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ORIGINAL ARTICLE

Risk stratification of pT1b urothelial carcinoma based on spatial relationships between invasive tumour and muscularis propria on TURB specimens for predicting muscle-invasive urothelial carcinoma in radical cystectomy: A new proposal

Ji Min Kim[1] and Sanghui Park[1]*

[1]Department of Pathology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

Abstract

Introduction: In bladder cancer, the presence of lamina propria invasion (pT1) poses a significant clinical challenge due to varied tumour behaviours and risk of disease progression. Efforts to substage pT1 urothelial carcinoma (UC) using diverse systems have been made, but challenges persist in accurately predicting disease progression. This study introduces a novel risk stratification approach focusing on pT1b UC cases based on the spatial relationship between invasive carcinoma and the muscularis propria (MP) in transurethral resection of bladder (TURB) specimens. *Materials and Methods:* Retrospective analysis of pathology reports from 2017 to 2023 identified pT1 cases in TURB specimens, subcategorised using a 2-tiered approach. Exclusions were applied based on specific criteria, leading to a final cohort of 24 patients. We evaluated the tumour diameter and proximity to the MP from a "Tumour-MP (T-M) angle" perspective. A novel pT1b risk stratification method focusing on the T-M angle to differentiate low- and high-risk groups was developed, in which pT1b low-risk is defined as a T-M angle less than 180 degrees, and pT1b high-risk is defined as a T-M angle greater than 180 degrees. *Results:* In this study of 24 pT1b UC cases, 16 were categorised as pT1b low-risk and 8 as pT1b high-risk. Notably, the high-risk group showed a higher upstaging rate to advanced tumour stages (≥pT2) in radical cystectomy (RC) specimens compared to the low-risk group (88% vs. 56%, p = 0.015). *Conclusion:* This new risk stratification method presents promise in guiding early aggressive treatment decisions, though larger prospective studies are essential for further validation and clinical integration.

Keywords: pT1 urothelial carcinoma, pT1b, risk stratification, muscularis propria, angle, TURB, cystectomy

INTRODUCTION

Approximately 20% of patients who are newly diagnosed with bladder cancer are found to have invasion of the lamina propria (pT1).[1] It is widely acknowledged that pT1 urothelial carcinomas encompass a diverse range of tumours exhibiting distinct biological behaviors.[2] Though 30% of patients may not experience recurrence following initial transurethral resection of the bladder (TURB), up to 50% experience disease progression within five years of the initial diagnosis.[3,4] Hence, this condition poses a significant therapeutic dilemma for urologists and oncologists, as its treatment continues to be a subject of controversy. Some experts advocate for bacillus Calmette-Guérin therapy and salvage cystectomy in case of progression, while others propose upfront cystectomy due to the considerable rates of disease progression and disease-specific mortality.[5,6]

Based on this background, there have been several attempts to substage pT1 urothelial carcinoma (UC) for risk stratification and to set appropriate treatment directives. A pT1 UC histoanatomic substaging system in relation to the muscularis mucosae (MM)/vascular plexus using either a 3-tiered (above [pT1a], into [pT1b], and below [pT1c]) or a 2-tiered

**Address for correspondence:* Department of Pathology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, 1071, Anyangcheon-ro, Yangcheon-Gu, Seoul, Republic of Korea. Tel: (+82) 10-9915-3252 (S.P.); E-mail: *spark0430@ewha.ac.kr* (S.P.)

(above [pT1a] and below [pT1b]) approach was presented, and several studies investigating its correlation with patient outcomes have been published.[7] Histoanatomic substaging has shown limitations in feasibility, technical challenges, and inconsistent prognostic ability due to the structural variations of the lamina propria layer and is not widely used.

In addition to this, an approach for pT1 UC micrometric substaging based on the depth of tumour infiltration in the submucosa has been proposed to identify patients at risk of cancer progression.[7] However, due to limitations often encountered in TURB specimens, such as poorly oriented and absent overlying mucosa, these approaches remain to be fully investigated.

Recently, the aggregate linear length of invasive carcinoma (ALLICA) with ≥2.3 mm cut-off measured by an optical micrometre has been considered the best predictor of progression to muscle invasive disease.[8]

In the current study, we sought to introduce a reproducible and easy-to-use substaging system by addressing the limitations of previous substaging systems. By evaluating the spatial relationship between the invasive carcinoma and muscularis propria (MP) in the TURB specimen, we attempted a risk stratification approach focusing solely on invasive UC below the MM in a TURB specimen (pT1b), and we aimed to examine the correlation between risk stratification through this new approach and the final tumour stage in radical cystectomy (RC).

MATERIALS AND METHODS

Patient selection

The present study was approved by the Institutional Review Board (IRB) at Ewha Womans University Medical Center (2023-12-006). The requirement for informed consent was waived by the IRB owing to the retrospective nature of the study. We retrospectively searched our pathology reports from 2017 to 2023 and identified cases diagnosed with subepithelial connective tissue invasion (pT1) in TURB specimens. Two pathologists (J.M.K and S.H) reviewed all applicable H&E slides of TURB specimens and corresponding RC specimens. We applied pT1 subcategorisation to TURB specimens using a 2-tiered approach (above the MM/vascular plexus [pT1a] and below the MM/vascular plexus [pT1b]).[7]

Cases that met any of the following criteria were excluded from this study:

1. Cases subcategorised as pT1a in TURB specimens.
2. Cases with cT2-cT4
3. Cases with the history of prior treatment (whether intravesical therapy or neoadjuvant chemotherapy)
4. Cases including clinically aggressive subtypes (micropapillary, plasmacytoid, and sarcomatoid) in TURB specimens.
5. Cases not including MP bundles in TURB specimens.
6. Cases not undergoing RC after TURB.
7. Cases with no residual carcinoma in RC specimens.

Finally, a cohort of 24 patients was included in our present study. Their clinical information, including age, sex, and time interval between TURB and RC, was collected. Tumours were graded according to the 2016 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs[9] and were staged according to the TNM system from the American Joint Committee on Cancer 8th Edition Cancer Staging Manual.[10] All methods were performed in accordance with the relevant guidelines and regulations, and Declaration of Helsinki.

New pT1b risk stratification development and histopathologic analyses

A previous study described pT1 substaging as beneficial in differentiating between pT1 tumours with definite small focal invasion and extensively invasive pT1 tumours, which may be very similar to pT2 tumours.[7] We observed that pT1b tumours often show patterns of invasion very close to or partially encasing the MP but that are non-diagnostic of pT2 invasion because the tumour nests do not completely encase intact MP bundles or show discohesive tumour cells infiltrating, dissecting into, or replacing MP bundles (FIG 1). Our approach was based on the hypothesis that such tumours would exhibit outcomes that differ from pT1b tumours without such features. We evaluated the tumour diameter and the proximity to MP from a "Tumour-MP (T-M) angle" perspective. The T-M angle was defined as the angle formed by two intersecting lines, one from the centre of one of the MP bundles to one end of the tumour aggregates nearby and the other from the centre of one of the MP bundles to the other end of the tumour aggregates nearby. We designated the straight angle (180 degrees) as the cutoff to encompass both tumour extensiveness and closeness to

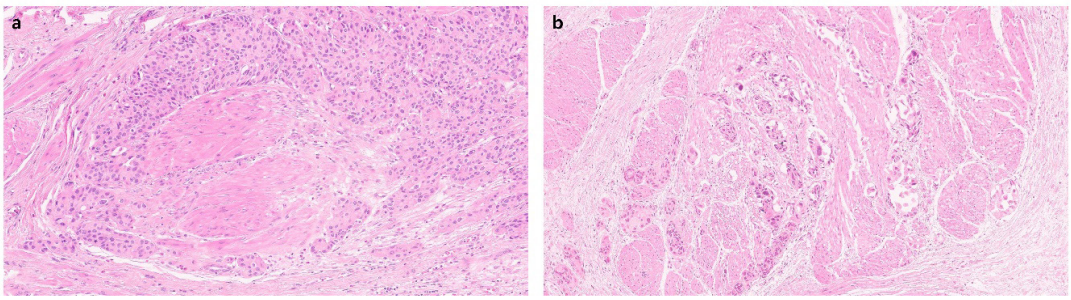

FIG. 1. Examples of muscularis propria (MP) invasion (pT2) at TURB. (a) Tumour nests completely encasing intact MP bundles (H&E, ×10). (b) Tumour cells infiltrating MP bundles (H&E, ×10).

the MP and it can be measured by an eyeball estimate without the need for any special tools. Based on this process, we devised the new pT1b risk stratification approach as follows:

(1) pT1b low-risk: T-M angle less than 180 degrees (acute and obtuse angles) (FIG 2a)
(2) pT1b high-risk: T-M angle greater than 180 degrees (reflex angle) (FIG 2b)

Statistical analysis

Clinicopathologic variables were compared using the Chi-square and two-sample t tests. Statistical analyses were performed using SPSS® software version 20 (SPSS Inc., Chicago, IL). A p-value <0.05 was considered statistically significant.

RESULTS

Sixteen of the 24 pT1b UC cases displayed ≤180 degrees T-M angles (pT1b low-risk), and 8 formed >180 degrees T-M angles (pT1b high-risk). The clinicopathologic characteristics of the two groups in the series of 24 patients are summarised in TABLE 1. In the pT1b low-risk group, the patients consisted of 14 men and 2 women with a mean age of 65 years (range, 47-75 years). In the pT1b high-risk group, the mean age of the patients was 70 years (range, 56-82 years) in 5 men and 3 women. The mean interval time from initial TURB to RC was 4 months (range, 1-24 months) and 2 months (range, 1-4 months) in the pT1b low-risk and pT1b high-risk groups, respectively. All 24 cases were high-grade invasive UC. Most cases were of the conventional type in the RC specimens of both groups (n=10 [62%] and n=5 [63%] in the pT1b low-risk and pT1b high-risk groups, respectively). A small subset of cases showed histologic subtypes in their RC specimens, including squamous differentiation (n=2), glandular differentiation (n=1), micropapillary (n=2), and plasmacytoid (n=1) in the pT1b low-risk group and squamous differentiation (n=2) and sarcomatoid (n=1) in the pT1b high-risk group. Three patients (34%) in the pT1b low-risk group showed aggressive subtypes, while only one patient (14%) in the pT1b high-risk group exhibited aggressive subtypes. Interestingly, in the pT1b low-risk group, patients who were upstaged in RC tended

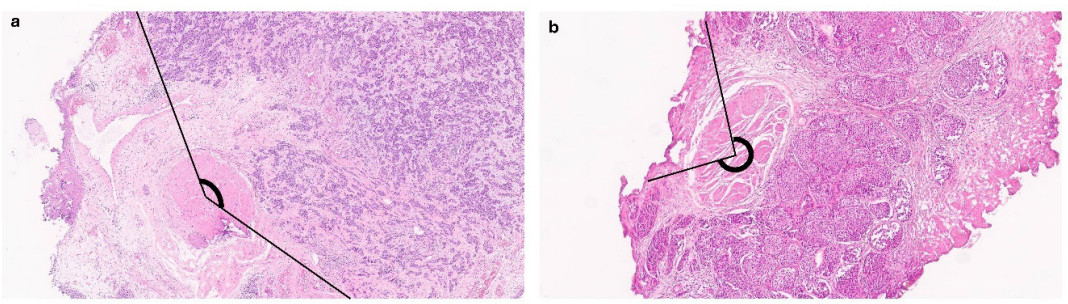

FIG. 2. Examples of the new pT1b risk stratification in our study. The "T-M angle" was defined as the angle formed by two intersecting lines, one from the centre of one of the muscularis propria (MP) bundles to one end of the tumour aggregates nearby and the other from the centre of one of the MP bundles to the other end of the tumour aggregates nearby. (a) Representative H&E slide of pT1b low-risk shows T-M angle less than 180 degrees (acute and obtuse angles) (H&E, ×10). (b) Representative H&E slide of pT1b high-risk shows T-M angle greater than 180 degrees (reflex angle) (H&E, ×10).

TABLE 1: Clinicopathologic features of pT1b low-risk group and pT1b high-risk group at TURB

	TURB						
Variables	**pT1b low-risk (n=16)**			**pT1b high-risk (n=8)**			**p value**
	Unchanged (n=7, 44%)	Upstaged (n=9, 56%)	p value	Unchanged (n=1, 12%)	Upstaged (n=7, 88%)	p value	
Age, mean (range), year	66 (47-73)	65 (57-75)	0.827	73	70 (56-82)	0.676	0.153
Sex			0.849			0.168	0.244
Male	6 (86%)	8 (89%)		0	5 (71%)		
Female	1 (14%)	1 (11%)		1 (100%)	2 (29%)		
Tumour stage on RC			<0.001			0.018	0.015
pT1	7 (100%)	0		1 (100%)	0		
pT2	0	3 (33%)		0	0		
pT3	0	6 (67%)		0	5 (71%)		
pT4	0	0		0	2 (29%)		
Tumour histologic subtype on RC			0.090			0.686	0.699
Conventional	6 (86%)	4 (44%)		1 (100%)	4 (57%)		
Squamous	0	2 (22%)		0	2 (29%)		
Glandular	1 (14%)	0		0	0		
Plasmacytoid	0	1 (12%)		0	0		
Micropapillary	0	2 (22%)		0	0		
Sarcomatoid	0	0		0	1 (14%)		
Time interval between initial TURB and RC, mean (range), month	4 (1-19)	5 (1-24)	0.993	1	2 (1-4)	0.283	0.448

RC Radical cystectomy; *TURB* Transurethral resection of the bladder

to show aggressive histologic subtypes compared to patients with unchanged tumour stage in RC ($p = 0.090$). Among the 24 pT1b cases included in our cohort, 16 (67%) were upstaged to pT2 or higher in their RC specimens. Notably, the pT1b high-risk group showed a significantly higher rate of advanced tumour stage (≥pT2) than the pT1b low-risk group in the RC specimens (88% vs. 56%, $p = 0.015$).

DISCUSSION

Our pT1b risk stratification approach revealed a significant association with the final pathologic tumour stage at RC. The pT1b high-risk group showed more frequent upstaging (≥pT2) at RC compared to the pT1b low-risk group.

Previous studies have shown upstaging of pT1 UC at rates ranging from 33-50%.[7] In our study, upstaging was identified in 67% of the total of 24 cases and in 88% of the pT1b high-risk group. Our study indicates a slightly higher rate of upstaging compared to the figures reported in previous literature, as we exclusively focused on pT1b invasive UC. It also suggests that if the T-M angle exceeds 180 degrees (pT1b high-risk), there is a strong probability of final tumour stage of pT2 or higher, implying that these patients could benefit from early radical cystectomy.

Several studies[11-16] demonstrated micropapillary, plasmacytoid, and sarcomatoid UC as histologic subtypes with a tendency toward advanced stage and cancer progression. Kamat et al.[17] reported a 67% disease progression to cT2 or higher in non-muscle-invasive micropapillary bladder cancer patients who underwent bladder-sparing therapy with intravesical bacillus Calmette-Guérin therapy. Based on this, we excluded cases showing aggressive histologic subtypes at TURB, as we believed that these subtypes could influence risk stratification based solely on the angle between the invasive carcinoma and MP. Interestingly, even after this exclusion, 3 of 16 (19%) pT1b low-risk cases and 1 of 8 (13%) pT1b high-risk cases showed aggressive subtypes in their RC specimens. In particular, in the pT1b low-risk group, there was a tendency to show a higher frequency of advanced final tumour stage at RC in cases exhibiting aggressive histologic subtypes in comparison to cases without aggressive histologic subtypes. This finding demonstrates that the TURB specimen does not adequately represent the entire tumour and implies that aggressive histologic subtypes may influence pT1b risk stratification based on the T-M angle between the invasive carcinoma and the MP. Consequently, the presence of aggressive histologic subtypes at TURB can be a contraindication when applying our new pT1b risk stratification approach for predicting muscle-invasive UC.

The risk stratification approach proposed in our study is the first to measure T-M angles rather than tumour length (tumour invasion depth or tumour diameter), distinguishing it from previously published studies with its focus on pT1 UC substaging systems. Although the irregular arrangement of the muscularis mucosae does not affect these substaging systems, measuring the depth of invasion is still challenging, especially in poorly oriented specimens. Moreover, accurate measurement of the distance between the overlying mucosal basement membrane and the deepest invasive tumour cells requires the presence of an overlying urothelium (or tumoural noninvasive component), which may not always be present in all tissue fragments, leading to potential limitations in measuring millimetric depth of invasion. In contrast to this, our risk stratification approach could be applied to 100% of TURB specimens. There are several limitations in this study. One is the small number of enrolled patients. The present study specifically focused on cases of pT1b invasive UC and only enrolled cases that did not show aggressive histologic subtypes in their TURB specimens. Also, since early cystectomy is not typically performed on pT1 conventional UC patients, the number of patients who can obtain a correlated final RC specimen is extremely limited. Another limitation is that this is a retrospective study including data collected from a single institution, resulting in a lack of randomisation and potential bias. Larger cohorts and further multicentre studies will be necessary to validate the findings of our small series.

CONCLUSION

The current study is the first to propose a pT1b risk stratification approach based on the T-M angles on TURB specimens. Pathological upstaging to muscle-invasive disease or beyond at RC was more frequent in pT1b high-risk patients than in pT1b low-risk patients. From the current data, risk stratification of pT1b is recommended to make a clinical decision regarding early RC. Further, larger and prospective studies are warranted to evaluate whether our pT1b risk stratification approach can be used for clinicians to move toward earlier aggressive treatment.

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REFERENCES

1. Andius P, Johansson SL, Holmäng S. Prognostic factors in stage T1 bladder cancer: tumour pattern (solid or papillary) and vascular invasion more important than depth of invasion. Urology 2007;70:758-762.
2. Brimo F, Wu C, Zeizafoun N, Tanguay S, Aprikian A, Mansure JJ, Kassouf W. Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. Hum Pathol. 2013;44(1):95-102.
3. Cheng L, Bostwick DG. Progression of T1 bladder tumours: better staging or better biology?: reply. Cancer 1999;86:910-912.
4. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol. 2003;169(1):96-100; discussion 100.
5. Kassouf W, Kamat AM, Zlotta A, *et al*. Canadian guidelines for treatment of non-muscle invasive bladder cancer: a focus on intravesical therapy. Can Urol Assoc J. 2010;4(3):168-173.
6. Segal R, Yafi FA, Brimo F, Tanguay S, Aprikian A, Kassouf W. Prognostic factors and outcome in patients with T1 high-grade bladder cancer: can we identify patients for early cystectomy?. BJU Int. 2012;109(7):1026-1030.
7. Paner GP, Montironi R, Amin MB. Challenges in Pathologic Staging of Bladder Cancer: Proposals for Fresh Approaches of Assessing Pathologic Stage in Light of Recent Studies and Observations Pertaining to Bladder Histoanatomic Variances. Adv Anat Pathol. 2017;24:113-127.
8. Leivo MZ, Sahoo D, Hamilton Z, *et al*. Analysis of T1 Bladder Cancer on Biopsy and Transurethral Resection Specimens: Comparison and Ranking of T1 Quantification Approaches to Predict Progression to Muscularis Propria Invasion. Am J Surg Pathol. 2018;42:e1-e10.
9. Ulbright TM, Amin MB, Balzer B, *et al*. WHO Classification of Tumours of the Urinary System and Male Genital Organs. In Moch H, Humphrey PA, Ulbright TM, Reuter VE, editors, WHO Classification of Tumours of the Urinary System and Male Genital Organs.. 4 ed. Vol. 8. 2016. p. 189-226
10. Bochner B, Hansel D, Efstathiou J, *et al*. Urinary Bladder. In: Mahul B. Amin SBE, Frederick L. Greene, David R. Byrd, Robert K. Brookland, Mary Kay Washington, Jeffrey E. Gershenwald, Carolyn C. Compton, Kenneth R. Hess, Daniel C. Sullivan, J. Milburn Jessup, James D. Brierley, Lauri E. Gaspar, Richard L. Schilsky, Charles M. Balch, David P. Winchester, Elliot A. Asare, Martin Madera, Donna M. Gress, Laura R. Meyer (ed), AJCC Cancer Staging Manual: Springer Cham; 2017:757-765.
11. Wright JL, Porter MP, Li CI, Lange PH, Lin DW. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. Cancer 2006;107:721-728.
12. Wang J, Wang FW, Lagrange CA, Hemstreet Iii GP, Kessinger A. Clinical features of sarcomatoid carcinoma (carcinosarcoma) of the urinary bladder: analysis of 221 cases. Sarcoma 2010;2010.
13. Dayyani F, Czerniak BA, Sircar K, *et al*. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. J Urol. 2013;189(5):1656-1661.
14. Kamat AM, Gee JR, Dinney CP, *et al*. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. J Urol. 2006;175:881-885.
15. Ghoneim IA, Miocinovic R, Stephenson AJ, *et al*. Neoadjuvant systemic therapy or early cystectomy? Single-center analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.
16. Compérat E, Roupret M, Yaxley J, *et al*. Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. Pathology 2010;42:650-654.
17. Kamat AM, Dinney CP, Gee JR, et al. Micropapillary bladder cancer: a review of the University of Texas M. D. Anderson Cancer Center experience with 100 consecutive patients. Cancer 2007;110:62-67.