



Pathological Evaluation of Horizontal Extension in Non-Muscle Invasive Bladder Cancer Resected using TURBO (Transurethral Resection of Bladder Tumor in One Piece) Technique

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Abstract

Using TURBO technique, we accurately evaluated horizontal extension of non-muscle invasive bladder tumors in relation to clinical and pathological parameters. Non-muscle invasive bladder tumors sized less than 20 mm were resected with an approximately 5-mm margin from the stalk using the TURBO technique. Specimens from 52 cases were pathologically examined to determine the amount of horizontal extension, which was analyzed for correlations with several clinical and pathological parameters, including tumor size and stalk diameter.

Twenty cases (38.5%) were found to have horizontal extension of cancer, ranging from 0.6 to 6.1 mm (median 2.8 mm). The existence of horizontal extension was significantly more often associated with primary (17/32; 53.1%) than recurrent (3/20; 15.0%) tumors ($p=0.014$) and likely to be associated with high grade tumors ($p=0.053$). Tumors with a stalk greater than 2 mm were more significantly associated with horizontal extension (18/37; 48.6%) in contrast to those with a smaller stalk (2/15; 13.3%) ($p=0.040$), though no such trend was observed in terms of tumor size ($p=0.202$). Furthermore, horizontal extension length was significantly correlated with stalk diameter/tumor size ratio ($r=0.5060$), but not with tumor size ($r=-0.2203$) or stalk diameter ($r=0.1847$).

Our findings showed that resection with a wider surgical margin are required in cases with a tumor stalk diameter thicker than 2 mm, especially in those with a stalk diameter/tumor size ratio of 0.4 or more. Our results are considered to be the first useful evidence showing the need for horizontally complete resection of non-muscle invasive bladder cancer.

Keywords: En bloc resection technique; Horizontal extension; Non-muscle invasive bladder tumors; Stalk diameter/tumor size ratio; TURBO

Introduction

A transurethral resection of bladder tumor (TURBT) procedure is the gold standard diagnostic tool as well as treatment method for bladder cancer, especially in cases of non-muscle invasive tumors. However, that method occasionally results in insufficient tumor specimens for accurate pathological examination results, because of fragmentation into pieces and/or degeneration by thermal damage. Therefore, conventional TURBT may sometimes lead to pathological under-diagnosis by neglecting micro-stromal invasion, or vertically and/or horizontally incomplete excision in cases requiring a second transurethral resection.

A new technique for en bloc resection of bladder tumors without fragmentation, termed TURBO (transurethral resection of bladder tumor in one piece), has been recently reported [1,2]. While a similar technique using a laser has also been presented [3]. These methods for en bloc resection of bladder tumors are considered more likely to contribute to improvements in accurate pathological diagnosis by avoiding fragmentation of and direct thermal damage to bladder tumors during the procedure. As reported by Ukai et al. [4] as well as others [1-3], use of TURBO or a similar method provides for more accurate histological diagnosis, especially regarding the depth of lamina propria invasion, as compared to conventional TURBT, because specimens obtained by TURBO were found to be well oriented with a well maintained 3-D architecture. However, the usefulness of TURBO for

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Received Date: 25 Jul 2016

Accepted Date: 17 Aug 2016

Published Date: 13 Sep 2016

Citation:

Ueda Y, Zozumi M, Suzuki T, Kanematsu A, Nojima M, Hirota S, et al. Pathological Evaluation of Horizontal Extension in Non-Muscle Invasive Bladder Cancer Resected using TURBO (Transurethral Resection of Bladder Tumor in One Piece) Technique. *Clin Oncol.* 2016; 1: 1093.

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Table 1: Characteristics of patients and tumors.

		Horizontal extension (n)			p
		Total (n)	Yes	No	
Age (years)		52	70 (58-83)	74 (30-95)	0.605
Gender	Male	45	17	28	0.872
	Female	7	3	4	
Primary/recurrent	Primary	32	17	15	0.014
	Recurrent	20	3	17	
Urine cytology	Negative	39	14	25	0.753
	Positive	5	2	3	
T stage	pTa	47	17	30	0.577
	pT1	5	3	2	
Grade	Low	27	7	20	0.053
	High	25	13	12	
Tumor size (mm)		52	6.4 (2.6-17)	4.8 (0.8-13.2)	0.153
Stalk diameter (mm)		52	3.2 (0.7-9.2)	2.6 (0.5-10)	0.23

evaluating resected bladder tumors in regard to horizontal extension has yet to be reported.

In the present study, we examined both horizontal extension and vertical invasion of specimens obtained by TURBO, and then analyzed the correlation between horizontal extension and several clinical and pathological parameters, including tumor size and stalk diameter, in non-muscle invasive bladder tumors.

Materials and Methods

Materials

Between September 2009 and December 2013, 68 patients underwent TURBO at our institution for bladder tumors sized less than 20 mm suspected to be non-muscle invasive cancer without carcinoma in situ based on preoperative endoscopic findings and clinical information. Of those surgical specimens, 52 showed adequate quality for a detailed pathological examination to evaluate horizontal extension and vertical invasion, and were analyzed for the present study. Median patient age was 73 years old (30 to 95 years) and males were predominant (n=45, 86.5%). The analyzed specimens included 32 primary (61.5%) and 28 solitary (53.8%) tumors (Table 1).

TURBO technique: As previously reported [1,2,4]. TURBO was performed using a 26-Fr resectoscope equipped with a 45° needle electrode (TURis, Olympus Medical Systems, Japan). Briefly, with this method, the tumor is initially carefully investigated in terms of size, stalk shape, and visible horizontal extension of disease around the mass. Using the 45° needle electrode, marks are made circumferentially at approximately 5 mm from the edge of the stalk. After connecting the marks circularly with the electrode, the tumor is then resected horizontally through the superficial muscular layer by electric cutting with a loop electrode while pushing the bottom with the tip of the sheath. The tumor specimen is thus obtained with surrounding normal tissue and a superficial muscular layer. In each of the present cases, the main tumor was resected by TURBO, while other daughter tumors and apparent low-grade lesions were incised using conventional TURBT or a cold cup biopsy technique to reduce operation time. There were no complications encountered, such as perforation of the bladder wall or postoperative urinary tract infection.

Tissue processing for pathological examination: Following resection of the tumor specimen, the bottom was immediately stretched and pinned onto a piece of paper. After fixing with 20% buffered formalin overnight, the specimen was embedded in agarose using a double embedding technique [5] (Figure 1). Next, serially sectioning was performed, and the pathological diagnosis was determined and confirmed by two pathologists. Parameters such as tumor size and stalk diameter, and horizontal extension length were evaluated by a single pathologist using a virtual slide system (Scan Scope XT, Aperio, USA) (Figure 2).

Statistical analysis: Statistical analysis was performed using StatMate (ATMS Co. Ltd, Japan), with p values <0.05 shown by a chi-square test and r values >0.4 shown by a correlation coefficient test considered to indicate significance.

Results and Discussion

All tumors were diagnosed as urothelial carcinoma, while 47 cases (90.4%) were pathologically defined as pTa and 5 (9.6%) as pT1. Among the pT1 tumors, micro-stromal invasion was observed in 3 (5.8% of all cases), which was considered to have been neglected and diagnosed as pTa if the specimen had been obtained by conventional TURBT.

Microscopic examinations were performed to determine tumor

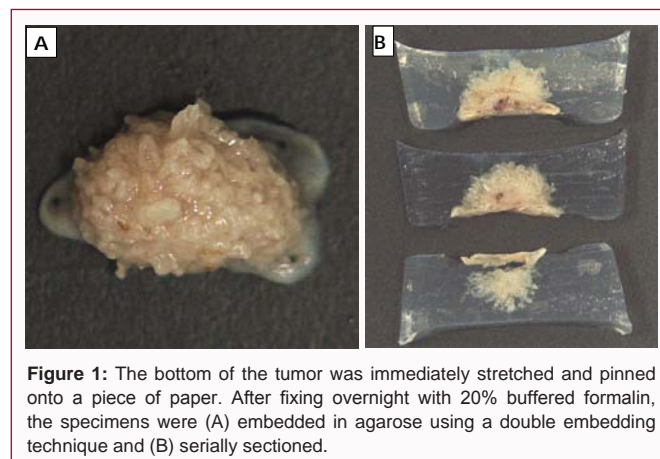


Figure 1: The bottom of the tumor was immediately stretched and pinned onto a piece of paper. After fixing overnight with 20% buffered formalin, the specimens were (A) embedded in agarose using a double embedding technique and (B) serially sectioned.

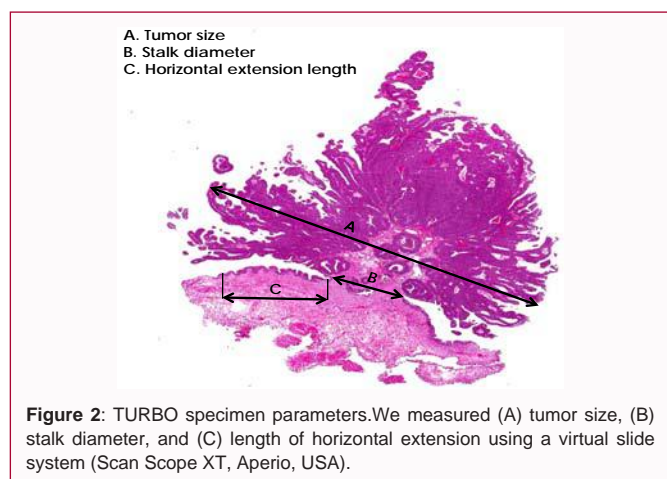


Figure 2: TURBO specimen parameters. We measured (A) tumor size, (B) stalk diameter, and (C) length of horizontal extension using a virtual slide system (Scan Scope XT, Aperio, USA).

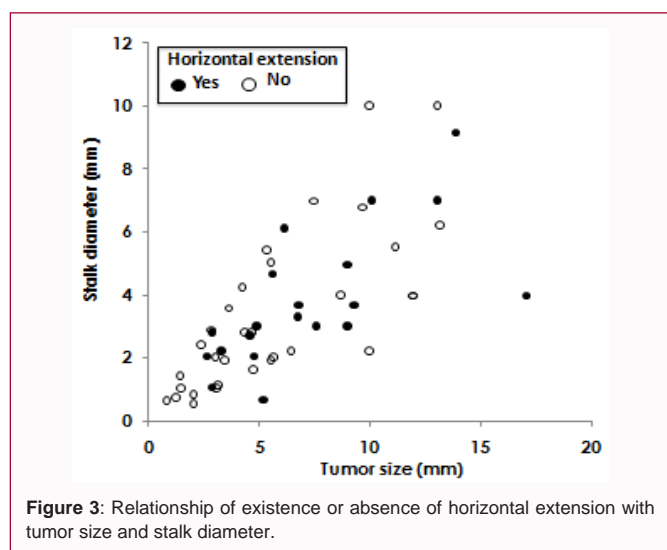


Figure 3: Relationship of existence or absence of horizontal extension with tumor size and stalk diameter.

horizontal extension, which indicated that 43 (82.7%) tumors were completely resected, while 9 (17.3%) showed a horizontal surgical margin positive for cancer. Of the 52 present tumors, 20 (38.5%) were found to have a horizontal extension of cancer ranging from 0.6 to 6.1 mm (median 2.8 mm), which was significantly more associated with primary (17/32, 53.1%) as compared to recurrent (3/20, 15.0%) tumors ($p=0.014$), and also more likely to be associated with high grade tumors ($p=0.053$), whereas age, gender, urine cytology, and pT stage showed no such associations. Median tumor size and stalk diameter of tumors showing horizontal extension were 6.4 mm (2.6-17 mm) and 3.2 mm (0.7-9.2 mm), respectively, while those of tumors without horizontal extension were 4.8 mm (0.8-13.2 mm) and 2.6 mm (0.5-10 mm), respectively, with no significant differences noted (Table 1).

Conversely, when the existence or absence of horizontal extension was overlooked for determining the relationship with tumor size and stalk diameter, larger tumor size or thicker stalk diameter seemed to be associated with horizontal extension of cancer (Figure 3). Therefore, several cutoff points for tumor size and stalk diameter were applied for determining the relationship of presence of horizontal extension. Tumors with a stalk greater than 2 mm in diameter were significantly associated with horizontal extension (18/37; 48.6%) in contrast to those with a smaller stalk (2/15; 13.3%) ($p=0.040$). However, that trend was not observed in terms of tumor size ($p=0.202$) (Table 2).

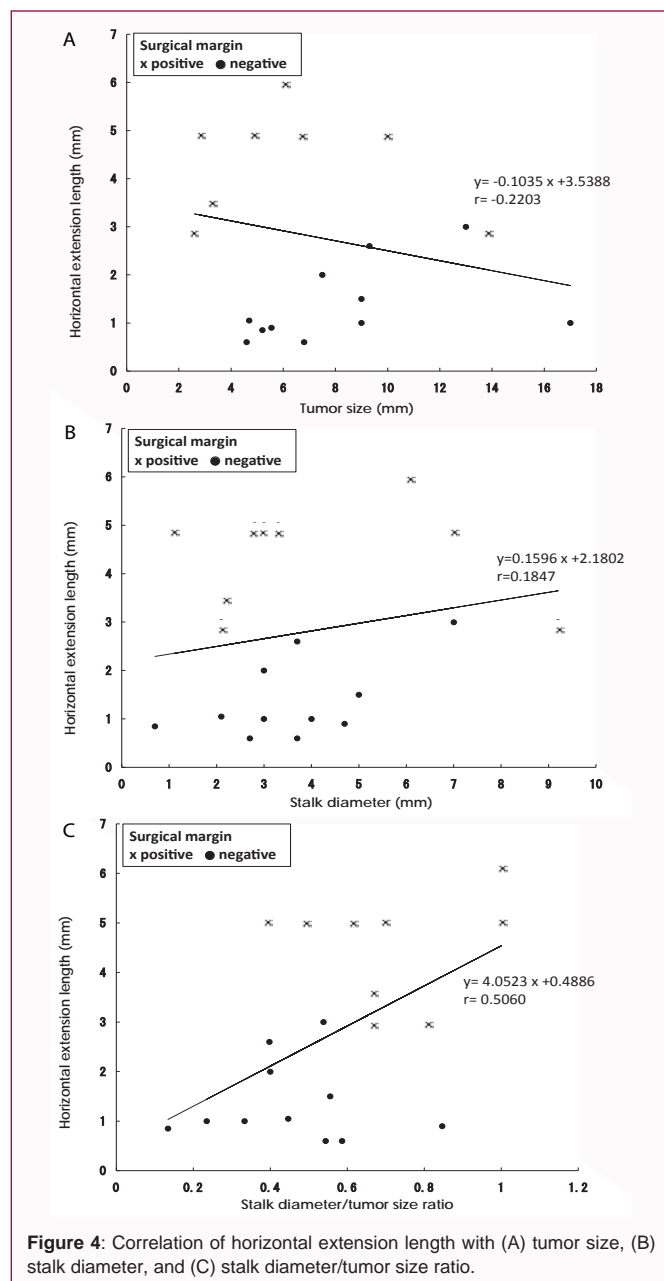


Figure 4: Correlation of horizontal extension length with (A) tumor size, (B) stalk diameter, and (C) stalk diameter/tumor size ratio.

When the correlations of horizontal extension length with tumor size and stalk diameter were analyzed, no significant association was observed ($r = -0.2203$ and $r = 0.1847$, respectively) (Figure 4A and B). On other hand, we found that horizontal extension length was significantly correlated with the stalk diameter/tumor size ratio ($r = 0.5060$), suggesting that resection with a wider surgical margin is required in cases with a stalk diameter/tumor size ratio of 0.4 or greater (Figure 4C).

A previous study reported that a residual tumor is found in 20-78% of patients who undergo a second transurethral resection and whose initial diagnosis was pT1 [6]. While others have reported pathological findings of specimens obtained in a second transurethral resection showing that 2-28% of such patients were pT2 [7,8]. A second transurethral resection is strongly recommended in cases with a pathological diagnosis of high grade or pT1 tumor initially treated by TURBT [9]. Thus, particularly for non-muscle invasive cancer, an important role of transurethral surgery is not only complete

Table 2: Association of horizontal extension.

	Size/diameter (mm)	Total (n)	Horizontal extension, n (%)		p
		52	Yes	No	
Tumor	≤5	24	7 (29.2)	17 (70.8)	0.202
	>5	28	13 (46.4)	15 (53.6)	
Stalk	≤2	15	2 (13.3)	13 (86.7)	0.040
	>2	37	18 (48.6)	19 (51.4)	

resection of the tumor, but also harvest of a high quality specimen for accurate pathological diagnosis. However, specimens obtained with conventional TURBT are occasionally insufficient for an accurate pathological examination, because of fragmentation into pieces or degeneration from thermal damage.

Several recent studies have noted that the depth of tumor invasion is significantly correlated with progression in patients with T1 cancer [10-12]. Younes et al. [10] reported that patents with a tumor that has invaded to the level of the muscularis mucosae had a 5-year survival rate of 75%, whereas that was only 11% in those with tumors invading through the level of the muscularis mucosae. Orsola et al. [11] also reported that the depth of invasion noted with TURBT specimens is an independent prognostic factor for T1 bladder cancer, because the rate of progression in cases with a tumor showing deep invasion of the lamina propria was significantly higher as compared to those without such deep invasion.

In this regard, TURBO can provide specimens more optimal for pathological diagnosis, because the tumor is resected en bloc with surrounding normal tissue including normal epithelium, lamina propriae, and a superficial muscular layer without direct thermal damage. Ukai et al. [4] reported that definite pathological staging was possible in 93% of their TURBO specimens, including 30 pTa, 58 pT1, and 2 pTa cases, while 7 cases (7%) had a deep resection positive margin for cancer and were ambiguously staged. Similarly, in our study, 5 pT1 cases (9.6%) were found among 52 superficial bladder tumors, of which micro-stromal invasion was observed in 3 (5.8%), which may have been neglected and diagnosed as pTa if the specimen had been obtained by conventional TURBT.

Another advantage of TURBO for pathological diagnosis of bladder tumors is the possibility for accurate evaluation of horizontal extension. Urologists use empirical means to determine the surgical margin prior to resecting a bladder tumor, as there are no reported methods for accurate evaluation of horizontal extension in cases of non-muscle invasive bladder cancer. In the present cases, 9 of 52 tumors (17.3%) resected with an approximately 5-mm margin from the stalk showed a horizontal surgical margin positive for cancer, suggesting that at least a 10-mm margin from the stalk may be required for complete resection of a superficial bladder tumor, even those sized 20 mm or less. We found that horizontal extension was significantly associated with a stalk diameter greater than 2 mm, but did not find an association with larger tumor size. Another interesting finding is that even though horizontal extension length was not associated with tumor size or stalk diameter, it was significantly correlated with the stalk diameter/tumor size ratio. These results indicate that a larger tumor or thicker stalk alone is not always indicative of longer horizontal extension, whereas the stalk diameter/tumor size ratio may be an important indicator to determine surgical margin from the stalk.

Taken together, for achievement of complete resection as well

as obtaining a sufficient specimen for pathological examination in cases of non-muscle invasive bladder cancer, stalk diameter as well as stalk diameter/tumor size ratio should be carefully observed before performing the procedure. Resection with a wider surgical margin should also be required in cases with a stalk diameter thicker than 2 mm, especially when the stalk diameter/tumor size ratio is 0.4 or greater, as observed in the present study. To the best of our knowledge, the present findings provide the first useful evidence for the need of horizontally complete resection of non-muscle invasive bladder cancer. Along this line, the effectiveness of narrow band imaging (NBI) in conjunction with TURBT has been reported for visualization of minute bladder tumors [13,14]. For assessment of the usefulness of NBI for complete resection of a horizontally extended bladder tumor, we are now conducting an assessment of TURBO with NBI.

Finally, complete resection of a bladder tumor may contribute to control sympatric tumor recurrence. As for cases with deep resection, of 5 patients shown to have pT1 disease based on TURBO specimen findings, 1 underwent a radical cystectomy and 2 suffered from heterotopic pTa-recurrence, whereas none of our patients developed invasive disease during the follow-up period (data not shown). On the other hand, in regard to horizontal resection, sympatric recurrence was observed in 1 (12.5%) of the patients with a horizontal surgical margin positive and in 2 (4.7%) of those without such a margin positive, which was not a significant difference ($p=0.89$) (data not shown), though this result may have been due to the small number of cases as well as modification caused by postoperative intravesical instillation.

Conclusion

Our findings showed that resection with a wider surgical margin is required in cases with a tumor stalk diameter thicker than 2 mm, especially in those with a stalk diameter/tumor size ratio of 0.4 or more. To the best of our knowledge, the present findings provide the first useful evidence for the need of horizontally complete resection of non-muscle invasive bladder cancer. However, the present study was performed in a retrospective manner and the sample size was small, thus larger prospective studies are needed to investigate factors that contribute to better clinical outcomes.

Acknowledgement

The present study was supported by a grant from the Hyogo Clinical Urologists Association in 2013.

In lieu of formal ethics committee approval for this retrospective study, the principles of the Helsinki Declaration were followed. In addition, all patients provided written informed consent after receiving a guarantee of confidentiality.

References

1. Kawada T, Ebihara K, Suzuki T, Imai K, Yamanaka H. A new technique for transurethral resection of bladder tumors: rotational tumor resection using a new arched Electrode. *J Urol.* 1997; 157: 2225-2256.
2. Ukai R, Kawashita E, Ikeda H. A new technique for transurethral resection of superficial bladder tumor in 1 piece. *J Urol.* 2000; 163: 878-879.
3. Saito S. Transurethral en bloc resection of bladder tumors. *J Urol.* 2001; 166: 2148-2150.
4. Ukai R, Hashimoto K, Iwasa T, Nakayama H. Transurethral resection in one piece (TURBO) is an accurate tool for pathological staging of bladder tumor. *Int J Urol.* 2010; 17: 708-714.

5. Zozumi M, Nakai M, Ito T, Matsuda I, Hao H, Tsukamoto Y, et al. New double embedding technique for specimens of endoscopic submucosal dissection using agarose: comparison with other media. *J Clin Pathol*. 2010; 63: 904-909.
6. Schwaibold HE, Sivalingam S, May F, Hartung R. The value of a second transurethral resection for T1 bladder cancer. *BJU Int*. 2006; 97: 1199-1201.
7. Sivalingam S, Probert JL, Schwaibold H. The role of repeat transurethral resection in the management of high-risk superficial transitional cell bladder cancer. *BJU Int*. 2005; 96: 759-762.
8. Jakse G, Algaba F, Malmström PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol*. 2004; 45: 539-546.
9. Richterstetter M, Wullich B, Amann K, Haeberle L, Engehausen DG, Goebell PJ, et al. The value of extended transurethral resection of bladder tumor (TURBT) in the treatment of bladder cancer. *BJU Int*. 2012; 110: E76-E79.
10. Younes M, Sussman J, True LD. The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. *Cancer*. 1990; 66: 543-548.
11. Orsola A, Trias I, Raventós CX, Español I, Cecchini L, Búcar S, et al. Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. *Eur Urol*. 2005; 48: 231-238.
12. Bernardini S, Billerey C, Martin M, Adessi GL, Wallerand H, Bittard H. The predictive value of muscularis mucosae invasion and p53 over expression on progression of stage T1 bladder carcinoma. *J Urol*. 2001; 165: 42-46.
13. Cauberg EC, Mamoulakis C, de la Rosette JJ, de Reijke TM. Narrow band imaging-assisted transurethral resection for non-muscle invasive bladder cancer significantly reduces residual tumor rate. *World J Urol*. 2011; 29: 503-509.
14. Zheng C, Lv Y, Zhong Q, Wang R, Jiang Q. Narrow band imaging diagnosis of bladder cancer: systematic review and meta-analysis. *BJU Int*. 2012; 110: E680-E687.