression.

The role of LVI as a prognostic factor for progression and survival is still a controversial issue. Two studies established that LVI was not a predictor of survival. Finally, Lotan et al. concluded that LVI was associated with poorer OS in patients with positive lymph nodes (18). Similarly, in our study, the third Kaplan–Meier chart shows that the positive lymphovascular group had a lower 5-year OS rate (42%_). It is important to note that most publications reporting its prognostic correlation with pathologic stage, lymph node metastases, and survival have done so in cystectomy cohorts, and only few have looked at its value in Pt1 disease on TURB specimens (15). The current study was designed to reflect our routine practice in a tertiary center, in which we report LVI when clearly observed on hematoxylin and eosin slides and restrict immunohistochemical studies for endothelial and lymphatic markers to the rare equivocal and problematic cases (19). This study has a limitation, which is small sample size.

Conclusion

Deeper invasive tumors and wider tumor size appear to predict poor prognosis in Pt1 BC patient's survival. LVI findings are also a determinant of progression and poor

prognosis. We recommend reporting LVI, tumor depth, and tumor diameter in the final pathology report.

Conflict of interest

None to disclose

Author contributions

All authors contributed equally to writing and editing the original draft.

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