Original Article

Safety, feasibility, and quality of holmium laser *en-bloc* resection of nonmuscle invasive bladder tumors – A single-center experience

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ABSTRACT

Introduction: Conventional transurethral resection of bladder tumor (cTURBT), despite its piecemeal resection and associated limitations, remains the most widely practiced technique of TURBT. Resecting the tumor in a single piece would avoid most of the drawbacks of cTURBT. Our objective was to assess the feasibility, safety, and quality of Holmium (Ho) laser *en-bloc* resection (ERBT) for nonmuscle-invasive bladder cancer (NMIBC).

Materials and Methods: We retrospectively studied 67 patients who underwent Ho laser EBRT for primary NMIBC. Data were collected regarding tumor size, number and location, intraoperative complications, and postoperative course. Patients were grouped as first 20, next 20 (21–40), and last 27 cases to assess how the quality of resection improved with increasing experience.

Results: The mean tumor size was 28.7 ± 7.9 mm, with 34.3% of the patients having a tumor larger than 3 cm. While 43 patients (64.17%) had a single tumor, the rest had multiple tumors, ranging from 2 to 9 in number. The mean total duration of resection was 38.7 ± 11.6 min. No case required conversion to cTURBT. No patient experienced obturator reflex or bladder perforation. Detrusor muscle was present in 85.07% of the resections. With increasing experience, requirement for bladder irrigation and the incidence of postoperative clot evacuation decreased ($P < 0.0001$ and $P = 0.31$, respectively), and the detrusor-positive rate in the specimen increased ($P = 0.24$). The mean duration of catheterization was 1.76 ± 0.54 days.

Conclusion: Ho laser ERBT is safe and feasible for complete resection of NMIBCs with no risk of obturator-nerve reflex and a high rate of detrusor-positive specimens.

INTRODUCTION

Bladder cancer (BCa) accounts for around 7% of all malignancies. With more than 400,000 new cases diagnosed worldwide in 2012, this represents a huge oncologic and economic burden.[1] Around 75%–80% of these patients have nonmuscle-invasive bladder cancer (NMIBC) at presentation.[2] A complete transurethral resection, followed by surveillance and/or intravesical immunotherapy or chemotherapy, according to risk stratification, represents the current standard of care for NMIBC.[3]

A well-performed initial TURBT is a crucial step in the management of NMIBC. Important indicators of an adequate TURBT include completeness of resection and presence of detrusor muscle in the specimen.[4,5] A conventional piecemeal resection TURBT has been the preferred method by virtue of its feasibility and long-term data on oncological outcomes. However, it has inherent limitations, most notably

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tissue fragmentation, scattering of tumor cells, risk of an obturator reflex (OBR) with perforation, 30%–50% chance of absence of detrusor muscle in the specimen and hence, requirement for a re-staging TURBT.[6-8] Other concerns include risk of severe bleeding requiring a triple-lumen Foley catheter postoperatively, clot retention, and the continuous use of a large resectoscope sheath in the urethra.[9]

Various attempts have been made to overcome these shortcomings. It began with TURBT in "one-piece" using a modified electrode, and gradually moved on to using Nd: YAG and Holmium (Ho) laser for tumor vaporization.[10-12] However, these techniques were useful only for small, recurrent lesions. The first use of Ho-laser for *en-bloc* resection of primary bladder tumor was described by Das *et al*. in 1998.[13] Since then, multiple series and reviews have reported the feasibility, safety, and comparative efficacy of laser *en-bloc* resection of bladder tumor.[14-17] However, the technique has still not been widely adopted as there is paucity of data with regard to the feasibility of Ho-ERBT for multiple tumors and larger tumors (>2–4 cm), efficient method for extraction of the resected tissue, and the adequacy of resection regarding detrusor muscle biopsy.

Here, we describe our technique of Ho-ERBT and tissue extraction. We also analyzed the feasibility, adequacy, and safety with regard to perioperative complications of Ho-ERBT for NMIBC, including multiple and large lesions. We also tried to assess the learning curve of this procedure.

MATERIALS AND METHODS

Patients

A retrospective analysis of the patients undergoing Ho-ERBT for BCa at our institute from May 2014 to October 2019 was performed. Patients with a postresection histopathological diagnosis of muscle invasive bladder tumor or those detected with locally advanced or node-positive or metastatic disease on preoperative imaging were excluded from the study.

On presentation, a detailed history was obtained from all patients with regard to their presenting complaints, duration of symptoms, and comorbid conditions. All patients then underwent routine blood tests, a computed tomography urography if serum creatinine was below 1.5 mg/dl, a chest X-ray, and a urine cytology evaluation.

Surgical technique

All *en-bloc* resections were performed by a single surgeon (PNM), with the patient in lithotomy position under regional or general anesthesia. Obturator nerve block was not administered to any patient.

The procedure began with a bimanual examination of the bladder mass after draining the bladder followed by a thorough cystoscopic examination. A 24 Fr continuous irrigation resectoscope with a laser bridge (Richard Wolf, Knittlingen, Germany) was used through which a 550 μ Ho laser fiber (100 W, Lumenis, Yokneam, Israel) was passed ensheathed in a 5 Fr ureteric catheter. For one of our 14-year-old patients, a 19 Fr cystoscopic sheath was utilized, and the laser fiber was passed within a 5 Fr ureteric catheter via the working channel. The laser energy setting ranged from 1.2 to 2 Joules with a frequency of 40–50 Hz. Normal saline (0.9%) was used as the irrigant in all the cases.

To begin with, whenever possible, it is important to get under the tumor to identify its stalk. A circumferential incision is then marked around the stalk at a margin of around 2–5 mm. For nonpedunculated tumors, the incision is marked around the visible margin of the tumor. The margin runs closer to the tumor or stalk when near the ureteric orifice.

En-bloc resection is then performed by deepening the incision into the bladder wall under the mucosa to include the detrusor muscle. The resection starts at 6'o clock (the part of the incision toward the bladder neck) and continues toward 12'o clock to excise the tumor along the previously marked mucosal margin. Hemostasis is achieved by coagulation with a defocused Ho-laser beam.

Tumors on the anterior wall and dome are considered difficult sites for *en-bloc* excision as it is not possible to get under the tumor. Here, after marking the mucosal incision, the stalk or the base of the tumor is excised from the sides. The first cut on the mucosa is lateral to the tumor (8'o clock to 10'o clock and 2'o clock to 4'o clock) and then cut from sides medially toward the center of the tumor. All throughout, it is important to remain under the tumor at the detrusor level.

After *en-bloc* resection of all lesions, an Ellik's bladder evacuator was used to extract the tissue. In three cases, the tumor required fragmentation into 2–3 pieces for extraction. Immediate postresection instillation of 40-mg mitomycin-C was performed as per recommendations.[3] For our initial patients, we used a 20 Fr three-way Foley catheter with normal saline irrigation till hematuria settled, but, later, shifted to using a 16 Fr two-way Foley catheter whenever possible as deemed fit by clinical judgment.

Adequacy of resection was assessed by completeness of resection and presence of detrusor muscle in the resected specimen. All cases were assessed for intraoperative complications such as OBR, bladder perforation, and severe bleeding. Postoperative variables such as duration of catheterization, requirement of bladder irrigation, need for postoperative clot evacuation, and length of hospital stay were also studied.

We grouped our patients into the following three subgroups: first 20 cases, next 20 (21–40), and the last 27 cases. We sought to determine whether the need for postoperative bladder irrigation and the incidence of severe bleeding requiring clot evacuation decreased as our experience with ERBT increased.

Statistical analysis

Continuous data were summarized as mean ± standard deviation. Categorical data were compared by Chi-Square or Fisher's exact test. Data were analyzed in Microsoft Excel using the XLSTAT add-in (Addinsoft Inc., New York, USA). $P < 0.5$ was considered statistically significant.

RESULTS

A total of 67 patients with a mean age of 57.8 ± 15 years (range 14–82) underwent Ho-ERBT for NMIBC during the study period. Out of these, 43 (64.17%) had a single tumor, while the rest had multiple tumors, ranging from 2 to 9 in number. The largest single tumor excised was of 40 mm, while the largest cumulative size (multiple tumors) was 90 mm. Patient and tumor characteristics with regard to tumor size, number, location, T stage, grade, and European Association of Urology risk stratification are summarized in Table 1. All resections were done for primary NMIBC.

Table 2 summarizes intra and postoperative characteristics. All cases could be completed by Ho-ERBT and no conversion to conventional TURBT was required. All resected tumors could be evacuated through the 24 Fr resectoscope sheath using an Ellik's evacuator, except for four cases. In three of the remaining four cases, the resected mass was cut into 2–3 pieces with laser for extraction, while in one patient with large solid tumor, the use of a soft tissue morcellator was required. Both cutting of the resected mass and morcellation could be safely performed. No patient developed OBR or bladder perforations in this study.

Postoperative bladder irrigation was done in 19 of the first 20 cases (95%), which decreased to 7 in the next 20 cases (35%) and finally to 5 in the last 27 cases (15.5%); this difference was found to be statistically significant ($P < 0.0001$). The incidence of severe bleeding requiring postoperative clot evacuation also decreased from 4 in the first 20 cases, to 1 in the next 20 and to none in the last 27 cases, although this difference was not found to be statistically significant ($P = 0.314$). The presence of detrusor muscle in the biopsy increased from 15 in the first 20 cases (75%) to 17 in the next 20 (85%) to 25 in the last 27 cases (92.59%) ($P = 0.246$). No patient required blood transfusion. The mean duration of catheterization was 1.76 ± 0.54 days, while the mean length of hospital stay was 2.45 ± 0.75 days.

Table 1: Patient and tumor characteristics

Variable	*n*	Mean±SD
Sex		
Male	52	NA
Female	15	
Age (years)		
<40	6	57.8±15
40-49	17	
50-59	10	
60-69	15	
>70	19	
Tumor number		
Single	43	2.26±1.14
Multiple	24	
Tumor size (mm) (of largest in multiple tumors) (cm)		
<3	44	28.7±7.9
>3	23	
Tumor location		
Lateral wall	51	NA
Bladder neck and trigone	5	
Dome	4	
Multiple sites	7	
T stage		
Ta	55	NA
T1	12	
Tumor grade		
LG	43	NA
HG	24	
EAU risk category		
Low	26	NA
Intermediate	16	
High	25	

EAU=European Association of Urology, NA=Not available, SD=Standard deviation

Table 2: Perioperative characteristics

Variable	Result	*P*
Duration of total en-bloc resection in min (Mean + SD)	38.7 + 11.6	
Duration of resection per tumor in min (Mean + SD)	23.1 + 10.7	
Obturator reflex (*n*)	0	
Bladder perforation (*n*)	0	
Conversion to conventional TURBT (*n*)	0	
Blood transfusion (*n*)	0	*P*<0.0001
Post-operative bladder irrigation (n)		
First 20 cases	19	
Next 20 cases	7	
Last 27 cases	5	*P*=0.314
Severe bleeding requiring clot evacuation (*n*)		
First 20 cases	3	
Next 20 cases	1	
Last 27 cases	0	*P*=0.246
Detrusor muscle present in biopsy (*n*)		
First 20 cases	15	
Next 20 cases	17	
Last 27 cases	25	
Duration of catheterization in days (Mean + SD)	1.76 + 0.54	
Duration of hospital stay in days (Mean + SD)	2.45 + 0.75	

SD=Standard deviation, cTURBT=Conventional transurethral resection of bladder tumor

DISCUSSION

TURBT is a critical initial step in the diagnosis and staging of bladder tumors. For NMIBCs, it is also a vital component of therapy. The importance of a complete and adequate tumor removal cannot be overemphasized. Conventional

TURBT (cTURBT) involves electroresection of the tumor in small fragments. The very process of resecting a tumor in pieces is unique to cTURBT. Resection into small fragments leads to concerns about the completeness of resection, bleeding, cancer cell implantation, and increased risk of recurrence. To circumvent this and remove the tumor completely as a single piece, laser ERBT has been described. Ho-laser has excellent cutting and hemostatic properties[18] and is well suited for ERBT. Das *et al*., in 1998, were the first to describe Ho-laser ERBT in 23 patients with primary NMIBC.[13] Following this, there have been multiple reports evaluating the role of laser ERBT (Ho and Thulium laser) for primary NMIBC.[14,19-21] We studied the feasibility and safety of Ho ERBT in 67 patients over the last 5 years.

Most of the available reports on laser ERBT deal with tumors up to 3 cm with very limited data on larger tumors.[14,20,22-24] The mean tumor size in our study was 28.7 ± 7.9 mm, with a third of the patients having a tumor of size >3 cm. Complete resection by the *en-bloc* technique was achieved in all cases with no conversion to cTURBT. One of the concerns raised about larger tumors is that they would require fragmentation prior to extraction, which would partially defeat the purpose of ERBT.[15] In this study, resected tumor could be extracted in toto through the resectoscope sheath in 63 out of the 67 cases. Bladder tumor being a soft mass lesion can easily mold itself, and large tumors can be extracted intact via the resectoscope sheath as a single piece. For very large and solid masses, breaking the tumor in 2–3 pieces and morcellation are both safe. Although it can be argued that piecemeal removal is akin to cTURBT, and there could still be dispersal and implantation of cancer cells, we feel that the suction and negative pressure of morcellator would reduce this risk. In addition, the other advantages of ERBT such as reduced bleeding and no obturator spasms outweigh this assumed disadvantage. Thus, our results indicate that laser ERBT is feasible even for larger tumors >3 cm.

It is believed that certain tumor locations may make patients ineligible for ERBT.[25] Kramer *et al*. in their review article suggest that approximately 30% of patients were not appropriate for ERBT due to tumor size, formation, and/or location.[15] They feel that many surgeons avoid ERBT in cases when tumors are located at the anterior and posterior bladder walls, at the bladder neck, and when tumors exceed the size of 3 cm. In this series, we have not excluded these sites or sizes. Although most of the tumors in our series were located on the lateral wall, we did have four cases in the dome and five cases in the trigone and bladder neck. We were able to resect all these tumors with the *en-bloc* technique.

Zhu *et al*.[22] reported that they used a combination of laser *en-bloc* resection and vaporization for tumors located on the anterior wall and the dome. However, Migliari *et al*.[24] reported the feasibility of *en-bloc* resection for tumors located at the dome and trigone using Thulium laser. Our results are in agreement with those of the latter group. Furthermore, as the depth of tissue penetration of Ho laser is only 0.4 mm, using this laser for resection of tumors at the dome is not associated with any risk of intraperitoneal extravesical thermal injury.

The average number of tumors in an individual patient in our series was 2.26, with 35.87% patients having multiple tumors ranging from 2 to 9 in number. Multiplicity of tumors did not pose a problem with laser ERBT, which was in sync with previous reports.[14,20-22,24]

Intraoperative OBR with possible resultant bladder perforation is a serious complication of cTURBT. This occurs due to flow of electric current through the obturator nerve while resecting tumors on the lateral walls.[26] As no electrical energy is used in Ho laser resection, OBR does not occur. We too did not experience any OBR or bladder perforation in our patients. This was similar to the findings in prior series on laser ERBT.[14,19,20,24] The risk of OBR theoretically persists even when *en-bloc* resection is performed with electrical current using loops of modified shapes. Absence of OBR is one of the major advantages of laser ERBT over cTURBT and *en-bloc* excision by electrocautery.

The Ho laser has precise cutting and efficient hemostatic properties.[27] In our series, severe bleeding with postoperative clot evacuation was required in only 4 of the 67 patients. Fulguration of bleeding points, if needed during clot evacuation, was performed by electrocautery. In addition, none of the patients required blood transfusion. Postoperative bladder irrigation was required in 31 patients, with most of them in the initial learning curve. The use of irrigation and risk of bleeding needing clot evacuation declined with time as our experience increased.

The duration of catheterization (mean 1.76 days) was also comparable to that reported in previous reports of Ho ERBT, which is shorter than that reported for cTURBT.[14,20,22] In our initial cases, we kept the catheter for 2–3 days and with increasing experience, the duration of the catheter reduced to 24–36 h. A recent review by Li *et al*. concludes that the catheter duration reduces in laser resection of bladder tumor by a mean duration of more than 1 day.[28]

All these benefits, namely, low incidence of postoperative clot evacuation, decreased requirement of postoperative bladder irrigation, and shorter duration of catheterization, are all linked to each other and may be attributed to the efficient hemostasis achieved with Ho laser. In fact, the potent coagulative property of Ho laser also offers a relatively bloodless field during the resection.

A pivotal component of an adequate TURBT is the presence of detrusor muscle in the biopsy specimen as it provides vital

staging information. Akand *et al*. in their review on quality control indicators for cTURBT noted a 15%–66% rate of absence of detrusor in the resected specimen.[29] Contemporary series with laser ERBT have reported detrusor-positive rates ranging from 78% to 100%.[10,21,27,28,30] Our results indicate an 85.07% overall rate of presence of detrusor muscle in the resected specimen. This rate improved from 75% in our first 20 cases to 85% in the next 20 and finally to 92.6% in the last 27 cases. Although there was an increasing trend, this difference was not statistically significant. However, another way to look at these results is that even in the initial cases, the detrusor-positive rate of the biopsy was not significantly worse than that in the most recent reports. This again points to the feasibility and ability of Ho ERBT to have detrusor muscle in the resected specimen.

All the patients who did not show detrusor muscle in postoperative biopsy were not subjected to restage TURBT. It was done only in patients with high-grade, multiple, large tumors. In patients with small, low-grade tumors, restaging TUR-BT was not indicated.[31] Restaging was done by laser, cTUR-BT, or by punch biopsy based on intraoperative findings.

We divided our ERBT cases into the first 20, next 20 (21–40), and the last 27 cases to study the impact of increasing experience on various parameters of the resection. We noted that, with increasing experience, the incidence of severe bleeding with the requirement of postoperative clot evacuation decreased. In addition, there was a significant decline in the need for postoperative bladder irrigation. The quality of the resection in terms of presence of detrusor in the resected specimen also improved. Based on these findings, we propose that the learning curve for Ho ERBT is around twenty cases.

We acknowledge the limitation of the retrospective design of our study. However, our results lay the platform for further research regarding ERBT. Prospective and long-term studies are needed to decide if we can avoid immediate postoperative instillation with ERBT because there is no tumor fragmentation and subsequent implantation? It also needs to be evaluated if the risk of recurrence reduces after ERBT?

CONCLUSION

Ho laser ERBT is a safe and feasible technique for bladder tumors. It can achieve complete resection of NMIBCs in various bladder locations and also for multiple and large tumors. Further, Ho laser offers the advantages of absence of obturator reflux and efficient hemostasis. We found that with increasing experience, the incidence of severe bleeding and requirement of postoperative bladder irrigation reduce. In addition, the high rate of detrusor-positive specimens highlights the adequacy of resection. The learning curve for Ho ERBT is not steep. We propose wider adoption of laser ERBT for NMIBCs. This would help in providing us with robust data to evaluate the ultimate oncologic aim of doing an *en-bloc* resection – to decrease recurrences in NMIBCs.

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