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Original Article

Resection marginal width and positive margin of transurethral resection of bladder tumor are associated with bladder cancer early recurrence

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Abstract: Objective: To investigate the relationship between the marginal width of transurethral resection of bladder tumor (TURBT) and bladder cancer recurrence to define the ideal resection marginal width. Methods: Medical records of 143 patients with non-muscle invasive bladder cancer were retrospectively reviewed. The patients were divided into three groups according to the width of resection margin. All patients were followed for a minimum of 24 months to investigate the timing of tumor recurrence and recurrence *in situ*. Log-rank test, Cox regression, and Kaplan-Meier estimator were performed to compare the three groups, respectively. Results: Tumor size, primary/recurrent tumor, pathological grade, resection marginal width, and margin status affected the tumor recurrence. The same factors also affected the tumor recurrence *in situ*. The recurrence and the recurrence *in situ* rate of 10 mm marginal width group were significantly higher than 15 mm and 20 mm marginal width groups ($P = 0.005$); similarly, the recurrence and the recurrence *in situ* rate in patients with positive margin were higher than those with negative margin ($P < 0.001$). The postoperative complication rate in 20 mm marginal width group was significantly higher compared with the 10 mm and 15 mm groups ($P = 0.041$). Conclusions: The positive margin of TURBT is associated with increased risk of both tumor recurrence and recurrence *in situ*. We recommend a marginal width of 15 mm as the preferable standard, based on reduced the rates of recurrence, without any significant increase in the postoperative complications found in this group.

Keywords: Non-muscle invasive bladder cancer, transurethral resection of bladder tumor, tumor margin, tumor recurrence, tumor recurrence *in situ*

Introduction

Bladder cancer (BC) is 9th most common malignant tumors in the world. The majority (70%) of the cases of BC are diagnosed with non-muscle invasive bladder cancer (NMIBC) [1]. Presently, the standard first-line treatment for NMIBC is transurethral resection of bladder tumor (TURBT), followed by instillation of intravesical chemotherapy [2]. The key to a high-quality and successful TURBT is the complete removal of bladder tumor without leaving any residual tumor. However, TURBT is not able to prevent recurrence due to either presence of residual disease or instability of the urothelium, making it a clinically important problem that needs urgent attention. Although urothelial carcinoma is regarded as a field change disease, early recurrence is mostly a result of residual cancer, infinite proliferation or re-growth of the tumor or intra-operative tumor cell cultivation. The post-operative recurrence rate of NMIBC is as high as 15%-70% within one year, progressing to about 7%-40% within 5 years, including 30%-81% of recurrence *in situ* (recurrence at the site of previous tumor resection) [3-5]. The tumor residual rate in patients undergoing repeat TURBT within 2-6 weeks is reported to 30%-75% [6]. Presently, a number of nomograms are available to predict the rate of recurrence and

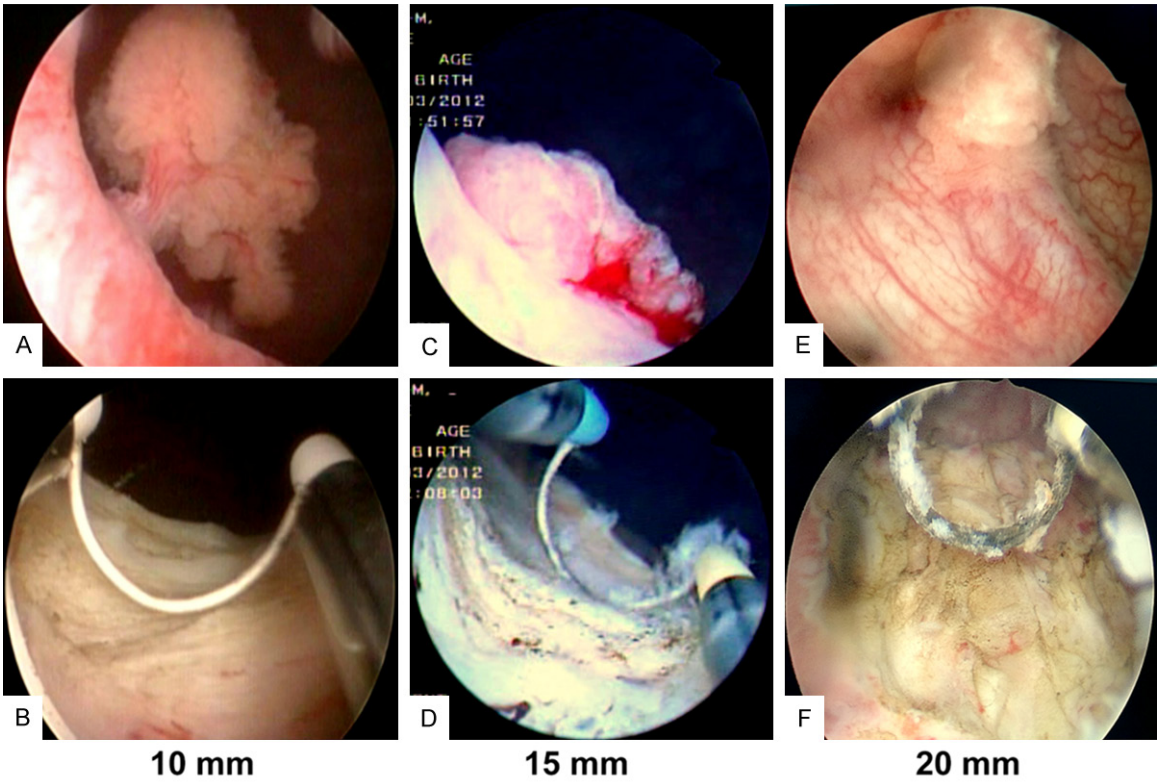

Figure 1. Images of bladder tumors were captured pre-operatively under cystoscopy (A, C and E). Bladder tumors were resected by applying TURBT, and surgical fields, as well as different surgical margins, were post-operatively displayed (B for 10 mm margin, D for 15 mm margin and F for 20 mm margin, respectively).

progression. These nomograms are based on tumor number, size, grade, T stage, concomitant CIS and prior recurrence rate [7, 8].

TURBT is the cornerstone of management of NIMBC. A complete TURBT is the key to reducing early postoperative recurrence of BC. Presently, no reliable clinical determinant can confirm the complete removal at TURBT. The overall accuracy of CT scan for local staging is only 50% [9]. The presence of bladder detrusor muscle in the surgical specimen helps to evaluate the efficacy of the TURBT surgery and guide repeat-TURBT [10-12]. Adjunctive aids used during transurethral resection, i.e. narrow-band imaging and fluorescence cystoscopy, have helped in better identification of local disease, but their use is limited due to cost constrains [13]. For high-grade bladder tumor, repeat-TURBT has been shown to decrease tumor recurrence and to upstage the disease in up to 40% [14]. However, even after TURBT, where the resection depth reached the visible bladder detrusor muscle and with a negative muscular pathological report, some patients later progressed to the muscle-invasive stage and required radical cystectomy. Specimens from these patients reported a residual tumor rate of up to 41.2% [6, 15, 16]. Thus, it is logical to not only completely remove the tumor but also resect beyond the visible margin [17]. Presently, the ideal bladder tumor resection marginal width to reduce the tumor recurrence is not clearly specified in the guidelines. Kolozsy et al. found that 20 mm marginal width could reduce the tumor residual rate to less than 35% [18]. Herr et al. found that 20 mm marginal width led to more complications such as post-operation bleeding, ureter orifices injury, and bladder perforation or rupture [19]. Therefore, presently, the tumor marginal width in TURBT does not have a unified standard. This ambiguity motivated us to interrogate a more reasonable resection margin.

In this study, patients with NIMBC who underwent TURBT were reviewed to investigate the relationship of resection marginal width and tumor recurrence (entire bladder) and recurrence *in situ* (local recurrence at the site of the

previous resection). We also looked at the complication and morbidity rate to determine the ideal resection margin for TURBT.

Material and methods

Clinical information

A retrospective chart review was performed for 161 patients undergoing TURBT for non-muscle invasive (pTa or pT1) urothelial carcinoma at the Department of Urology, Tongji Hospital (China), from January 2011 to December 2013. Eighteen patients were excluded. One hundred and forty-three patients undergoing TURBT (only once) were finally included in this study. The exclusion criteria were as followed: (1) the patients with follow-up of fewer than 24 months, (2) those who did not receive the standard of care, i.e. intravesical chemotherapy, (3) associated diagnosis of carcinoma *in situ* (*Tis*), (4) abnormal blood coagulation profile or blood glucose, raised creatinine and poor cardiopulmonary function. This study was approved by the local independent ethics committee of the Tongji Hospital (No.TJ-C20141216).

Surgical procedure

Patients under general anesthesia were placed in dorsal lithotomic position. The Karl-Storz white light electrocautery resection system was used. During the TURBT, we estimated the distance of the margin by using the width of the loop as a reference, and calculated the distance from the gross tumor by multiplying this distance (5 mm). The margin of resection was marked circumferentially around the tumor by fulguration. The diathermy was used to dissect the visible tumor tissue, followed by resection of deep detrusor muscular tissues, and finally, the areas around the tumor lateral to the excised tumors were resected. Based on the finding noted on the surgical report, we divided the patients into three groups with the margin of resection 10 mm, 15 mm and 20 mm away from the edge of resected tumors (**Figure 1**). Tumors with diameters less than 1 cm were resected en-bloc, and larger lesions were fractionated. In case of multiplicity, the same strategy or resection margin was applied for each tumor. For pathological reporting of positive surgical margin, the last circumferential TURBT chip furthest away from the tumor was separately submitted for histology. All pathology specimens were initially evaluated by three junior pathologists and later reviewed by a single senior pathologist.

One hundred and thirty-four (94%) patients underwent single instillation of chemotherapy (50 mg epirubicin hydrochloride/40 ml) within 24 h after TURBT. Nine patients (6%) with suspected bladder perforation underwent delayed instillation of intravesical chemotherapy on day 7 after TURBT. The patients were stratified and underwent auxiliary treatment according to the postoperative risk (2012 European Association of Urology Guidelines for risk stratification). Low-risk patients no longer underwent chemotherapy. Moderate or high-risk patients underwent intravesical instillation chemotherapy, once a week for the first 8 weeks, then once a month for 10 months. All the patients were followed up for 24 months [20]. The first surveillance cystoscopy was performed in the third month after surgery and then repeated once every 3 months. The follow-up was terminated if the tumor recurrence happened. Local recurrence single or multiple were defined as recurrence *in situ,* if they occurred at the same location as the primary tumor after initial resection, and recurrence if it occurred elsewhere in the bladder. For multiple lesions, recurrence was regarded as local recurrence if tumor appeared at the same location as one of the sites of primary tumors [21]. The variables studies included the following: (1) postoperative pathological reports, (2) intra-operative bladder perforation or rupture and postoperative bleeding evaluated by using the Clavien-Dindo classification system.

Statistical analysis

The parametric data are presented as the mean ± standard deviation. The categorical data is compared by Chi-square test. The Log-rank test was used to compare tumor recurrence and recurrence *in situ* among the three groups. With tumor recurrence as a termination event, the tumor size, primary/recurrent, pathological stage, resection scope, positive/negative margin, tumor recurrence, and recurrence *in situ* were included in the multivariate risk analysis by Cox regression. The Kaplan-Meier estimator was used to perform the survival analysis of the tumor recurrence and recurrence *in situ*. Statistical analysis was performed with SPSS 19.0 statistical software (IBM Inc.,

Table 1. Difference in tumor recurrence and recurrence *in situ* by Log-rank test in NMIBC patients

	Total	Recurrence	Recurrence time (months)	Log-Rank	*P* value	Recurrence in situ	Recurrence in situ time (months)	Log-Rank	*P* value
Tumor size									
< 1 cm	36	13	9.9 ± 5.6	31.78	< 0.001	5	6.2 ± 1.9	9.57	0.008
1-3 cm	84	37	7.7 ± 4.9			18	5.4 ± 2.8		
> 3 cm	23	19	4.2 ± 4.3			8	1.4 ± 0.5		
Number of tumors									
Single	62	26	9.0 ± 5.9	2.76	0.096	9	4.8 ± 1.3	3.78	0.052
Multiple	81	43	6.1 ±4.4			22	4.4 ± 3.4		
Primary/Recurrence									
Primary	83	33	7.5 ± 5.4	6.20	0.013	14	4.7 ± 4.0	3.05	0.081
Recurrence	60	36	6.9 ± 5.0			17	4.3 ± 1.8		
Tumor category									
Ta	109	49	8.2 ± 5.3	4.54	0.331	23	5.4 ± 2.8	0.74	0.390
T1	34	20	4.7 ± 3.9			8	1.9 ± 1.1		
Tumor grade									
G1	27	8	14.0 ± 6.8	15.78	< 0.001	3	9.0 ± 3.5	9.38	0.009
G2	52	21	8.5 ± 4.8			8	5.6 ± 3.0		
G3	64	40	5.1 ± 3.5			20	3.4 ± 2.0		
Resection Margin									
10 mm	46	30 (65.2%)	6.1 ± 4.9	10.72	0.005	20 (43.4%)	4.3 ± 3.0	20.43	< 0.001
15 mm	62	24 (38.7%)	8.4 ± 5.4			8 (12.9%)	5.4 ± 3.2		
20 mm	35	15 (42.9%)	7.4 ± 5.3			3 (8.6%)	3.7 ± 1.5		
Positive/Negative Margin									
Negative	105	40 (38.1%)	9.0 ± 5.3	31.32	< 0.001	7 (6.7%)	5.6 ± 2.5	68.38	< 0.001
Positive	38	29 (76.3%)	4.6 ± 3.8			24 (63.2%)	4.2 ± 3.0		

Table 2. Multivariate Cox analysis on tumor recurrence

	P value	HR	95% CI
Tumor size	< 0.001		
1-3 cm *vs.* < 1 cm	0.900	0.954	0.456-1.996
> 3 cm *vs.* < 1 cm	< 0.001	7.802	2.980-20.428
Primary *vs.* Recurrence	0.002	2.665	1.437-4.945
Tumor Grade	0.184		
G2 *vs.* G1	0.805	1.125	0.411-2.873
G3 *vs.* G1	0.203	1.845	0.719-4.733
Resection Margin	< 0.001		
15 mm *vs.* 10 mm	0.001	0.346	0.186-0.646
20 mm *vs.* 10 mm	< 0.001	0.267	0.128-0.556
Positive margin *vs.* Negative margin	0.049	1.781	1.002-3.168

HR: Hazard ratio, CI: Confidence interval.

Table 3. Multivariate Cox analysis on tumor recurrence *in situ*

	P value	HR	95% CI
Tumor size	0.027		
1-3 cm *vs.* < 1 cm	0.460	0.651	0.209-2.031
> 3 cm *vs.* < 1 cm	0.148	2.634	0.710-9.772
Tumor Grade	0.212		
G2 *vs.* G1	0.283	2.147	0.533-8.651
G3 *vs.* G1	0.086	3.167	0.851-11.789
Resection Margin	0.002		
15 mm *vs.* 10 mm	0.005	0.283	0.116-0.687
20 mm *vs.* 10 mm	0.005	0.145	0.038-0.558
Positive margin *vs.* Negative margin	< 0.001	8.816	3.386-22.954

HR: Hazard ratio, CI: Confidence interval.

Armonk, NY, USA). Statistical significance was at $P < 0.05$.

Results

Clinical characteristics

One hundred and forty-three patients with bladder cancer were enrolled, comprising 123 males and 20 females, aged 31 to 82 years, with an average age of 57.13 years. They underwent TURBT and were followed up postoperatively for 24 months, with the tumor recurrence as a termination event. Among the recruited patients, 83 were primary patients (58.0%) and 60 were recurrent patients (42.0%), including 62 cases with single tumor (43.4%) and 81 with multiple tumors (56.6%). Of these, 46 (32.2%), 62 (43.4%), and 35 (24.5%) cases had a marginal width of 10 mm, 15 mm, and 20 mm, respectively; 109 cases (76.2%) were pTa, and 34 cases (23.8%) were pT1 stage. Moreover, 27 (18.9%), 52 (36.4%), and 64 (44.8%) cases were pathological grade G1, G2, and G3, respectively; and 38 cases (26.6%) had a positive margin. The rates of positive marginal in the three groups (10 mm, 15 mm, and 20 mm) were 43.4% (20/46), 19.4% (12/62), and 17.1% (6/35), respectively. Furthermore, 69 cases (48.3%) developed recurrence and 31 cases (21.7%) had *in situ* recurrence.

Difference in tumor recurrence and recurrence in situ among groups

The Log-rank test of tumor recurrence and recurrence *in situ* among the tested groups was performed (**Table 1**). The results showed that tumor size, primary/recurrent tumor, pathological stage, resection scope, and positive/negative margin affected the bladder tumor recurrence ($P < 0.05$), whereas tumor size, pathological stage, resection scope, and positive margin affected the tumor recurrence *in situ* ($P < 0.05$).

Cox multiple regression analysis of NMIBC recurrence and recurrence in situ

Cox regression analysis was performed, taking tumor recurrence as a termination event, with tumor size, primary/recurrent tumor, pathological stage, marginal width, and positive/negative margin as covariates. The results showed that if the tumor was recurrent and tumor diameter > 3 cm, the positive postoperative margin was the independent risk factor, and the increase in marginal width was the independent protective factor affecting NMIBC recurrence (**Table 2**). With tumor recurrence *in situ* as a termination event, the tumor size, pathological stage, marginal width, and positive/negative margin were analyzed as covariates. The results showed that positive postoperative margin was the independent risk factor, and an increase in marginal width was the indepen-

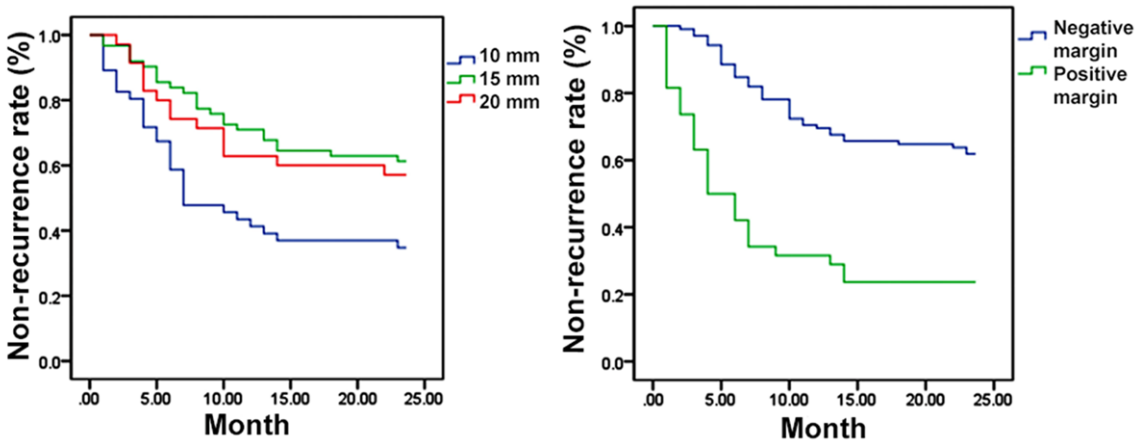

Figure 2. Kaplan-Meier estimator survival curve estimates of 24-month recurrence-free survival for three different resection marginal width groups (Left), and for positive or negative resection margin groups (Right) (tumor recurrence as the termination event).

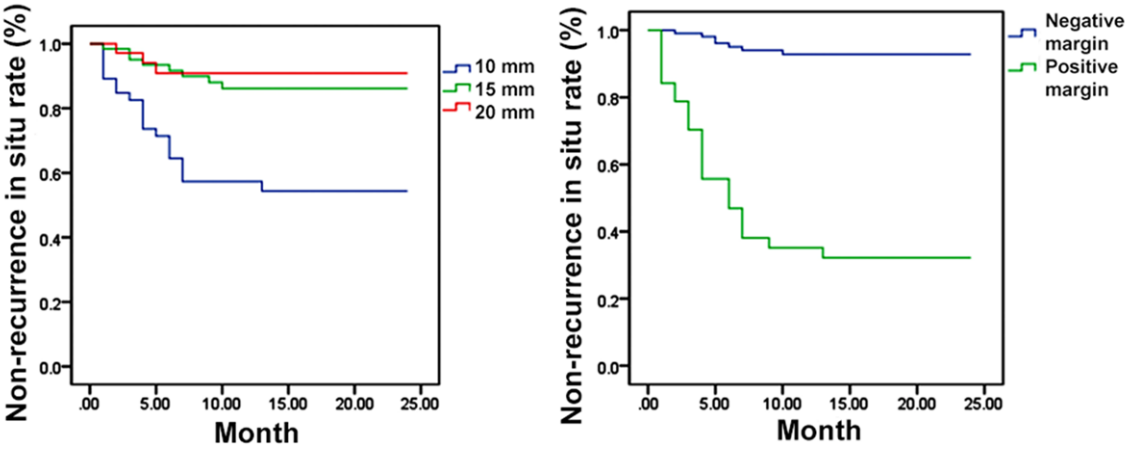

Figure 3. Kaplan-Meier estimator survival curve estimates of 24-month recurrence *in situ* free survival for three different resection marginal width groups (Left), and for positive or negative resection margin groups (Right) (tumor recurrence as the termination event).

dent protective factor affecting NMIBC recurrence *in situ* ($P < 0.05$) (**Table 3**).

Survival curve analysis of NMIBC patients by using the Kaplan-Meier estimator

With tumor recurrence as a termination event, the survival curve of patients with NMIBC having different resection marginal width and the positive/negative margin was plotted using the Kaplan-Meier estimator. The tumor recurrence rate was significantly higher for patients with 10 mm marginal width compared with those with 15 mm and 20 mm marginal width ($P = 0.005$). The recurrence rate was also significantly higher for patients with positive margin compared with those with negative margin ($P < 0.001$) (**Figure 2**).

With tumor recurrence *in situ* as a termination event, the survival curve of patients with NMIBC having different resection marginal width and the positive/negative margin was plotted. The rate of tumor recurrence *in situ* was significantly higher in patients with 10 mm marginal width compared with those with 15 mm and 20 mm marginal width ($P < 0.001$). The rate of tumor recurrence *in situ* was similarly more in patients with positive margin compared with those with negative margin ($P < 0.000$) (**Figure 3**).

Patterns for peri-operative factors to margin positive rate and width of resection margin

No statistic correlation had been found between tumor size, number of tumors and prima-

Table 4. Multivariate logistic regression model for factors on different width of resection margin

	P value	OR	95% CI for OR
Tumor size			
< 1 cm	0.129	-0.807	-1.849-0.235
1-3 cm	0.781	0.128	-0.771-1.026
> 3 cm			
Number of tumors			
Single	0.176	-0.455	-1.114-0.204
Multiple			
Primary/Recurrence			
Primary	0.727	-0.116	-0.768-0.536
Recurrence			

Statistical significance is at P < 0.05.

ry/recurrence to the width of resection margin in a multivariate logistic regression model (**Table 4**). And for Ta and T1 groups, resection margin positive rate and width of resection margin were not statistically different (P = 0.668, P = 0.968). However, the margin positive rate was influenced by grade of the tumor (P < 0.001), which meant high-grade bladder tumor was likely to have a higher margin positive rate (**Table 5**).

Incidence of complications in patients with different marginal width

The Clavien-Dindo postoperative complication grading system was employed to evaluate different groups. No grade IV or V case was found in this study. The results showed that the surgical bleeding rate increased with the growth of marginal width. The bladder perforation or rupture rate was significantly (P = 0.041) higher for patients with 20 mm margin compared with those with 10 mm and 15 mm margins. The incidence of complications increased in patients with 20 mm margin who underwent TURBT (**Table 6**).

Discussion

TURBT is a mini-invasive and highly repeatable standard surgical procedure for treatment of NMIBC. A high-quality TURBT should strictly comply with the principle of achieving negative resection margin, which is of great significance to improve the outcome. However, due to factors like tumor size, single/multiple tumors, primary/recurrent tumor, and surgeon's surgical skills, about 70% patients are found to have recurrent tumor after initial resection. Previous clinical research mostly focused on the resection depth of TURBT to ensure the detrusor muscular tissues were obtained in the specimens. We acknowledge the importance of the resection depth. However, we also consider that the width of margin of resection surrounding the tumor has long been overlooked. There is a recent interest in the width of peripheral tumor margin surrounding a resection area as an important factor to prevent local recurrence [20]. Jancke *et al.* conducted a 3 years follow-up study of TURBT oncological outcomes and demonstrated that the positive margin rate was 26%, and the recurrence rate of patients with positive margin was 83%. On the contrary, the recurrence rate of patients with negative margin was 57% [21]. The rate of recurrence *in situ* was 58% for patients with positive margin, while it was only 19% for those with negative margin. Ectopic recurrence was found in 39% *vs*. 25% cases with positive and negative margin, respectively. According to the findings presented in this work, they provided novel insight into the role of positive margin as a risk factor causing the tumor recurrence and recurrence *in situ* in patients with NMIBC. Another study conducted by Jancke *et al*. found that the tumor maximum diameter > 3 cm was related to ectopic tumor recurrence and recurrence *in situ* [22]. In the current study, we noted that positive margin, primary tumor, and tumor diameter > 3 cm were independent predictive risk factors for NMIBC tumor recurrence. Furthermore, the tumor diameter > 3 cm was also an independent risk factor predicting NMIBC recurrence *in situ*. In our study, the rates of tumor recurrence and recurrence *in situ* were significantly higher in patients with positive margin than those with negative margin (recurrence rate 76.3% *vs*. 38.1%, P < 0.001; the rate of recurrence *in situ* was 63.2% *vs*. 6.7%, P < 0.001). These are highly consistent with the findings of the previous studies which suggested that the positive margin was an important risk factor contributing to the higher recurrence and recurrence *in situ* of bladder cancer. Thus, in short, positive lesions in the margin may be a proxy variable. Richterstetter *et al*. expanded the width and depth of margin (expanded TUR) and noted that the total tumor margin residual rate was 22%, and about 94% of the residues were found in the margin rather than in the base-

Table 5. Patterns for T stage and grade to margin positive rate and width of resection margin

	Margin			Resection Margin			
	Negative	Positive	*P* value	10 mm	15 mm	20 mm	*P* value
T stage			0.668*				0.968**
Ta	81	28		35	48	26	
T1	24	10		11	14	9	
Grade			< 0.001**				0.061**
G1	24	3		15	9	3	
G2	45	7		13	26	13	
G3	36	28		18	27	19	

*Chi-square test, **Fisher exact test, statistical significance is at P < 0.05.

Table 6. Comparison of surgical complications in different resection margins

Resection Margin	Total	Bleeding					Bladder perforation				
		I	II	III	Total	Rate%	I	II	III	Total	Rate%
10 mm	46	7	2	1	10	21.7	0	2	0	2	4.3
15 mm	62	17	1	1	19	30.6	0	1	1	2	3.2
20 mm	35	8	1	5	14	40.0	0	2	3	5	14.3

ment [17]. Furthermore, expanded TUR could pronouncedly reduce the tumor margin positive rate, as well as the rate of tumor recurrence *in situ* to 5.1%. These results had unambiguously demonstrated that adequate width, as well as depth during TURBT, was necessary to reduce the tumor recurrence. In our study, we also noted a significant difference in the postoperative recurrence rate among 10 mm, 15 mm and 20 mm groups (38.7% *vs*. 65.2%, *P* = 0.001; 42.9% *vs*. 65.2%, *P* < 0.001); hazard ratios (HR) were 0.346 and 0.267, respectively. Multivariate relating to the recurrence in situ was analyzed by Cox regression. Significant differences were found in the postoperative recurrence *in situ* among 10 mm, 15 mm and 20 mm groups (12.9% *vs*. 43.4%, *P* = 0.005; 8.5% *vs*. 43.4%, *P* = 0.005). Similar patterns were found in HR as 0.283 and 0.145, respectively. This strongly suggests that the increase in marginal width plays as an independent protective role in preventing both the recurrence and recurrence *in situ* of NMIBC.

The tumor recurrence rates and recurrence *in situ* rates in patients with 15 mm and 20 mm margins were compared in current study, and we noted that the tumor recurrence rates for the two groups were 38.7% vs. 42.8%, respectively (*P* > 0.05), while the rates of tumor recurrence *in situ* were 12.9% vs. 8.5%, respectively. Nonetheless, no significant difference was found between the two groups (*P* > 0.05).

Post-operation surgical complications were evaluated by Clavien-Dindo system. The results showed the rates of bladder perforation or rupture and post-operation bleeding in patients with 20 mm marginal width were higher than those with 10 mm marginal width (40.0% *vs*. 21.7% and 14.3% *vs*. 4.3%, respectively). We also found that the rates of bladder perforation or rupture and post-operation bleeding in patients with 20 mm marginal width were higher than those with 15 mm marginal width (40.0% *vs*. 30.6% and 14.3% *vs*. 3.2%, respectively; *P* = 0.041). Overall, these findings reveal that the 20 mm marginal resection would increase the risk of bladder perforation or rupture and post-operation bleeding rates without promising further advantage of reduction in tumor recurrence rate, whereas the 15 mm margin resection might be sufficient to reduce the rates of tumor recurrence and recurrence *in situ* without leading a significant increase in the occurrence of postoperative complications. Hence, we propose that the 15 mm margin resection should be considered as a potential standard for TURBT. In particular, fulguration around the margin as mentioned before may reduce tumor dissemination and recurrence by sealing the blood vessels and achieving further tumor necrosis, without increasing the risk of postoperative complications.

In the last several years, the re-TURBT, performed in 2-6 weeks after TURBT, has come to the forefront of attention for NMIBC. The potential benefits reported included ensuring complete tumor removal, re-staging as well as preventing postoperative tumor recurrences [5, 23, 24]. Ali *et al*. reported that patients with multiple tumors and those with maximum diameter > 3 cm benefited from re-TURBT [25]. Our study proposes that patients with tumor residu-

al on margins might also benefit from re-TURBT. However, this was not the objective of the current study.

The limitations of this study should also be noted. Firstly, being a retrospective study, selection bias was possible. The patients enrolled in this study were not randomly divided, but according to the surgical methods of different urologists. Secondly, in the multiple linear regression analysis, the effect of multicollinearity among variables between tumor size, single/multiple tumors, primary/recurrent tumor, clinical stage, marginal width, pathological type, surgical skills and learning curve of surgeons cannot be eliminated and may interfere within prediction of recurrence rate. Thirdly, this study was a single-center study; hence, the lack of multicenter data, to a certain extent, reduced the significance of the present findings. In addition, the follow-up time in this study was limited. Thus, the results may only reflect the outcome of the relationship between the marginal width and the short-term prognosis for patients who underwent TURBT.

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Disclosure of conflict of interest

None.

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