ORIGINAL ARTICLE

COMPARISON OF RECURRENCE RATE BETWEEN "*EN BLOC*" RESECTION OF BLADDER TUMOUR AND CONVENTIONAL TECHNIQUE FOR NON-MUSCLE INVASIVE BLADDER CANCER

Muhibullah Bangash, Muhammad Hammad Ather, Nasir Khan*, Shoaib Mohammad, Zeeshan Uddin

Urology Section, Aga Khan University Hospital Karachi, *Khyber Teaching Hospital, Peshawar-Pakistan

Background: Conventional transurethral resection of urinary bladder tumour (TURBT) using a wire loop diathermy violates the basic principle of oncological surgery, i.e. dissection through normal tissue. However, in the *en bloc* technique, the tumour is removed as a single specimen. We compared the quality of specimen and recurrence rate at three months (first check cystoscopy) in both the *en bloc* and conventional resection techniques. **Methods:** The subject accrual was done from June 1st, 2017 till June 30th, 2019 at a tertiary care hospital. Patients with newly diagnosed bladder tumour, solitary or multiple ≤3 cm were included in the study. Patients with carcinoma in situ, prior TURBT, or muscle-invasive bladder cancer were excluded. Eighty-two patients were available for final analysis, 41 in each group. **Results:** Mean age, gender ratio, tumour features (grade, stage, median number, and size) were comparable in the two groups. Median Operative time [interquartile range- (IQR)] was 30 (25–39.5) minutes in the *en bloc* group as compared to 45 (33–63.5) minutes in the conventional group ($p < 0.001$). The detrusor muscle was seen at the base of the primary tumour in all 41 (100%) *en bloc* cases as compared to 23 (56 %) cases in the conventional group ($p<0.001$). Overall recurrence at the first surveillance cystoscopy was 17%, with an insignificant difference between the groups. Recurrence at primary site was 19.5% in conventional TURBT compared to *en bloc* resection (n=1, 2.4%), ($p = 0.013$). **Conclusion:** *En bloc* resection decreases the recurrence rate at the primary site. *En bloc* TURBT is a safe technique, providing high-quality specimens for histopathological evaluation and reducing the need for the second TURBT.

Keywords: *En bloc* TURBT; conventional TURBT; Non-muscle-invasive bladder cancer; Recurrence rate; Detrusor muscle

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INTRODUCTION

Transurethral resection of bladder tumour (TURBT) is the initial management option to diagnose, stage, and treat a bladder tumour.[1] Overall there is a 70% recurrence rate following TURBT, with increased risk at first follow-up cystoscopy routinely performed after 3 months of initial TURBT.[2,3] Some of the factors that could lead to recurrence include incomplete resection, persistence and regrowth of residual tumour or tumour cells spillage in irrigation fluid that results in new recurrence. Other factors for high recurrence can be tumour biology and field change.[4]

The conventional piecemeal TURBT is widely practiced with a wire loop attached to the diathermy unit. However, the technique defines the basic oncological principles of surgery, i.e., negative surgical margins and liberation of tumour cells into irrigation fluid. Theoretically, this facilitates tumour cell implantation and seeding on the denuded mucosa. Furthermore, tumour tissues destroyed and fragmented by resection may not contain deeper layers that lead to pathological under staging and subsequent second TURBT. Various studies have reported the absence of detrusor muscle in 50% of the conventional TURBT specimens.[5] These deviations affect the efficacy of postoperative therapeutic plans, adding more cost, morbidity, and increasing the rate of tumour recurrence.[6]

The *en bloc* resection technique follows the basic principles of oncological surgery.[7] To remove the whole tumour in a one-piece Collins knife can be used by a circumferential mucosal incision around the tumour, undermining and resecting the whole tumour. In this way tumour along with normal tissue, margins are resected that adheres to the oncologic surgery principle in en bloc TURBT. Reduced recurrence rates in *en bloc* TURBT are shown in the previous studies but this is still debatable.[1] Other studies show that *en bloc* TURBT produces an excellent histopathology specimen.[8]

En bloc TURBT is an excellent improvement in the initial management of bladder cancer as a more precise and complete resection is performed. However, there is still a dearth of evidence that *en bloc* TURBT does reduce short term recurrence rate as compared to the conventional technique. In the current study, we have compared *en bloc* TURBT with conventional

TURBT to assess accurate pathologic staging as indicated by the presence of detrusor muscle in the original resection specimen and not separate deep biopsy and if this translates into a lower local recurrence rate.

MATERIAL AND METHODS

We performed this non-randomized study at a tertiary care hospital, after institutional review board approval, from June 1st, 2017 till June 30th, 2019.

The sample size was calculated using the WHO software. The known recurrence rate after excision of bladder tumour via conventional method at first check cystoscopy is 28%.[3] To detect at least a 14% absolute change in recurrence rate at 3 months, keeping the level of significance as 0.05 and power of a study to be 80%, we needed at least 37 patients in each group for analysis. Anticipating a 10% loss to follow up, we planned to include 41 patients in each group of our study.

All adult patients' ≥18 years of age, presenting for the first time with bladder tumour on imaging, with single tumour/multiple lesions none more than 3cm were included. Maximum tumour size selection for *en bloc* resection was made intraoperatively on the surgeons' discretion. We excluded patients with recurrent tumours, a muscle-invasive tumour or carcinoma in situ on histopathology, cases that required the second cystoscopy in 2–6 weeks due to absent detrusor muscle (except pTa/low-grade tumours), concomitant urothelial cancer of the upper urinary tract, those who lost to follow and patients showing progression at 3 months.

Both *en bloc* TURBT and conventional TURBT were performed in a lithotomy position using standard 26 Fr. Karl Storz® resectoscope. *En bloc* TURBT was performed with a Collins knife attached to monopolar diathermy. Initially, a rim was marked around the tumour in normal urothelium, which was then deepened cautiously and the tumour lifted from the base and resected all in a single piece. A routine resection loop was used for conventional piecemeal TURBT in which the tumour was cut in layers from top to base until a complete tumour was excised. All the procedures were performed by consultant urologists with more than 10 years of experience. For collecting data, a standard bladder diagram was made on operating notes. The statistical analysis was done on SPSS version 22. Both conventional TURBT and *en bloc* TURBT groups were compared based on recurrence at the first follow-up cystoscopy and detrusor presence at the base of the initial specimen. Basic demographic and other clinical features were compared using frequency tables. Chi-square test was used for comparison of categorical variables between the two groups. p-value <0.05 was considered significant. Kolmogorov-Smirnov test was used for determining the normal distribution. To compare the means, the independent sample t-test was used. Medians were compared using the Mann-Whitney-U test. Both the groups were further compared using univariate and multivariate analysis concerning the outcome variable with the cox-regression model.

The outcome variables used for comparison were recurrence rates at 3 months (first follow-up cystoscopy) and presence of detrusor muscle in histopathologic specimens between the *en bloc* and conventional TURBT techniques in patients with non-muscle invasive bladder cancer.

RESULTS

Forty-nine patients underwent *en bloc* TURBT during the study duration from June 1st, 2017 till June 30th, 2019 at a university hospital. Eight (16.3%) were excluded, of which 4 (8.16%) had muscle-invasive bladder cancer, 1 (2%) patient had cystitis cystica and 3 (6%) were lost to follow. Finally, 41-*en bloc* TURBT cases with a similar number of conventional TURBT cases were performed during the study duration according to selection criteria. Basic demographics and tumour features are compared in table-1. Of the total 82 participating subjects, 70 (85.4%) were male patients and 12 (14.6%) were female patients; hence the overall proportions of male to female were 6:1. The mean age of the study population was 58.52 (± 13.63) years and similar in both the groups. Median operative time [interquartile range- (IQR)] was significantly shorter in the *en bloc* group, i.e., 30 (25–39.5) minutes as compared to 45 (33–63.5) minutes in the conventional group ($p < 0.001$). The largest tumour size resected by *en bloc* technique was 3cm. Median tumour size 2.50 cm (2 – 3.0) in both the groups. Mean age, gender ratio, tumour features (grade, stage, median number, and size) were comparable in both the *en bloc* and conventional TURBT groups. The maximum duration of the catheter was 10 days in *en bloc* resection and 11 days in the conventional group. The maximum duration of irrigation was 12 hours in the *en bloc* group and 16 hours in the conventional group. The median duration of irrigation was less, i.e., 3 (3–12) hours in *en bloc* resection as compared to 6 (3–12) hours in conventional resection but it was found insignificant (p <0.20). The median catheter duration and overall complications were similar in both the groups (Table-1).

The primary outcomes of the study, i.e. the recurrence at three months and the presence of detrusor muscle at the base of the initial specimen are compared between the two groups in table-2. Overall, 14 patients (17.1%) had recurrence at the first surveillance cystoscopy, recurrences were few in the *en bloc* group, 4 (9.8%) as compared to 10 (24.4%) in the conventional group with no statistical difference (p=0.14). On histopathology, detrusor muscle was seen at the base of

the primary tumour in all 41 (100%) *en bloc* cases as compared to 23 (56.1%) cases in the conventional group (p <0.001). In the remaining 14 (34.2%) out of 18 (43.9%) patients in the conventional group, detrusor muscle was present in a separate deep muscle biopsy and 4 (9.8%) patients required the second TURBT after histopathology was reported.

In table-3, univariate analysis was used to compare the relative risk of different variables on tumour recurrence in both groups. Only tumour size was found to increase the relative risk of recurrence in *en bloc* resection group, i.e., each centimetre increase in tumour size doubles the relative risk for recurrence at first check cystoscopy performed after 3 months. In the conventional TURBT group, operative time and duration of the catheter were statistically significant variables to recurrence at 3 months (p= < 0.25). Age, gender, tumour number, grade, stage, and duration of irrigation were found insignificant on univariate regression analysis comparing the two groups concerning recurrence at 3 months which shows homogeneity in both groups. After adjusting for co-variates, on multivariate analysis (Table- 4), none of the variables was significant in the *en bloc* resection group in association with recurrence at 3 months. Operative time and duration of catheter remained statistically significant variables on multivariate analysis in the conventional TURBT group (p=<0.25). It means that an increase in operative time significantly increases the relative risk of recurrence in conventional TURBT. However, relatively less recurrence in *en bloc* TURBT cases cannot be statistically attributed to lesser operative time as compared to the conventional group.

Table-5 shows features of tumours that have recurred at 3 months. Recurrence at primary site was more common in conventional TURBT (n = 8, 19.5%) in comparison to *en bloc* resection (n = 1, 2.4%), (p = 0.013). Most recurrences were of low grade (pTa) in conventional TURBT (n = 10, 17.1%) when compared to *en bloc* resection group (n =1, 2.4%), (p = 0.03).

Table-1: Basic demographic data on the two groups

Variable	Total	En bloc TURBT	Conventional TURBT	*p*-value
Age (mean±SD)	58.52 ± 13.63	58.46±14.98	58.59±12.32	0.968
Gender: n (%)				0.756
• **Male**	70 (85.4)	34 (82.9)	36 (87.8)	
• **Female**	12 (14.6)	7 (17.1)	5 (12.2)	
Tumour number Median (IQR)	1.00 (1–2)	1.00 (1–2)	1.00 (1–2.5)	0.926
Tumour size (mm) Median (IQR)	2.5 (2–3)	2.50 (2–3)	2.50 (1.8–4)	0.451
Tumour Grade n (%)				0.814
• **Low**	53 (64.6)	27 (65.9)	26 (63.4)	
• **High**	29 (35.4)	14 (34.1)	15 (36.6)	
Tumour Stage n (%)				0.913
• **pTa**	39(47.6)	20 (48.8)	19 (46.3)	
• **pT1**	43 (52.4)	21 (51.2)	22 (53.7)	
Operative time (minutes) Median (IQR)	35 (28-55)	30 (25–39.5)	45 (33–63.5)	<0.001
Duration of irrigation (hrs) Median (IQR)	6 (3–12)	3 (3–12)	6 (3–12)	0.204
Duration of catheter (days) Median (IQR)	5 (3–7)	5 (3.5–7)	5 (2.5–6)	0.244
Complications: n (%)	13 (15.9)	6 (14.6)	7 (17.1)	0.762
• **Haematuria**	8 (9.8)	3 (7.3)	4 (9.8)	0.687
• **AUR**	2 (2.4)	1 (2.4)	1 (2.4)	1.000
• **UTI**	3 (3.7)	2 (4.9)	1 (2.4)	0.548

Table-2: Outcome Variables

Variable	Total	*En bloc* TURBT	Conventional TURBT	*p*-value
Recurrence at 3 months	14 (17.1)	4 (9.8)	10 (24.4)	0.140
Detrusor muscle at the base of primary tumour	52 (63.4)	41 (100)	23 (56.1)	< 0.001

Table-3: Univariate Analysis:

Variables	*En bloc* TURBT		Conventional TURBT	
	RR (95% Confidence interval)	*p*-value	RR (95% Confidence interval)	*p*-value
Gender	NS	0.567	NS	0.457
Tumour number	NS	0.670	NS	0.971
Tumour size	2.040 (0.792–5.256)	0.140*	NS	0.457
Tumour grade	NS	0.702	NS	0.667
Tumour stage	NS	0.363	NS	0.392
Operative time	NS	0.918	1.025 (0.991–1.059)	0.147*
Duration of irrigation	NS	0.348	NS	0.389
Duration of catheter	NS	0.658	0.747 (0.549–1.017)	0.064*

* Significant at p-value < 0.25 by using cox regression analysis, NS = Not significant

Table-4: Multivariate analysis

Variables	*En bloc* TURBT		Conventional TURBT	
	RR (95% Confidence interval)	*p*-value	RR (95% Confidence interval)	*p*-value
Tumour Size	NS	0.140	NS	1.220
Operative Time	NS	0.876	1.044 (1.003–1.087)	0.034
Duration of Catheter	NS	0.641	0.709 (0.517–0.971)	0.032

Table-5: Bladder tumour characteristics on recurrence at three months

Variable	*En bloc* TURBT	Conventional TURBT	*p*-value
Recurrence site			
• Primary site	1 (2.4)	8 (19.5)	0.013
• New site	1 (2.4)	1 (2.4)	1.000
• Both sites	2 (4.9)	1 (2.4)	0.548
Tumour number	3.00 ± 0.817	2.00 ± 0.975	0.091
Tumour size (mm)	2.00 ± 1.155	1.00 ± 0.302	0.213
Tumour Grade			
• High	3 (7.3)	1 (2.4)	0.061
• Low	1 (2.4)	10 (24.4)	0.003
Tumour Stage			
• pTa	1 (2.4)	7 (17.1)	0.025
• pT1	3 (7.3)	1 (2.4)	0.305
• PUNLMP	0 (0.0)	3 (7.3)	0.079

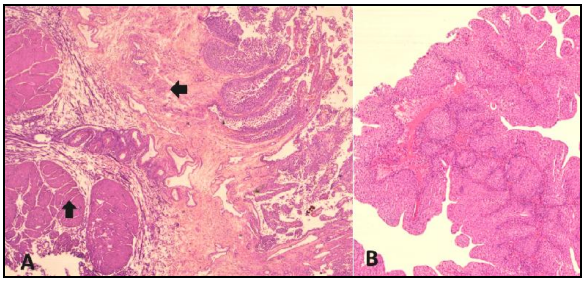

Figure-1: H&E slides of two of the en bloc TURBT specimens. They show relatively better anatomical orientation of the tumour with relation to underlying lamina propria (←A) and muscularis propria (↑A). Some of the samples were better preserved with minimal cautery artifacts (B)

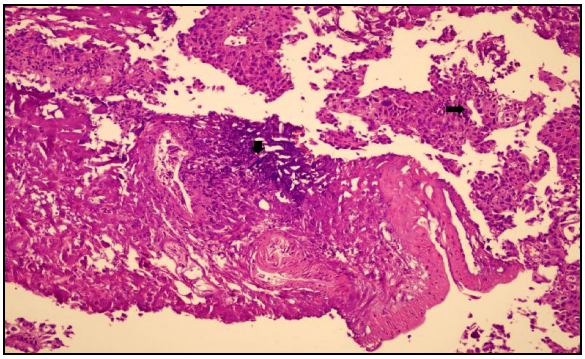

Figure-2: H&E slides of one of the specimens showing fragmentation (→) with marked cautery artifacts (↓), more common in conventional TURBT.

DISCUSSION

Bladder cancer ranks as the ninth most frequently diagnosed cancer globally. The highest incidence rates are observed in men in Southern and Western Europe, North America, as well in certain countries in Northern Africa or Western Asia.[9] In Pakistan, bladder cancer is reported to be accounting for 5.6% of all cancers, with the incidence of 8.9 cases per 100,000 individuals.[10] Removing the entire visible tumour, with a 1cm healthy mucosal margin and muscle in the initial specimen is considered as an ideal TURBT.[7] The presence of detrusor muscle helps in the assessment of the completeness of resection. It also reduces the need for the second TURBT, recurrence rate, and upstaging. It also prevents delays in the administration of intravesical therapy.[11] The presence of detrusor muscle in the initial specimen and the recurrence at the previous resection site, are the ways described by Herr[12], to assess good quality resection.

It was noticed that most of the specimens showed a relatively better anatomical orientation of the tumour with relation to underlying lamina propria and muscularis propria with better cytological preservation of the tumour, during the pathological evaluation of cases in our study (Figure-1). In these cases, it was much easier for the pathologist to assess the presence or absence of tumour invasion and tumour grade. In a few cases, an attempt to assess the margin clearance was also made by measuring the distance of the tumour from the site of excision but it was difficult to assess clear margins in our cases as monopolar diathermy was used for *en bloc* resection. Most of the cases in conventional TURBT did show tumour fragmentation and cautery artifacts (Figure-2). Intravesical Mitomycin-C was administered in all the patients within 2–6 hours of resection. The European Association of Urology risk categories' classification was used for further intravesical immunotherapy in both the groups and none of the patients reported any significant complication.

The groups were comparable in terms of median tumour size and number. However, median operative time was statistically shorter in the *en bloc* resection group (30 min vs 45 min, p=0.001). This was an interesting finding in our study as other studies results are very variable ranging from 21–56 minutes in *en bloc* group and ranges from 20–46 minutes in the conventional group.[13] Shorter operative time may be attributed to the adequate haemostasis achieved with *en bloc* resection as compared to conventional TURBT. In the conventional TURBT group, operative time was statistically significant on univariate analysis concerning recurrence at 3 months. It means that an increase in operative time can potentially increase the relative risk of recurrence. A theoretical explanation for this fact can be due to decreased risk of implantation of floating tumour cells if operative time is decreased. Statistical significance of the duration of the catheter on univariate analysis has no clinical explanation and no study has reported this finding. However, the recurrence rate in *en bloc* TURBT although less than the conventional group was not found significant. None of the variables were found significant in the *en bloc* resection group in association with recurrence at 3 months on multivariate analysis.

The deep muscle is absent in the initial specimen in 30–50% of the cases.[14] Our study on 41 patients with *en bloc* resection, showed the presence of detrusor muscle in all the specimens (100%). Hurle *et al.*[15] showed detrusor muscle in all the 74 (100%) cases, similar to our study results. This shows that *en bloc* resection provides a better quality of resection with the complete specimen (including detrusor muscle) than conventional TURBT. While in conventional group 4 (9.8%) patients required a second TURBT after histopathology was reported, due to inadequate sampling of the specimen. This added to additional costs and delay in the instillation of chemotherapy.

There were 4 out of 41 (9.8%) recurrences on first follow-up cystoscopy in *en bloc* TURBT in our study, which is comparable to 4 out of 74 cases (5.4%) in Hurle *et al.* study.[15] There is no significant reduction of recurrence in *en bloc* group in most of the previous studies. Only one (2.4%) patient had a recurrence at the primary site in *en bloc* resection group as compared to 8 (19.5%) patients in conventional TURBT (p = 0.013). Other studies also reported fewer recurrences in *en bloc* TURBT at primary sites, i.e., 1 (16%) in *en bloc* group vs 6 (40%) in the conventional group[1]. In the *en bloc* resection, a lower recurrence at the previous resection site can be attributed to a better quality of the specimen and complete resection while the higher recurrence at the primary site in the conventional group could be possibly due to incomplete resection.

En bloc TURBT is a safe procedure as all patients in our study had only minimal complications, managed conservatively, none required holding of intravesical therapy or prolonged catheterization time. None of the patients in the *en bloc* group had bladder perforation in our study. However, Hurle *et al.*[15] reported one extraperitoneal bladder perforation. Hence *en bloc* TURBT is a safe procedure in carefully selected patients. It is not recommended for tumours larger than 3cm and at a difficult location of the bladder wall (dome or anterior wall).

The current study is prospective and comparative. Small sample size, short-term follow-up duration, single-centre, and non-randomized study design are some of the limitations of our study.

It would be of interest to see the recurrence rate, disease progression, and progression-free survival after a follow-up of one year, comparing *en bloc* and conventional technique of the current cohort of patients to see mid and long-term results. Although *en bloc* TURBT is now in clinical practice in many centres with mixed oncological outcomes, further randomized studies are still recommended using bipolar, laser fibre, and newer technologies.

CONCLUSION

En bloc TURBT is a safe technique, providing high-quality specimens for histopathological evaluation and reducing the need for the second TURBT. No definitive conclusion can be made regarding the recurrence rate until the mid and long term follow up results are available.

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AUTHORS' CONTRIBUTION

MB: Literature search, questionnaire design, data collection, data analysis, data interpretation, drafting. MHA: Study design and concept, literature search, data interpretation. NK: Questionnaire design, literature search, drafting. SM: Data collection, drafting. ZU: Histopathology pictures and description, critical review.

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Address for Correspondence:

Muhibullah Bangash, Urology Section, Aga Khan University Hospital Karachi-Pakistan
Cell: +92 333 939 2932
Email: muhibbangash@gmail.com