ORIGINAL PAPER

FUNCTIONAL UROLOGY

Thulium laser en bloc resection is a safe and efficacious alternative to conventional bipolar transurethral resection of bladder tumors

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Introduction Bipolar transurethral resection of bladder tumors (bTURBT) is the standard of care technique for the management of bladder tumors; however, new techniques such as thulium laser en bloc resection of bladder tumors (TmLRBT) have been introduced as alternatives to bTURBT. In this study, detrusor muscle acquisition, perioperative outcomes and survival outcomes after TmLRBT and bTURBT were prospectively compared in patients with primary bladder tumors (1–5 cm).

Material and methods This prospective interventional study, conducted over ten years, involved 542 patients under a single surgeon. Inclusion criteria were a single tumor of 1–5 cm. The primary endpoint was the presence or absence of detrusor muscle. Perioperative criteria included operative time, hospital stay length, catheterization duration, bladder perforations, readmissions, and complication incidence. Recurrence-free survival (RFS) and cancer-specific survival (CSS) were analyzed using the Kaplan-Meier method with subgroup comparisons by the log-rank test.

Results Of 449 patients, 211 underwent TmLRBT and 238 underwent bTURBT. Detrusor muscle was present in 201 (95.2%) TmLRBT patients vs 154 (64.7%) bTURBT patients ($p < 0.001$). Complications were less frequent in the TmLRBT group ($p < 0.05$). Hemoglobin drop ($p < 0.001$), hospital stay ($p < 0.001$), catheterization duration ($p < 0.001$), and operative time ($p < 0.001$) were all significantly lower in the TmLRBT group. Kaplan-Meier analysis showed no significant differences in RFS ($p = 0.255$) and CSS ($p = 0.258$) between the groups.

Conclusions TmLRBT demonstrated significantly better detrusor muscle inclusion and perioperative outcomes compared to bTURBT.

Key Words: thulium ‹› TURBT ‹› bladder cancer ‹› bladder tumor ‹› bipolar resection

INTRODUCTION

Bladder cancer is the 4th most common malignancy in men and has a prevalence of 3–4 times higher in men than in women [1]. Despite ongoing debate about the optimal technique for bladder tumor resection, transurethral resection of bladder tumors (TURBT) remains the standard for treating non-muscle invasive bladder cancers [2]. Nevertheless, in the most experienced hands, recurrence after initial TURBT can reach up to 50–70% and may be attributed to incomplete resections of the tumor [3]. Proper staging and grading during TURBT depend critically on collecting detrusor muscle in the specimen [4]. Additionally, the presence of detrusor muscle in the initial sample is associated with a decreased 3-year cancer recurrence rate [5].

Recent innovations in the field of urology have led to advances in bladder tumor resection using different types of lasers [6]. Studies have shown that en bloc can offer several essential advantages over standard TURBT, including a higher muscle detection rate, a better quality of pathology specimens, a lower complication rate, and higher recurrence-free survival [7]. Other studies have shown that TURBT is not inferior to en bloc where muscle layer detection rate and recurrence risk are concerned [8]. Out of different surgical lasers, the thulium laser has gained momentum [6, 7]. Thulium laser en bloc resection of bladder tumors (TmLRBT) can provide shallow, smooth, and controlled incisions, allowing for better acquisition of the detrusor muscle. This allows for better visualization during the procedure [9]. TmLRBT also reduces the necessity for secondary resections, alleviating the overall burden on the patient [10]. In this study, we focused on the presence of detrusor muscle in the biopsy sample and various perioperative outcomes with RFS and CSS when comparing conventional bipolar TURBT (bTURBT) to TmLRBT.

MATERIAL AND METHODS

Patients

This prospective non-blinded interventional study was conducted between July 2009 and December 2019, involving a single surgeon at two teaching institutions. The study was registered with the institutional ethics committee and the number was IRB ITCBM511237/2012. After written informed consent, a retrospective review of a prospectively collected database of patient treated with either TmLRBT or bTURBT over a 10-year period was collected. Patients included in the study presented with a first-time single tumor on imaging and flexible cystoscopy. The tumor size was limited to those greater than 1 cm and less than 5 cm. The size and location of the bladder tumor were first assessed by computed tomography (CT) urogram and then confirmed by direct visualization with office cystoscopy in all included patients. Of 542 patients initially selected for the study, 449 met the above-listed criteria. Hence, they were included in the analysis (93 were excluded due to multiple tumors at resection) (Figure 1).

Thulium laser en bloc resection of bladder tumors technique

After identifying the tumor, the normal mucosa was marked 1 cm away from the tumor base by using thulium energy. Laser settings were approximately 1.5–1.6 joules, 20–25 hertz, and the power was approximately 30 watts (W). Blood vessels entering the base of the tumor were coagulated before starting the procedure. Normal Saline solution was used for irrigation during the resection. The incision was deepened from the normal mucosa until the detrusor muscle plane was reached. Retrograde resection was then started in the deep layer of the detrusor, all while coagulating the feeding vessels encountered. The angle of the loop and beak of the resectoscope (26F) helped elevate the tumor and access its base deep until the whole tumor was resected. Once the tumor was detached, it could then be removed. After stopping the inflow of saline and resting the tumor in the trigone and base area of the bladder, the tumor was cut into pieces using the laser. Intravesical mitomycin-C after resection was used as per the practice at our institute.

Bipolar TURBT was performed using a commercially available bipolar electro-cautery system. TURBT was performed using a dedicated 26F resectoscope with saline irrigant. Power settings on the machine were 120 W for cutting and 160 W for coagulation current. The bladder tumor was resected piecemeal for sessile tumors, >1 cm and en-bloc for pedunculated tumors. A deep muscle biopsy was attempted during each resection. Hemostasis was achieved during each procedure and confirmed by stopping irrigation. At the end of the operation, if necessary, an 18F foley catheter was

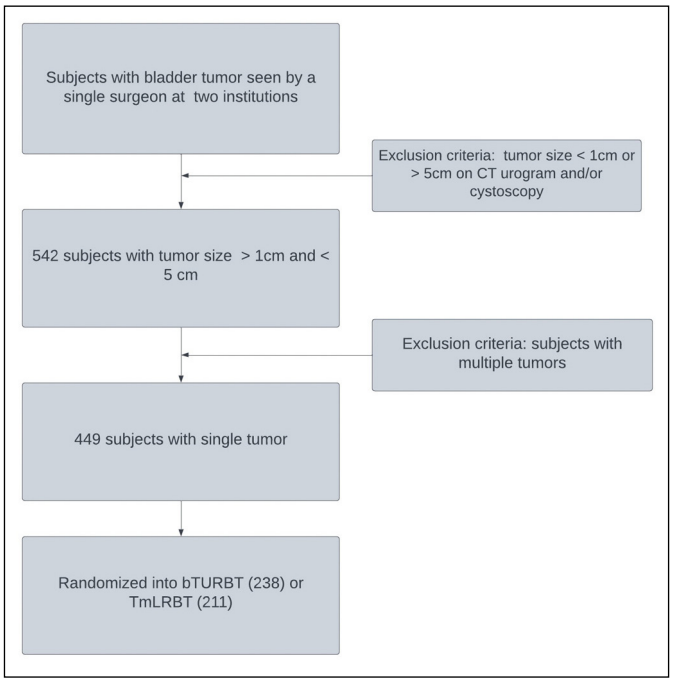

Figure 1. *Flowchart showing the number of subjects enrolled in the study with the exclusion criteria.*

placed. A restaging TURBT was performed in all TaHG and T1HG tumors.

Data collection

Demographics for both groups were collected. The histopathological examination was performed according to the 2008 World Health Organization (WHO) – International Society of Urological Pathological grading system [11]. The endpoint was the presence or absence of detrusor muscle. Other perioperative criteria were assessed. Estimated blood loss (EBL) was reflected by the fall in hemoglobin levels measured before and one day after TURBT. Other areas of interest were measured, including total operative time (time taken for patient to be in and out of the operating room), mean length of hospital stay, duration of catheterization, the number of bladder perforations (if any), number of readmissions and incidence of complications. Surgery complications were defined based on the Clavien-Dindo Classification system [12].

Qualitative data were expressed as number (n), percentage (%) and quantitative data as mean, standard deviation (SD) and range (minimum-maximum). Student's t-test was used to assess continuous variables with normally distributed data and Mann-Whitney U test was used for non-normally distributed data. Pearson 2 test was used for comparison of categorical variables. Significant test-results were quoted as two-tailed probabilities. Recurrence-free survival (RFS) and cancer specific survival (CSS) was performed using the Kaplan-Meier method with comparison of subgroups by the log-rank test. Statistical significance was defined as a p-value < 0.05 and analysis was performed using the IBM SPSS version 27 (International Business Machines Corporation, Armonk, N.Y., USA).

RESULTS

Of 449 patients, 211 were included in the TmLRBT group, while bTURBT encompassed 238. Table 1 shows patients' demographics and the difference in the pathological tumor characteristics between study groups and Table 2 shows perioperative outcomes for each group. Mean age was 78.3 and 80.8 years in both groups, respectively (p = 0.03). EBL measured in terms of drop in Hb (g/dl) was significantly higher in bTURBT cohort (p <0.001). Operative time (p <0.001), length of hospital stay (p <0.001), and catheterization time (p <0.001) were statistically significantly shorter in the TmLRBT group. One perforation was encountered in the TmLRBT group compared to 8 in the bTURBT group (p <0.001). Overall complication rate was 3.3% vs 7.14%, respectively (p <0.07). In the TmLRBT group, one patient had a Clavien Dindo grade III complication and required re-TURBT with a laser to control bleeding. Regarding the bTURBT group, 2 patients had considerable perforation that required take back and peritoneal drain placement.

Out of 211 patients who underwent TmLRBT, 201 (95.2%) showed the presence of detrusor muscle

Table 1. *Comparison of the demographics and pathological tumor characteristics between the TmLRBT and TURBT groups*

Parameter	TmLRBT (n = 211)	bTURBT (n = 238)	p-value
Gender			
Male, n (%)	128 (60)	147 (62)	0.66
Female, n (%)	83 (40)	91 (38)	0.67
Age (years), mean (range)	78.3 ±11.7 (42–89)	80.8 ±13.5 (38–91)	0.03
Presence of detrusor muscle, n (%)	201 (95.2)	154 (64.7)	<0.001
Pathological stage, n (%)			
Ta LG	103 (49)	109 (46)	0.52
Ta HG	31 (14.7)	35 (14.7)	1.0
T1 HG	55 (26)	52 (21.8)	0.29
T2	22 (10.3)	42 (17.5)	0.02
Location, n (%)			
Lateral wall	138 (65.4)	143 (60)	0.23
Dome	29 (13.7)	45 (19)	0.13
Posterior wall	44 (20.9)	50 (21)	0.97

T1HG – T1 high grade; TaHG – Ta high grade; TaLG – Ta low grade; TmLRBT – thulium laser en bloc resection of bladder tumors; TURBT – transurethral resection of bladder tumors

Table 2. *Comparison of the perioperative outcomes between the TmLRBT and TURBT groups*

Parameter	TmLRBT (n = 211)	bTURBT (n = 238)	p-value
Drop in hemoglobin (gm/dl), mean (range)	0.4 ±0.29 (0.1–1.1)	0.48 ±0.35 (0.1–1.3)	<0.001
Total operative time, mean (range)	47.6 ±25.12 (21–108)	68.9 ±28.56 (26–125)	<0.001
Length of hospital stay (hours), mean (range)	17.4 ±11 (4–48)	29.8 ±12 (4–52)	<0.001
Catheter time (hours), mean (range)	8.5 ±17.5 (2–72)	17.1 ±17.5 (2–71)	<0.001
Number Perforations, n (%)	1 (0.4)	8 (3.36)	0.02
Number of complications, n (%)	7 (3.3)	17 (7.14)	0.07
Clavien-Dindo I	4	10	
Clavien-Dindo II	2	5	
Clavien-Dindo III	1	2	
Number of readmissions, n (%)	5 (2.4)	11 (4.6)	0.2

TmLRBT – thulium laser en bloc resection of bladder tumors; bTURBT – bipolar transurethral resection of bladder tumors

on the final histological examination. In comparison, 154/238 (64.7%) in the bTURBT group showed detrusor muscle inclusion on final pathology (p <0.001). Neither group had a statistically significant difference regarding the final pathological stage and grade. Similarly, primary tumor location was comparable between both groups (Table 2).

Even though the rate of disease recurrence was almost 2 times higher in the group of patients with tumors resected with bTURBT, the difference was not statistically significant when compared to the group of patients treated with TmLRBT (p = 0.174). Kaplan-Meier analysis showed no differences in recurrence free (p = 0.255) (Figure 2) and cancer-specific survival (p = 0.258) (Figure 3) between the groups. We performed a *post hoc* power analysis to determine the number of patients needed in each group to detect a statistically significant difference in recurrence rates between the two groups. We used the χ^2 test and considered an α level of 0.05 and a power of 0.8. With a group size ratio of 0.48, and a proportion of events of 6.7% for the group of TURBT, and 12.5% for the group treated with bTURBT, the sample size for each group needed to be 599 and 289, respectively.

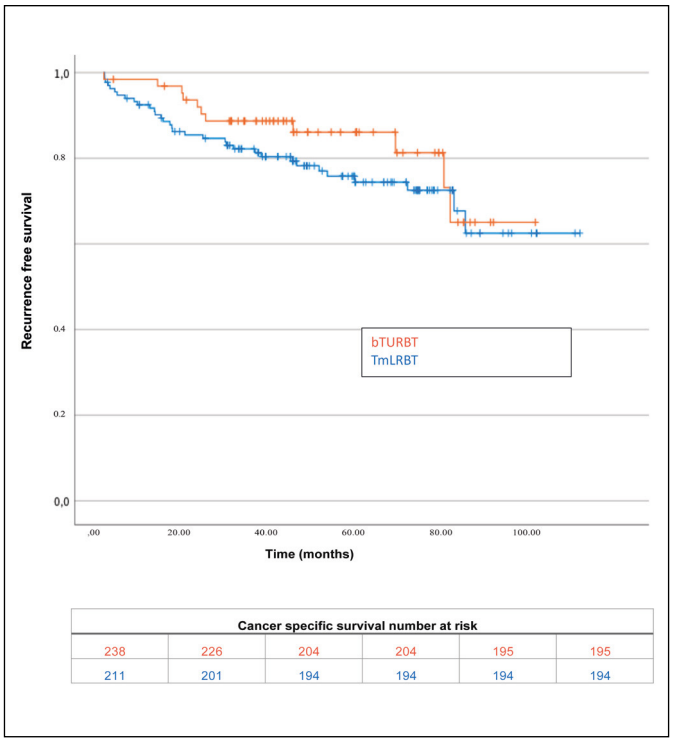

Figure 2. *Difference in recurence-free survival between patients undergoing bTURBT vs TmLRBT (p = 0.255).*

bTURBT – bipolar transurethral resection of bladder tumors; TmLRBT – thulium laser en bloc resection of bladder tumors

DISCUSSION

The European Association of Urology guidelines recommend performing either the en bloc resection or resection in fractions in case of non-muscle invasive bladder cancer (strength rating: strong) [13]. Nevertheless, TURBT remains the most adopted technique in treating these cancers. A key element in a successful TURBT is the inclusion of the detrusor muscle along with the tumor. Failure to retrieve any detrusor muscle on the initial TURBT requires an additional re-staging of TURBT, which undesirably affects patients' perspectives [14]. Additionally, recurrence rates have been known to be as high as 50–80% within the first year, especially at the original site of the tumor [15, 16].

En bloc resection aims to remove the tumor in one piece without scattering it with the resection loop. When assessing our study's primary endpoint of detrusor muscle presence, there was a strong positive correlation with the en bloc group. This correlates with previous reports confirming its efficacy in ensuring muscle layer retrieval in the specimen in most cases [6–10].

Three factors have been identified as critical factors in tumor recurrence rate after TURBT: cell implantation, tumor biology, and incomplete resection [16]. TmLRBT offers theoretical advantages of preserving tumor architecture and limiting tumor dispersal.

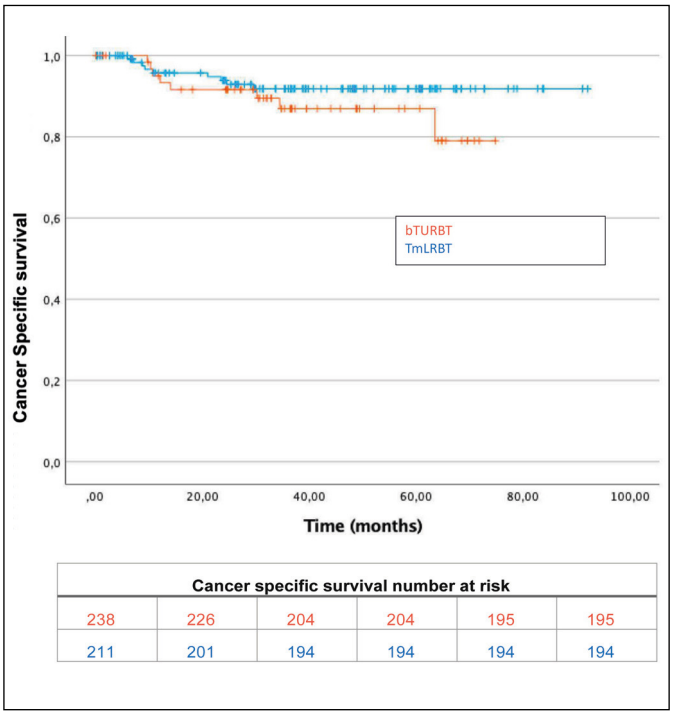

Figure 3. *Difference in cancer-specific survival between patients undergoing bTURBT vs TmLRBT (p = 0.258).*

bTURBT – bipolar transurethral resection of bladder tumors; TmLRBT – thulium laser en bloc resection of bladder tumors

By using our TmLRBT technique, at least one of these variables can be better mitigated, which may lead to reduced recurrence rates.

Regarding perioperative outcomes, TmLRBT was proven to be more efficacious when compared to bTURBT. While the EBL was not significantly different between both groups, visual acuity was notably better in TmLRBT, allowing the surgeon to perform a more accurate operation. As a result of improved vision, there was only one bladder perforation in the TmLRBT group compared to 8 in the bTURBT group. Length of hospital stay, and catheterization time were significantly shorter in patients who underwent TmLRBT, which certainly favored their overall satisfaction. The overall and high-grade complication rates were higher in the bTURBT group but not statistically significant.

Our results regarding the laser group's superior pathological and perioperative outcomes are in concordance with others in the literature [17]. Laser treatment provides excellent performance as far as hemostasis is concerned. This can be attributed to the ability of the laser to vaporize the immediate and surrounding tissues [18]. Conventional resection can be technically challenging in specific bladder locations, such as the dome, where the wall is the thinnest, and the lateral wall, where the obturator reflex is commonly encountered. The current study showed that tumor location did not differ between both groups. TmLRBT can be safely applied to any bladder location with favorable outcomes.

To our knowledge, our study includes the largest patient cohort comparing the two modalities in a prospective randomized fashion. However, it should be remembered that it represents a single surgeon with high expertise in lasers and endourology. Therefore, our favorable outcomes in the TmLRBT cohort should be regarded with extreme caution as we believe that bladder tumor resection using lasers is still challenging with a steep learning curve.

Thulium laser is one of a several lasers used to treat bladder cancers. Other lasers include holmium [19], potassium-titanyl-phosphate [20], and green-light lithium triborate lasers [21]. A thulium laser, however, has a wavelength of 2 μm, which is closest to the absorption peak of water, making it the most efficient at vaporization [22]. Consequently, thulium can also provide a shallower and more precise resection compared to its laser counterparts. Meanwhile, it can still provide optimum hemostasis.

There were, however, a few limitations to our study. This study only represents a single surgeon's experience. There could be variability in outcomes and complication rates between multiple surgeons. However, this can also be regarded as an advantage since the effect of variability in surgical skills or equipment was eliminated. Although our study shows the superior perioperative outcomes of TmLRBT, randomized control trials (RCTs) are needed to confirm the findings and investigate quality of life as perceived by the patients. Finally, although the TmLRBT is apparently more expensive, the financial aspect was beyond the scope of this study and, thus, was not included in the analysis.

CONCLUSIONS

TmLRBT is a safe and efficacious method of bladder tumor resection. TmLRBT is superior to bTURBT in terms of drop in hemoglobin, operative time, hospitalization time, catheterization time, complication rate, and pathological specimen acquisition. However, this does not translate into superior RFS and CSS. Further RCTs are needed to confirm these findings.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

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ETHICS APPROVAL STATEMENT

The study was approved by institutional ethics committee. IEC approval number was ITCBMS11237/2012.

AUTHOR CONTRIBUTION STATEMENT

Conception and design: Zaytoun, Buscarini.
Data acquisition: Buscarini, Petitti.
Analysis and interpretation of data: Tillu, Petitti.
Drafting of manuscript: Zaytoun, Tillu, Bada.
Critical revision of the manuscript for important intellectual content: Dovey, Kolanukuduru, Choudhary, Venkatesh.
Statistical analysis: Petitti.
Administrative, technical, material support: Buscarini, Zaytoun.
Supervision: Buscarini.

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