



Stratifying risk for multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors in non-muscle-invasive bladder cancer

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Purpose: The current stratification of risk groups regarding recurrence and progression of non-muscle-invasive bladder cancer (NMIBC) is problematic. We aimed to assess the long-term outcome and risk of multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors after transurethral resection of the bladder tumor (TURBT).

Materials and Methods: We categorized 1,621 patients with NMIBC who underwent TURBT into four risk groups according to the European Association of Urology (EAU) guidelines as follows: low-risk, intermediate-risk, high-risk, and study group. The overall, cancer-specific, disease recurrence-free, and disease progression-free survival rates were estimated by using the Kaplan–Meier method. Then, the impact of risk group was assessed by using a multivariable Cox regression model.

Results: The study group comprised 52 patients (3.2%) within a mean follow-up of 64.8 months. The disease recurred and progressed in 41 (78.8%) and 7 (13.5%) patients, respectively. Among the four groups, the study group showed the highest risk for 10-year recurrence after TURBT. The disease progression risk in the study group was between that of the intermediate- and high-risk groups. Cancer-specific and all-cause deaths occurred in one and four patients in the study group, respectively. The study group had a higher risk for disease recurrence than did the high-risk group; however, it did not have a higher risk for disease progression than in the high-risk group.

Conclusions: Multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors carry a higher risk for disease recurrence, but not progression, than in the EAU high-risk group of NMIBC.

Keywords: Outcome; Risk assessment; Urinary bladder neoplasms

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INTRODUCTION

Urothelial carcinoma of the bladder (UCB) is the most common cancer of the urinary tract [1]. More than 70% of

patients with UCB have non-muscle-invasive bladder cancer (NMIBC) confined to the mucosa or submucosa of the bladder. Transurethral resection of the bladder tumor (TURBT) is both diagnostic and therapeutic for patients with NMIBC

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[2]. After TURBT, the recurrence rate at 1 year is about 15% to 70%, and the progression rate at 5 years is approximately 7% to 40% in patients without postoperative intravesical bacillus Calmette–Guérin (BCG) therapy [3]. The key to improving the prognosis of NMIBC is to prevent recurrence and progression.

NMIBC includes a diverse spectrum of diseases; thus, the probabilities of disease recurrence and progression in NMIBC differ substantially [2,4]. Current risk group stratification with regard to the recurrence and progression of NMIBC is problematic. Some investigations have provided a broad category for recurrence and progression, although the significance of the prognostic factors for recurrence and progression differ [5,6]. The European Organization for Research and Treatment of Cancer (EORTC) reported a scoring system for predicting the risk for recurrence and progression in a patient with NMIBC [7]. The scoring system includes simple tables that provide easy calculation of an NMIBC patient's probability of recurrence and progression at 1 and 5 years after TURBT with regard to clinicopathological factors. The European Association of Urology (EAU) NMIBC guidelines introduced risk stratification based on prognostic factors and risk tables of the EORTC to facilitate management and follow-up recommendations [2]. The American Urological Association (AUA)/Society of Urologic Oncology (SUO) guidelines also presented risk stratification in three groups, incorporating the effect of prior intravesical BCG instillation on prognosis [8]. Despite similarities between the EAU and AUA risk stratifications, multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors are categorized into high-risk groups according to the EAU guidelines but as intermediate risk according to the AUA/SUO guidelines. Therefore, the present study aimed to assess the long-term outcomes and estimate the proper risk for multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors after TURBT.

MATERIALS AND METHODS

1. Ethical approval and informed consent

This study was approved by the Seoul National University Hospital (SNUH) Institutional Review Board (approval number: 1610-145-806). This study was a retrospective analysis that used patients' medical records; thus, it did not affect the patients' treatment or progress. The patient population varied from patients who had been followed up to those who had died, so it was difficult to obtain consent. For this reason, the SNUH IRB agreed to waive the need for informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

2. Patient selection and data collection

The patients were extracted from a single-institutional database of 1,731 patients with NMIBC who underwent TURBT between January 1993 and December 2013 based on the EAU guideline recommendations. Postoperative intravesical therapy was also performed according to the surgeon's discretion or the guideline recommendations. Cases of upper tract urinary cancer that were diagnosed previously or at the time of TURBT were excluded. None of the patients had prostatic stromal invasion or metastatic UCB at diagnosis. Therefore, only 1,621 patients were included in the study. Based on the EAU guidelines, patients with NMIBC were categorized into four risk groups [2]:

- Low-risk group: primary, solitary, Ta, G1 tumors < 3 cm, and no carcinoma *in situ* (CIS)
- Intermediate-risk group: all tumors did not meet the criteria of the two adjacent categories (the low- and high-risk groups)
- High-risk group: any tumor (T1, G3, CIS)
- Study group: multiple, recurrent, and large (≥ 3 cm) Ta and G1/G2 tumors

3. Pathologic review

The tumor stage and grade were reviewed and determined by uropathologists according to the 2009 American Joint Committee on Cancer TNM staging system [9] and the 1973 World Health Organization (WHO) grading system. For comparison, we also used the updated grading system of the WHO/International Society of Urological Pathology 2004/2016 [10].

4. Follow-up

Patient follow-up included history taking, physical examination, urinary cytology, and standard cystoscopy (the initial cystoscopy 3 months after TURBT, every 3 to 6 months for 2 years, every 6 months thereafter until 5 years, and then yearly) [2]. Computed tomography (CT) was performed at diagnosis and yearly thereafter to evaluate the upper urinary tract. If the tumor recurred, the patient underwent a new TURBT. In the case of positive urine cytology, bladder mapping biopsies, and prostatic urethral resection were performed. Disease recurrence was defined as initial pathologically confirmed tumor relapse in the urinary bladder or prostatic urethra. Disease progression was defined as tumor relapse in the urinary bladder or prostatic urethra at a higher T stage. The cause of death was determined by managing physicians through medical record review and was confirmed with death certificates. The new appearance of tumors in the upper urinary tract was considered to be a

new primary tumor, not as recurrence.

5. Statistical analyses

Overall, cancer-specific, disease recurrence-free, and disease progression-free survival curves were assessed between the four risk groups by use of the Kaplan–Meier method. The log-rank test was used to compare survival between the risk groups. A multivariable Cox regression model was used to assess the impact of risk stratification on disease recurrence and progression. Statistical analyses were performed using SPSS Statistics software (version 22; IBM Corp, Armonk, NY, USA).

RESULTS

1. Clinicopathologic features

Table 1 presents the characteristics of the 1,621 patients. Within a median follow-up of 55.0 months (interquartile range, 27.0–89.0 months), 133 (8.2%), 702 (43.3%), 734 (45.3%), and 52 (3.2%) patients were categorized into the low-risk, intermediate-risk, high-risk, and study groups based on the EAU risk stratification. All 327 patients who received postoperative BCG therapy were scheduled for maintenance therapy. Histologic variants were detected in 39 patients (2.4%), with the most common being aberrant differentiation of squamous cell carcinoma (19, or 1.2%), followed by glandular (10, or 0.6%) and micropapillary (4, or 0.2%) urothelial carcinomas.

2. Disease recurrence

Of the 880 patients (54.3%) with recurrence, 871 experienced recurrence within 5 years after TURBT. Rates of disease recurrence-free survival differed between risk groups and the study group (Fig. 1). There were significant differences between the low- and intermediate-risk groups ($p<0.001$), intermediate- and high-risk groups ($p<0.001$), and high-risk and study groups ($p=0.004$). Multivariable Cox regression analysis was conducted with adjustments for sex, age, histologic variants, and postoperative intravesical therapy (Table 2). The intermediate-risk (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.22–2.26), high-risk (HR, 2.23; 95% CI, 1.64–3.02), and study groups (HR, 3.71; 95% CI, 2.43–5.65) carried a significantly higher risk for disease recurrence than did the low-risk group ($p<0.05$). However, the HR between the study and high-risk groups was not statistically significant ($p=0.060$; HR, 1.369; 95% CI, 0.987–1.901).

3. Disease progression

Of the 152 patients (9.4%) with disease progression, 143

experienced progression within 5 years after TURBT. Of the seven patients with disease progression in the study group, two patients showed progression more than 10 years after TURBT. Disease progression-free survival differed between the risk groups. There was a significant difference between the intermediate-risk and study groups ($p=0.031$), but not between the low- and intermediate-risk groups ($p=0.189$) or between the study and high-risk groups ($p=0.304$). In the age-adjusted multivariable Cox regression analysis, the high-risk group (HR, 7.27; 95% CI, 2.30–22.95) had a significantly higher risk for progression than did the low-risk group ($p=0.001$), but the intermediate-risk group (HR, 1.87; 95% CI, 0.57–6.12) did not ($p=0.304$). The risk in the study group (HR, 4.94; 95% CI, 1.18–20.70) was lower than that of the high-risk group and higher than those of the low-risk ($p=0.029$) and intermediate-risk groups.

4. Overall survival and cancer-specific survival

Among the entire cohort, 296 patients (18.3%) died, and 258 patients died within 10 years after TURBT. Overall survival rates were significantly different between the intermediate- and high-risk groups ($p<0.001$) but not between the low- and intermediate-risk groups ($p=0.369$). Of all the mortality cases, 126 patients died of UCB and 114 patients died after TURBT within 10 years. Cancer-specific survival differed between the risk groups. There was a significant difference between the intermediate- and high-risk groups ($p<0.001$) but not between the low- and intermediate-risk groups ($p=0.183$).

5. Effect of postoperative intravesical therapy on outcome

BCG therapy is most commonly used for intravesical instillation. In the intermediate-risk group, the postoperative BCG instillation group showed better disease-specific survival than did the non-instillation group according to the Kaplan–Meier curve (log-rank $p=0.004$). In the high-risk group, the Kaplan–Meier curve showed better overall survival (log-rank $p=0.024$) and disease progression-free survival (log-rank $p<0.001$). Mitomycin C instillation showed the best disease recurrence-free survival in the high-risk group (log-rank $p=0.003$). In the study group, postoperative intravesical therapy did not affect oncological outcomes.

6. Association of other pathologic factors with the prognosis of non-muscle-invasive bladder cancer

As shown in Table 1, 53 patients experienced newly developed upper tract urothelial carcinoma (UTUC) during the

Table 1. Clinicopathologic features overall and by risk stratification group

Characteristic	Total	Low risk	Intermediate risk	High risk	Study group ^a
No. of patients	1,621 (100.0)	133 (8.2)	702 (43.3)	734 (45.3)	52 (3.2)
Male, sex	1,372 (84.6)	105 (78.9)	599 (85.3)	626 (85.3)	42 (80.8)
Age (y)	63.2±11.4	59.8±12.3	62.7±11.5	64.5±10.8	60.3±12.2
T stage					
Ta	927 (57.2)	133 (100.0)	702 (100.0)	40 (5.4)	52 (100.0)
Tis	65 (4.0)	-	-	65 (8.9)	-
T1	629 (38.8)	-	-	629 (85.7)	-
WHO grade					
G1	294 (18.1)	133 (100.0)	142 (20.2)	5 (0.7)	14 (26.9)
G2	1,057 (65.2)	-	560 (79.8)	459 (62.5)	38 (73.1)
G3	270 (16.7)	-	-	270 (36.8)	-
Histologic grade					
Low	826 (51.2)	133 (100.0)	546 (78.2)	113 (15.5)	34 (65.4)
High	786 (48.8)	-	152 (21.8)	616 (84.5)	18 (34.6)
Histologic variant	39 (2.4)	-	6 (0.9)	33 (4.5)	-
Recurrent	388 (23.9)	-	158 (22.5)	178 (24.3)	52 (100.0)
Tumor size					
Small (<3 cm)	1,183 (73.0)	133 (100.0)	566 (80.6)	484 (65.9)	-
Large (≥3 cm)	438 (27.0)	-	136 (19.4)	250 (34.1)	52 (100.0)
No. of tumors					
Single	842 (51.9)	133 (100.0)	389 (55.4)	320 (43.6)	-
2–7	498 (30.7)	-	224 (31.9)	234 (31.9)	40 (76.9)
≥8	281 (17.3)	-	89 (12.7)	180 (24.5)	12 (23.1)
Postoperative instillation	382 (23.6)	2 (1.5)	60 (8.5)	310 (42.2)	10 (19.2)
BCG	327 (20.2)	0 (0.0)	42 (6.0)	278 (37.9)	7 (13.5)
MMC	55 (3.4)	2 (1.5)	18 (2.6)	32 (4.4)	3 (5.8)
Disease recurrence	880 (54.3)	49 (36.8)	360 (51.3)	431 (58.7)	41 (78.8)
5 y	840 (51.8)	40 (30.1)	339 (48.3)	420 (57.2)	41 (78.8)
10 y	871 (53.7)	46 (34.6)	354 (50.4)	430 (58.6)	41 (78.8)
Disease progression	152 (9.4)	4 (3.0)	31 (4.4)	110 (15.0)	7 (13.5)
5 y	119 (7.3)	1 (0.8)	19 (2.7)	95 (12.9)	4 (7.7)
10 y	143 (8.8)	3 (2.3)	29 (4.1)	106 (14.4)	5 (9.6)
UTUC occurrence	53 (3.3)	2 (1.5)	14 (2.0)	32 (4.4)	5 (9.6)
10 y	49 (3.0)	1 (0.8)	12 (1.7)	31 (4.2)	5 (9.6)
Death due to cancer	126 (7.8)	3 (2.3)	30 (4.3)	92 (12.5)	1 (1.9)
10 y	114 (7.0)	1 (0.8)	25 (3.6)	87 (11.9)	1 (1.9)
All-cause death	296 (18.3)	15 (11.3)	101 (14.4)	176 (24.0)	4 (7.7)
10 y	258 (15.9)	11 (8.3)	87 (12.4)	156 (21.3)	4 (7.7)

Values are presented as number (%) or mean±standard deviation.

WHO, World Health Organization; BCG, bacillus Calmette–Guérin; MMC, mitomycin C; UTUC, upper tract urothelial carcinoma.

^a:The study group was categorized as having multiple, recurrent, and large (≥3 cm) Ta, G1/G2 tumors.

follow-up period. Kaplan–Meier survival curves showed significantly different 10-year UTUC-free survival between the risk groups, except between the high-risk and study groups (p=0.074); the study group showed the highest risk. Histological variants were found in 39 patients in the entire cohort (6 and 33 patients in the intermediate- and high-risk groups, respectively). Squamous cell carcinoma was the most common type of cancer. Kaplan–Meier disease recurrence-free

survival curves were not significantly different between the histologic variants in the intermediate- and high-risk groups.

DISCUSSION

In the present study, we found that the target study population had a higher risk for disease recurrence, but not progression, than did the high-risk EAU group. To the best

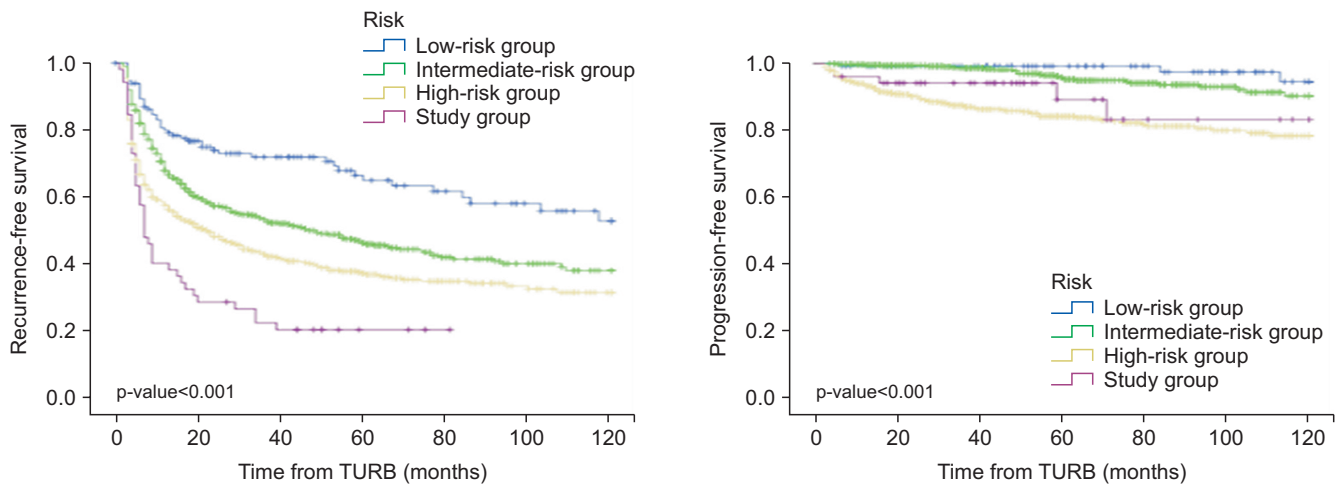


Fig. 1. Kaplan–Meier curves presenting disease recurrence-free and disease progression-free survival in 1,621 patients with non-muscle-invasive bladder cancer, categorized by European Association of Urology risk groups. TURB, transurethral resection of the bladder tumor.

Table 2. Multivariable Cox regression analyses for predicting disease recurrence and progression

EAU risk category	Disease recurrence			Disease progression		
	HR	95% CI	p-value	HR	95% CI	p-value
Low		Referent			Referent	
Intermediate	1.66	1.22–2.26	0.001	1.87	0.57–6.12	0.304
High	2.23	1.64–3.02	<0.001	7.27	2.30–22.95	0.001
Study group	3.71	2.43–5.65	<0.001	4.94	1.18–20.70	0.029

The data were adjusted by sex, age, histologic variants, and postoperative intravesical therapy.

HR, hazard ratio; CI, confidence interval; EAU, European Association of Urology.

of our knowledge, this study is the first to assess risk stratification and the long-term outcomes of multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors.

Management of recurrence and progression is the most important issue for patients with NMIBC. However, current standard surveillance methods are based on invasive and uncomfortable procedures, such as cystoscopy [8,11]; thus, risk stratification of patients is essential to optimize surveillance planning. Several prognostic factors for recurrence and progression of NMIBC have been studied. The well-established prognostic factors for disease recurrence are the prior recurrence rate, tumor size, and the number of tumors [7,9,12]. Concerning disease progression, the T stage and tumor grade are significant prognostic factors in several risk models [13].

Most guidelines share similar pathologic and clinical risk factors for recurrence and progression of NMIBC; however, there are differences in risk classification. The EAU categorized multiple, recurrent, and ≥ 3 -cm Ta, G1/G2 tumors into the high-risk group, even though these tumors fall into the intermediate-risk group according to the AUA risk stratification [8]. Although the intermediate-risk group would be conservatively managed with intravesical therapy, the high-risk group may be offered BCG therapy as a first option,

and if that fails, radical cystectomy may be considered [14]. Therefore, understanding the prognosis of multiple, recurrent, and ≥ 3 -cm Ta, G1/G2 tumors, which is the focus of this research, and categorizing the risk group of these tumors are essential.

We unexpectedly found that the risk for recurrence was higher in the study group than in the high-risk group. The fact that the study group had all three representative prognostic factors of recurrence, a prior recurrence rate, multiple tumors, and size ≥ 3 cm, supports this unexpected result. After in-depth review of the EORTC risk table, among the risk factors for recurrence, we found that three (the number of tumors, tumor size, and prior recurrence rate) had a greater impact than the other risk factors (the T stage, presence of CIS, and tumor grade) [7]. Another scoring model reported by the Club Urológico Español de Tratamiento Oncológico (CUETO) [15] included two clinical parameters (age and sex) and four pathologic parameters (number of tumors, prior recurrence history, presence of CIS, and tumor grade) as risk factors for recurrence. Among these parameters, prior recurrence history and the number of tumors are the most important parameters. Both risk tables agreed with the fact that more risk factors lead to worse recurrence-free survival

[7,15]. These previous study findings support our research conclusions that even in the Ta group of NMIBC, patients with all three important risk factors show a higher risk for disease recurrence.

Although the study group showed a higher recurrence rate than did the EAU high-risk group, it did not show worse progression than the EAU high-risk group. Based on the EORTC risk table [7], the weights of risk factors for progression differ from those for recurrence. For NMIBC progression, the T stage, presence of CIS, and tumor grade are more important than the number of tumors, tumor size, or prior recurrence rate. In the CUETO risk table, the most important risk factor for progression is the tumor grade, and prior recurrence history and number of tumors are weighted less than they are for recurrence [15]. We assume that the prognostic factors included in the study group (the prior recurrence rate, multiple tumor number, and size >3 cm) are not the important risk factors for NMIBC progression.

During the 10-year follow-up, recurrence and progression occurred in 880 (54.3%) and 152 (9.4%) patients with NMIBC, respectively. All patients with recurrence in the study group experienced recurrence within 5 years after TURBT. Although disease recurrence is common in NMIBC, progression and mortality are rare. This study showed a slightly lower potential progressiveness in the high-risk group than in the literature [16]. This is thought to be attributed to the isolation of the study group from the high-risk group. During the follow-up period, 296 patients (18.3%) died in the present study. The overall survival rate in our study was higher than that in another long-term follow-up study [17]. Balan et al. [17] reported an overall survival rate of 37.8% (62/164 patients) in patients with Ta G1/G2 NMIBC cancer. However, cancer-specific survival was also better than that in previous studies that reported a mean cancer-specific survival of 30% for NMIBC [18]. Because we used a strict follow-up protocol using cystoscopy and CT, survival with high recurrence and lower progression might have been due to the early detection of bladder cancer recurrence. However, further evaluation is needed to clarify this discrepancy in a well-designed prospective study.

Because of the small number of mortality cases in the study group (a single case [1.9%] of cancer-specific death), we did not include the study group in estimating the Kaplan–Meier curves for 10-year survival. The high-risk group showed a substantial rate of 10-year cancer-specific deaths, 87 patients (11.9%), at a significantly higher risk than in the other two groups. The insignificant difference in cancer-specific death between the low- and intermediate-risk groups is thought to be attributed to low rates of mortality in Ta

NMIBC.

In the current study, 1 (0.8%) and 12 (1.7%) patients in the low- and intermediate-risk groups, respectively, experienced UTUC within 10 years after TURBT. Seven patients presented with left-sided UTUC. Wright et al. [16] reported a UTUC rate of 0.8% more than 10 years after the diagnosis of UCB, and UTUC rates of 71% and 94% were shown within 5 and 10 years in patients with NMIBC in the low- and intermediate-risk groups, respectively. Similarly, 71.4% (10/14) and 85.7% (12/14) of UTUCs occurred within 5 and 10 years in the intermediate-risk group after TURBT in our study. Therefore, frequent radiologic studies of the upper urinary tract might not have been needed in the non-high-risk group of patients with NMIBC, which remained UTUC-free for 5 years. Histologic variants were detected in 39 patients, with the most common being aberrant differentiation of squamous cell carcinoma, followed by glandular and micropapillary urothelial carcinomas. Nine patients (47.4%), five patients (50%), and one patient (25%) with urothelial carcinoma with squamous differentiation showed 10-year recurrence; two patients (10.5%), zero patients, and one patient (25%) with urothelial carcinoma with glandular differentiation showed 10-year progression; and two patients (10.5%), zero patients, and one patient (33.3%) with micropapillary urothelial carcinoma showed 10-year cancer-specific death. This is comparable to the results of the high-risk group for NMIBC in our study. Kim et al. [19] reported that survival for urothelial carcinoma with squamous or glandular differentiation was comparable to that for pure urothelial carcinoma. A review of micropapillary variants from the University of Texas MD Anderson Cancer Center showed poor prognosis that required early radical cystectomy, which was in contrast with the findings of Fairey et al. [20], who reported similar outcomes of micropapillary urothelial carcinoma and urothelial carcinoma. It seems that the histological variants of NMIBC in the present study were not very aggressive; however, because of the small number of cases, further study is warranted concerning the prognosis of NMIBC in a large cohort.

The present study had several limitations. First, this study was retrospective and was designed in a single institution with multiple surgeons, which creates an inevitable risk of bias. Second, the small sample size of the target population was another major limitation. Because of the small target population, we needed a large NMIBC population. Since the old cohort had several limitations, including a lack of data and changes in guideline recommendations, we used a historical cohort from 1993 to 2013 to collect a large number of NMIBC cases. We noted many problems associated with using an old cohort, such as the inability to obtain clear

information on the intravesical therapy dose and cycle, and differences in management strategies, such as a relatively small number of repeated TURBTs. Third, the relatively small number of BCG treatments performed was another important limitation. However, this study focused on clinicopathologic features that have been widely assessed and reported as prognostic factors in previous investigations.

CONCLUSIONS

Multiple, recurrent, and large (≥ 3 cm) Ta, G1/G2 tumors carried a higher risk for disease recurrence than in the EAU high-risk group of NMIBC, but not a higher risk for disease progression than in the EAU high-risk group of NMIBC. We cannot reach a firm conclusion based on our study findings because of the limited number of patients in the study group; further large-scale studies are needed to verify our results.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Ja Hyeon Ku. Data acquisition: Jae Hyun Jung. Statistical analysis: Jungyo Suh. Data analysis and interpretation: Jae Hyun Jung and Jungyo Suh. Drafting of the manuscript: Jae Hyun Jung. Critical revision of the manuscript: Jungyo Suh. Obtaining funding: Ja Hyeon Ku. Administrative, technical, or material support: Cheol Kwak and Hyeon Hoe Kim. Supervision: Cheol Kwak and Hyeon Hoe Kim. Approval of the final manuscript: all authors.

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