Holmium LASER in Comparison with Transurethral Resection of the Bladder Tumor for Non-muscle Invasive Bladder Cancer: Randomized Clinical Trial with 18-month Follow-up

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Purpose: To evaluate the safety and efficacy of holmium LASER resection of the bladder tumor (HoLRBT) vs. transurethral resection of bladder tumor (TURBT) as the first treatment modality for non-muscle-invasive bladder cancer (NMIBC).

Materials and Methods: Eighty-eight patients with primary non-muscle invasive bladder cancer were allocated randomly in two groups who were treated with HoLRBT or TURBT. The intraoperative and postoperative characteristics and complications of the HoLRBT and TURBT groups were compared. The data of operation time, obturator nerve reflex rate, bladder perforation, bladder irrigation, catheterization time, hospital stay, and 1, 3, 6, 12, 18 months recurrence free survivals were considered in two groups.

Results: There was no significant difference in operative duration among the two groups. Compared with the TURBT group, HoLRBT group had fewer intraoperative and postoperative complications, including obturator nerve reflex, transient hematuria, and postoperative bladder irritation. There were no significant differences among the two groups in the transfusion rate and occurrence of urethral strictures. Patients in the HoLRBT group had less catheterization and hospitalization time in comparison to those in the TURBT group. There were no significant differences in the overall recurrence rate among the TURBT and HoLRBT groups.

Conclusion: HoLRBT can be regarded as a safe and efficient method with several advantages over TURBT. HoLRBT can be used as an alternative procedure for TURBT in patients with non-muscle invasive bladder cancer.

Keywords: bladder tumor; transurethral resection; complications; LASER.

INTRODUCTION

Bladder cancer is one of the most common urologic malignances. Approximately 75%-85% of the newly diagnosed bladder cancers are confined to the mucosa (Ta or Tis) or submucosa (T1), which is known as non-muscle-invasive bladder cancer (NMIBC).[1,2] Gold standard technique of transurethral electroresection of bladder tumor (TURBT) is the most commonly used surgical procedure for treating NMIBC patients.[3,4] However, this procedure could result in serious complications such as obturator nerve reflex, bladder perforation, stricture of the ureteral ostium, and post-operative bleeding especially in patients who take anticoagulants therapy.[5-8] To overcome the possible morbidities, various procedures operating with different systems and application techniques are recently available for the treatment of NMIBC, such as holmium resection of bladder tumor (HoLRBT).

Recent studies evaluated the efficacy and safety of HoLRBT technique in the treatment of NMIBC. However, most reports have planned HoLRBT as a secondary treatment for patients with confirmed pathologic diagnosis.[9-17]

In a study by Zhu et al. on patients with NMIBC, it was found that HoLRBT was superior to TURBT in terms of intraoperative complications with a similar recurrence-free survival rate in both procedures.[18]

In this clinical trial study, the feasibility and postoperative outcomes of HoLRBT as the first-line treatment in NMIBC were investigated and compared with TURBT as a gold-standard treatment.

MATERIALS AND METHODS

Study population

From 2017 to 2019, 123 patients with the presence of a suspicious lesion on imaging (ultrasound scan, computed tomography, and magnetic resonance imaging) were assessed for eligibility to enter the study. All patients underwent cystoscopy for once under sedation and cold-cup biopsy was obtained from all cases. Then bimanual bladder examination was performed at the same time.

Cystoscopically and pathologically proven primary bladder tumors [NMIBC (Ta and T1)] were included in this study. All patients requested surgical treatments and were fully informed and provided written consent.

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Table 1. Baseline characteristics of patients and tumor features of both groups.

Variable [a]	TURBT (N = 39)	HoLRBT (N = 40)	*P*-value
Gender (%)			
Male	35 (89.7)	38 (95)	0.3
Female	4 (10.3)	2 (5)	
Median age, yr ± SD	68.2 ± 9.8	65.8 ± 10.8	0.3
Location (%)			
Lateral	15 (38.5)	18 (45)	0.3
Other	24 (61.5)	22 (55)	
Tumor multiplicity (%)			
Single	23 (58.9)	25 (62.5)	0.63
Multiple	16 (41.1)	15 (37.5)	
Mean tumor size, mm ± SD	22.2±8.1	19.8 ± 10.7	0.25
T stage (%)			
Ta	26 (66.7)	25 (62.5)	0.47
T1	13 (33.3)	15 (37.5)	
Grade (%)			
Low	33 (84.6)	35 (87.5)	0.69
High	6 (15.4)	5 (12.5)	

Abbreviations: TURBT = transurethral resection of bladder tumor; HoLRBT= Holmium laser resection of bladder tumor; SD = standard deviation.
[a] Continuous variables were compared by independent samples *t*-test

Thirty-five patients were excluded from the study because of reported hydronephrosis and/or stage T3 and T4 of bladder tumor on imaging; the presence of carcinoma in situ at cold-cup biopsy, upper urinary tract tumor, untreated urinary infection, recurrent bladder cancer, and tumor diameter more than 3 centimeters in cystoscopy and disability or decline to give fully informed consent. The remained eighty-eight patients underwent physical examination and standard urological evaluation consisted of blood tests including blood cell count and serum chemistry.

The design of this research was approved by the bioethics board of the Medical Laser Application Research Center and it conformed to the ethical guidelines of the 1975 Helsinki Declaration. The trial is registered at Iranian Registry of Clinical Trials, IRCT201701078146N18.

Study design

This was a single-center (with balanced randomization [1:1]) parallel-group study conducted in the urology department of Tajrish Hospital in Tehran, Iran. Patients were randomly assigned one of two groups according to the method of treatment: TURBT group and HoLRBT group. Simple randomization was performed using computerized random numbers. The sample size was determined based on our unpublished pilot study with

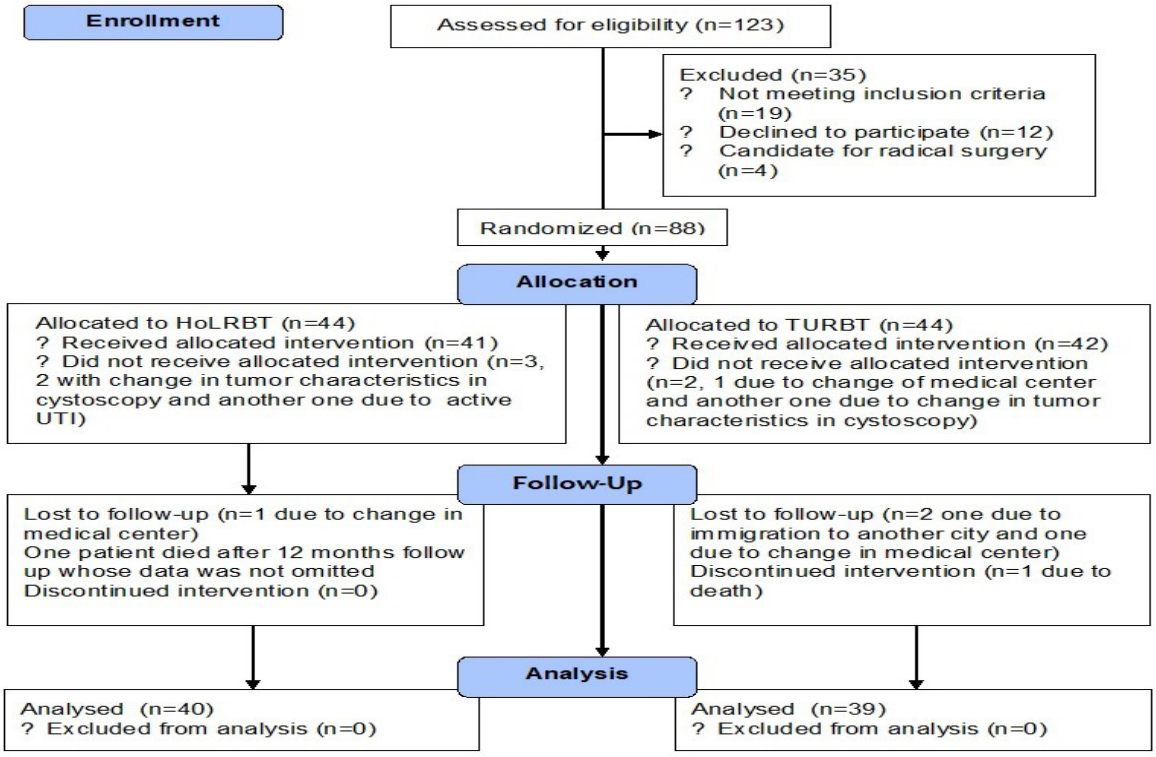

Figure 1. Flow diagram.TURBT = transurethral resection of bladder tumor; HoLRBT= Holmium laser resection of bladder tumor

Table 2. Intraoperative, early, and late postoperative outcomes as well as complications of patients of both groups

Variable [a]	TURBT (N = 39)	HoLRBT (N = 40)	*P*-value
Mean operative time, min ± SD	26 ± 10.5	28.5 ± 12	0.3
Mean serum sodium, mmol/l ± SD			
Preoperative	136.6 ± 4.0	137.7 ± 2.9	0.62
Postoperative	135.9 ± 4.1	135.7 ± 3.9	0.39
P value	0.16	0.09	-
Mean hemoglobin, g/l ± SD			
Preoperative	13.0 ± 1.8	13.1 ± 1.8	0.41
Postoperative	12.9 ± 1.8	12.9 ± 1.9	0.78
P value	0.32	0.3	-
Mean hospital stays, d ± SD	3.5 ± 1.1	0.5 ± 0.8	< 0.01*
Mean catheterization time, h ±SD	2.5 ± 1.1	1.1 ± 0.6	< 0.01*
Mean irrigation fluid, L ±SD	9.5 ± 3.3	8.6 ± 3.2	0.16
Intraoperative complications			
Obturator nerve reflex (%)	6 (15.4)	0 (0)	0.02*
Transient hematuria (%)	11 (28.2)	2 (5)	0.01*
Blood transfusion (%)	2 (5.1)	0 (0)	0.5
Bladder perforation (%)	3 (7.7)	0 (0)	0.2
Early (<30d) post-operative complications			
Clot retention (%)	1 (2.6)	0 (0)	0.7
Irritative symptom (%)	22 (56.4)	8 (20)	0.002*
Late (>30d) post-operative complications			
Urethral stricture (%)	2 (5.1)	0 (0)	0.5
Recurrent of tumor (%)	6 (15.4)	7 (17.5)	0.7
One month (%)	0 (0)	0 (0)	
Three months (%)	1 (2.6)	1 (2.5)	
Six months (%)	3 (7.7)	4 (10)	
Twelve months (%)	2 (5.1)	2 (5)	
Eighteen months (%)	0 (0)	0 (0)	

Abbreviations: TURBT = transurethral resection of bladder tumor; HoLRBT= Holmium laser resection of bladder tumor; SD= standard deviation; NS= non-significant; *= statically significant.
[a] Continuous variable were compared by independent samples *t*-test

regard to early recurrent rate of bladder tumor after the procedures. With consideration of type 1 statistical error <5%; and type 2 statistical error < 20% and a drop-out rate of 10%, a sample size of 44 patients in each group was estimated. During the study, 5 and 4 participants dropped out due to changing the medical center, detected urinary tract infection, or missing follow up. A total of 39 and 40 patients completed an 18-months follow-up in the TURBT and HoLRBT groups, respectively and their data were included in the final analysis. A summary of the study design and follow-up is provided in **Figure 1**.

Surgical technique

Pre-operative evaluation including laboratory tests and cardiovascular consultation were performed in all cases. Anti-platelet and anticoagulant drugs were stopped at least 1 week before the operation. All procedures were carried out under spinal anesthesia in the lithotomy position. TURBT and HoLRBT were performed by two different urologists who had previous experience of the procedures.

In group 1, Monopolar TURBT was performed in the standard manner with a 26 Fr Storz continuous irrigation resectoscope.

In group 2, surgery was performed using Holmium-YAG laser (Iranian National Institute for laser science and technology; Model: PMS 5644) in a pulsed wave mode. After introducing the 550-nm laser fiber through a 22 Fr continuous-flow laser cystoscope with irrigation of normal saline 0.9%, pulses of laser energy were fired at the papillary component of the tumor with a paintbrush type technique. The power is usually set at 0.9 J energy and frequency rate of 15-20 Hz while it was especially decreased to 0.6 J energy set near the bladder neck, trigon, and ureteric orifice area. The fiber was held 2 to 3mm away from the tissue. The exophytic component was treated and continued until the superficial muscle layer was visualized and ablated about 5 mm away from the tumor edge. When bleeding was observed, the laser beam was directed to that region to achieve hemostasis. After complete resection, careful coagulation of the tumor base and surrounding mucosa was done.

In both groups, multiple cold-cup biopsies were obtained from the tumor bed in order to take superficial and profound tissue samples. All of the specimens were sent for pathologic evaluation.

Finally, a three-way 20 Fr Foley catheter was inserted and irrigated by normal saline in cases with hematuria. Routine blood biochemistry profile was checked at 6 hours and the day after the operation. The patients were discharged if no hematuria was detected. Foley catheter was removed one day after cessation of hematuria. The patients were informed about possible late complications and the time of next necessary follow-up procedure. The use of postoperative intravesical chemotherapy was considered according to the European Association of Urology recommendations.[5]

Outcome assessment

The data related to operating time, obturator nerve reflex rate (spasm of adductor muscles of thigh due to obturator nerve stimulation), bladder perforation rate, gross hematuria, and bladder irritation rate, catheterization time, hospital stay, and histological results were recorded. Clinical and pathological stages were evaluated for all the patients according to the TNM 2010 staging system.[5]

Surveillance cystoscopy and urine cytology were used to detect the recurrence free interval as the primary study endpoint. A case of recurrence was considered to

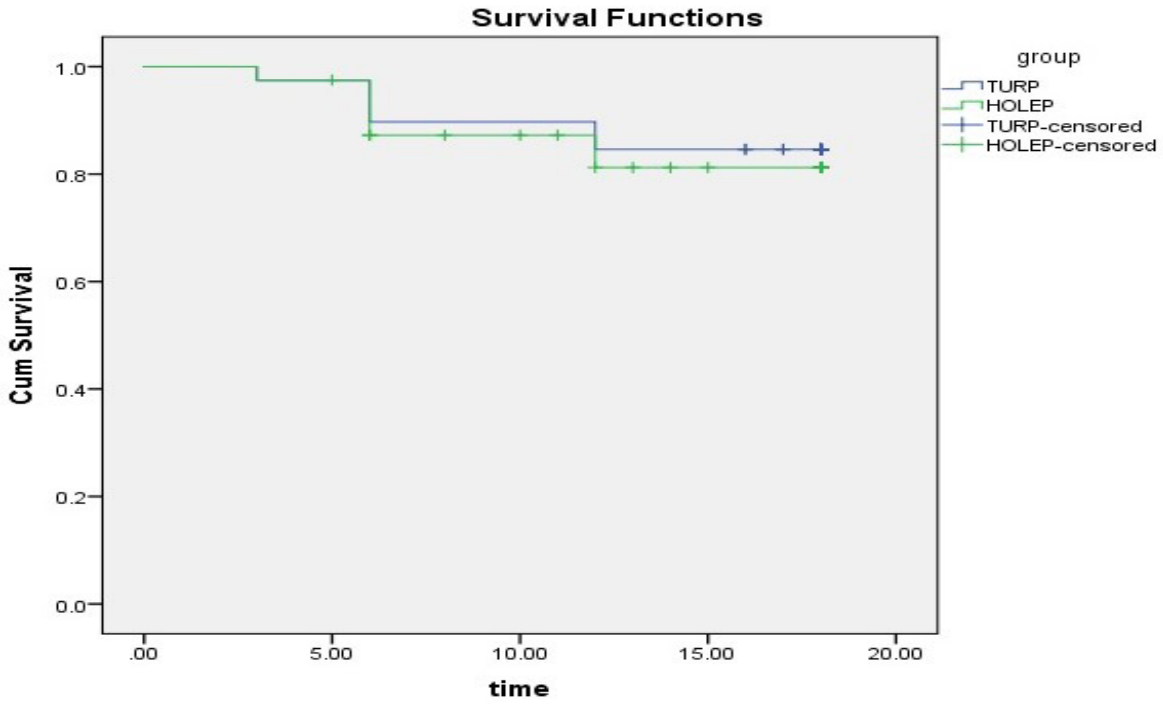

Figure 2. Kaplan-Meier estimate of recurrence-free survival in HoLRBT vs TURBT group.

be an event on the day of cystoscopy. The starting point was taken as the date of surgery. These parameters were assessed at 1, 3, 6, 12 and 18 months after the surgery. Data analysis was performed using SPSS software (Statistical Package for the Social Sciences, V. 21.0; SPSS Inc, Chicago, IL, USA) using Student's *t*-test, chi-square test and Fisher's exact test when appropriate. A P value < 0.05 was considered as statically significant.

RESULTS

The mean ± SD age of the patients was 68.2±9.8 years in the TURBT group and 65.8±10.8 years in the HoLRBT group (P = 0.3) with a male to female ratio of 90% and 95% respectively (P = 0.3).

As shown in Table 1, tumor characteristics in the HoLRBT and TURBT groups were comparable for stage (P = 0.47), grade (P = 0.69), multiplicity (P = 0.63), location (P = 0.3), and size (P = 0.25).

In TURBT and HoLRBT groups, the operation times were 26 ± 10.5 vs. 28.5 ± 12 minutes (P = 0.3); Foley catheterization times, 2.5±1.1 vs. 1.1 ± 0.6 hours (P < 0.01); and postoperative hospital stays were 3.5 ± 1.1 vs. 0.5 ± 0.8hours (P < 0.01) respectively.

Table 2 shows the baseline characteristics and detailed perioperative variables including operative duration, hospital stay, change in hemoglobin and serum level of sodium, and volume of irrigation solution.

Among patients of TURBT, bladder perforation was observed in 3 (7.7%) patients, 2 (5.1%) required blood transfusion, and 6 (15.4%) developed obterator nerve reflex during surgery; whereas none of these complications were observed in the HoLRBT group. Three patients with bladder perforation were managed successfully with conservative treatment including prolonged catheterization. The proportion of patients needing postoperative bladder irrigation due to transient hematuria in the HoLRBT group was 5% and in the TURBT group was 28.21% (P = 0.01).

Figure 2 depicts the overall recurrence free survival in the HoLRBT and TURBT groups. Overall recurrence rate throughout the 18-months of follow up were 6 (15.4%) and 7 (17.5%) in the TURBT and HoLRBT groups respectively. The Kaplan-Meier curve showed no significant difference in the overall recurrence-free rate between the HoLRBT and TURBT groups (P = 0.7).

All the recurrent cases had high grade tumors which shows a significant association between grade and recurrence (P = 0.04). The peri-ureteral lesions also had a higher recurrence rate (P = 0.002).

DISCUSSION

TURBT is still the gold standard treatment in patients with bladder tumors.[19] Despite its proven clinical outcome, the rate of intraoperative and postoperative morbidity led to the development of alternative surgical methods looking for producing equal results at a lower rate of intra- and postoperative complications. Short-term morbidity rate of 43.3% and a mortality rate of 0.1% along with a 3% transfusion rate were reported for TURBT.[20]

In an attempt to minimize the morbidity of TURBT, a number of minimally invasive procedures are being developed. The first laser treatment for bladder tumor was reported by Staehler et al. in 1978, using Nd: YAG laser.[9] Then, holmium laser was introduced and en-bloc resection of bladder tumors was performed by Saito in 2001.[11] In this study, the researchers show that HoLRBT as a first-line therapy for papillary bladder tumor can be an effective treatment with minimal complications in comparison to conventional TURBT especially in subjects with non-muscle-invasive tumors with size

less than 3 cm, solitary tumors, and low-grade malignancies.

Most relevant complications of TURBT include obturator nerve reflex (9%; range: 5–50), bleeding requiring blood transfusion (3%; range: 0–9), bladder perforation (1%; range: 0–10), clot retention (4.9%; range: 0–39), and urinary tract infection (4.1%; range: 0–22).[20] Also, the rate of urinary tract infection has shown to be higher in patients under TURBT method compared to those treated with HoLRBT technique.[21,22] In the current study, obturator nerve reflex, transient hematuria, and irritative symptoms were reported to be more frequent after TURBT than HoLRBT procedure. Yarvandi et al. suggested that the use of Thulium laser is a more feasible and effective method to prevent leg jerking in patients with bladder tumor.[23] Some authors published that HoLRBT had shorter operation time as well as catheterization time, and less hospital stay than TURBT.[22,24]

However, in our study, the operation time difference between the two groups was not significant.

Recent EAU-Guideline recommend en-bloc resection using Holmium-YAG laser in selected exophytic tumors which provide high quality resected specimens with the presence of detrusor muscle in 96-100% of cases.[5] The review by Teng[25] demonstrated that HoLRBT is safe and effective for low-grade papillary urothelial carcinoma or low-grade early TNM-stage urothelial carcinoma.

Based on EAU guideline-2020 and the EORTC Genito-Urinary Cancer Group, the non-muscle invasive bladder tumor recurrence rate was reported between %15 and 60%.[5] We found that there was no significant difference in the overall recurrence rate among the TURBT and HoLRBT groups. All these recurrences developed in high grade tumors as well as peri-ureteral lesions. Eissa et al. ()26), reported that local recurrence occurred in 28% of patients. It was noted that 57% of cases with recurrence showed some degree of dysplasia or malignancy in the lateral margin. In a meta-analysis by Teng et al.[25], there was no significant difference in the 1-year recurrence free survival between the two groups. However, the 2-year recurrence free survival favored the HoLRBT group. This might partly be because of the insufficient resection depth of lateral-wall tumor during TURBT, in order to reduce the risk of bladder perforation.[25] In HoLRBT, the holmium laser can instantly coagulate the blood and lymph vessels, reducing the chance of intraoperative dissemination of the cancer cells. Besides, holmium laser can resect neoplasm as well as adjacent tissues en bloc without touching the tumor, reducing the possibility of recurrence in situ.(27) Inability to design a double-blind clinical trial due to the different types of procedure and non-blindness of observers were major limitations of this study. Other main limitations include small sample size and exclusion of high-risk patients.

Finally, the HoLRBT therapeutic method can be regarded as a safe and efficient technique which has some advantages over TURBT including lower complication rate, lower medical costs, shorter hospital stay.18 In fact, HoLRBT could be used as an alternative therapeutic procedure for TURBT in terms of non-muscle invasive papillary urothelial carcinoma. However, further studies could be conducted with larger sample size, multi-center sampling, with inclusion of high-risk patients to attain more definite results. Also, comparison of different laser may also be considered for further studies among subjects to determine the best laser modality.

CONCLUSIONS

The gold standard treatment in patient suffering non-muscle invasive papillary urothelial carcinoma is TURBT. According to our study HoLRBT, as an alternative approach for TURBT, offers a safe and feasible procedure in the management of patients with papillary urothelial and the rate of intraoperative events such as obturator nerve reflex and bladder perforation and bleeding has been less observed than TURBT.

CONFLICT OF INTEREST

The authors do not have any proprietary interests in this study.

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