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REVIEW

Thulium laser treatment for bladder cancer

Wei Wang, Haitao Liu*, Shujie Xia*

Department of Urology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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Abstract Recent innovations in thulium laser techniques have allowed application in the treatment of bladder cancer. Laser en bloc resection of bladder cancer is a transurethral procedure that may offer an alternative to the conventional transurethral resection procedure. We conducted a review of basic thulium laser physics and laser en bloc resection procedures and summarized the current clinical literature with a focus on complications and outcomes. Literature evidence suggests that thulium laser techniques including smooth incision, tissue vaporization, and en bloc resection represent feasible, safe, and effective procedures in the treatment of bladder cancer. Moreover, these techniques allow improved specimen orientation and accurate determination of invasion depth, facilitating correct diagnosis, restaging, and re-evaluation of the need for a second resection. Nonetheless, large-scale multicentre studies with longer follow-up are warranted for a robust assessment. The present review is meant as a quick reference for urologists.

1. Introduction

Bladder cancer is the 11th most commonly diagnosed cancer worldwide. Approximately 75% of patients with bladder cancer present with non-muscle-invasive bladder cancer (NMIBC), confined to the mucosa (stage Ta, carcinoma *in situ*) or submucosa (stage T1) [1]. Transurethral resection of bladder tumor (TURBT) remains the gold standard treatment for bladder cancer. However, this type of procedure is associated with a significant risk of residual tumors, which are often under-staged after initial TURBT. According to the guidelines [1], persistent disease after resection of T1 tumors has been observed in 33%—55% of patients, and after resection of Ta Grade 3 tumor in 41.4%. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumor ranges from 4% to 25%, and it increases to 45% if there was no muscle in the initial resection. While complete and correct tumor resection is crucial to achieve a good prognosis, conventional

* Corresponding authors.
E-mail addresses: doctorlht69@163.com (H. Liu), xsjurologist@163.com (S. Xia).
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TURBT results in greater risk of recurrence. In order to overcome the limitations of conventional TURBT, various modifications of standard resection techniques have recently been developed. An important development is represented by transurethral thulium laser en bloc resection of bladder tumor (ThuLEBT), along with a catalogue of techniques based on other lasers, such as holmium laser (Ho:YAG) vaporization or en bloc resection of bladder tumor [2,3].

Although various laser types have been used in the treatment of bladder cancer, holmium and thulium lasers are most frequently employed. Similar results have been reported for both types of lasers with respect to feasibility, safety, and effectiveness in comparison with TURBT. However, the continuous beam of the thulium laser does not exhibit the tissue-tearing effect of the pulsed emissions of Ho:YAG, which is likely. This might be the reason for the exclusive application of the thulium laser for en bloc resection, while no application has been reported for vaporization of bladder cancer [4]. Thus, in the present review, we focused on ThuLEBT, a state-of-the-art technique for minimally invasive treatment of bladder tumors.

2. Technological and procedural details

2.1. Thulium laser

The thulium laser is a continuous wave that emits at a wave length of approximately 2013 nm. Its physical properties and effect on various tissues are virtually identical to those of the Ho:YAG, but with an even shallower depth (0.25 mm) of tissue penetration [5]. Due to the pattern of the continuous wave, the thulium laser allows smooth incision and vaporization of tissues with excellent efficiency [6]. Thulium laser devices with shallow penetration and power settings that can be adjusted according to tumor size provide relatively clear vision and satisfactory haemostatic effect during the operation. Under these circumstances, thulium laser-based techniques allow en bloc resection and ablation for the management of bladder tumors [7].

2.2. Thulium laser operation procedure

Several studies have reported on the operating procedure for the treatment of bladder cancer. Thulium lasers are usually generated using a 2-μm laser system (LISA laser products OHG, Katlenburg-Lindau, Germany) with a 2013-nm laser fibre. Laser energy can be delivered in continuous mode *via* a 550-μm fibre with a power of 5–15 W or 30–50 W, through a 24 Fr or 26 Fr 30-degree continuous flow endoscope [6,8–10].

Once the laser starts to operate, the laser fibre is held at a safety margin of 2–5 mm away from the tumor, which is sufficient for the laser energy to instantly vaporize the tumor. The efficiency of vaporization is proportional to the laser power, though using higher power does not lead to an increase in complication rates [3]. In order to complete the en bloc resection and obtain an adequate specimen, it has been suggested that, after finishing the surrounding line, the operation should proceed with a transurethral resection, to expose the base of the tumor up to the deeper layers, until the detrusor muscle is exposed; finally, the bladder wall is dissected *via* blunt laser incision. Larger tumors (size >3 cm) can be removed through the base of the bladder wall after being cut into two or three pieces. Saline irrigation is used throughout the procedure [6,8,11,12].

Once the tumors are removed, random, cold-cut biopsy specimens are taken from the tumor base and from an area within 2 cm of the tumor edge; the biopsy specimens must be harvested from areas which have adequately coagulated or been vaporized using laser energy, after removing the surrounding muscle layer.

3. Clinical outcomes

To assess the clinical outcomes associated with ThuLEBT, the present review noted the reported operative duration, perioperative complications, and tumor recurrence.

3.1. Operation time and complications

Based on the systematic review and meta-analysis regarding the management of NMIBC, Bai *et al*. [3] found no significant difference between thulium laser treatment and TURBT or Ho:YAG treatment with respect to operation time or hospitalization duration (mean difference: −0.69 h; 95% confidence interval (CI): −1.62–0.24 h; $p = 0.14$). However, Zhang et al. [11] and Chen et al. [13] found that operation time was significantly lower for patients undergoing TURBT than for those undergoing ThuLEBT (28.43 min *vs*. 31.5 min, $p = 0.044$; 56.5 min *vs*. 41.0 min, $p = 0.017$; respectively), which may have been due to the additional time required for the thulium laser to achieve a precise resection of the anterior wall of large tumors. Migliari et al. [12] reported a mean operative time of 25 min (range, 12–30 min) for resection of a single papillary tumor with a diameter of 2.5 cm (range, 0.5–4.5 cm), regardless of tumor location. For multiple NMIBCs, Liu et al. [8] found the mean operation time was 48 min per patient (range, 20–90 min), and 13.6 min per tumor (range, 5–25 min), the mean number and diameter of tumors were 3 cm (range, 2–5 cm) and 1.2 cm (range, 0.3–2.5 cm), respectively.

With respect to intra- and post-operative complications, Bai et al. [3] performed a systematic meta-analysis of seven studies and found that ThuLEBT was better than TURBT. Specifically, significant differences were observed between the group of patients treated by ThuLEBT and the group of patients treated by TURBT, with respect to obturator nerve reflex (risk ratio: 0.07; 95%CI: 0.02–0.23; $p < 0.0001$), bladder perforation (risk ratio: 0.16; 95%CI: 0.05–0.54; $p = 0.003$), bladder irrigation (risk ratio: 0.36; 95%CI: 0.19–0.69; $p = 0.002$), and duration of the catheterization (mean difference: −1.26 min; 95%CI: −1.79–(−0.73) min; $p < 0.00001$). Indeed, complications after ThuLEBT have been described in only five studies, with a total of 355 patients. Specifically, bladder perforation in conjunction en bloc resection was described in two studies, urethral stricture was described in two studies, and anterior urethral injury caused by transurethral resection was described in one study. The overall complication rate was 1.4%, and none of the complications were life-threatening. Acute peri- and post-operative bleeding was not mentioned in any of these studies. Taken together, these observations support the conclusion that thulium laser treatment represents a safe and efficient approach for managing bladder cancer.

3.2. Histopathological examination

Complete and correct tumor resection is essential in order to achieve a good prognosis. However, TURBT often causes fragmentation, artefacts, thermal damage, and tangential sections that might hamper the histopathological evaluation [14]. The thulium laser allows en bloc excision of tumors with excellent haemostasis and a clearer visual field; these features improve specimen orientation and enable the detrusor muscle to be clearly visible during blunt dissection [7]. Furthermore, histological reporting is more straight forward, and it can allow accurate reporting of the depth of invasion [4,12].

In terms of staging and grading, Wolters et al. [6], Liu et al. [8], and Migliari et al. [12] all found that 100% of the biopsy specimens contained detrusor muscle tissue suitable for correct staging. However, Zhang et al. [11] found that, of 27 specimens that did not contain detrusor muscles, nine specimens (6.3%, $n = 143$) came from patients undergoing TURBT, while 18 specimens (12.1%, $n = 149$) came from patients undergoing ThuLEBT. In addition, Kramer et al. [15] compared ($p = 0.18$) the content of detrusor muscle tissue in specimens harvested following electrical ($n = 150$, 96.2%) and laser ($n = 65$, 100%) en bloc transurethral resection. While the outcomes of these studies were clear, the reported differences did not reach statistical significance.

3.3. Tumor recurrence and progression

To date, no large, prospective, multi-centred studies with long follow-up periods have been conducted to investigate the efficiency of ThuLEBT. Based on currently available data, recurrence rates after ThuLEBT are expected to be similar or lower than those after Ho:YAG treatment or TURBT [3]. Liu et al. [16] first presented data from the 12-, 24-, and 36-month follow-up, with no difference between the group of patients who had undergone ThuLEBT (10.9%, 19.5%, and 31.3%, respectively) and the group of patients who had undergone TURBT (10.7%, 22.9%, and 33.9%; respectively). In a later study on the clinical outcomes of ThuLEBT, Ho:YAG, and TURBT, the same authors found that the currency rate at the 12-month follow-up was lowest in patients who had undergone ThuLEBT (thulium laser: 12%, TURBT: 17.2%, Ho:YAG: 25%) [8]. Zhong et al. [17] found that recurrence rate at the 24-month follow-up was similar between the patients who had undergone ThuLEBT (26.67%) or Ho:YAG treatment (24%), but lower than that for patients who had undergone TURBT (30.95%).

According to Kaplan—Meier survival curves from a recent study conducted by Chen et al. [13], there was no statistical difference between ThuLEBT and TURBT with respect to the rate of recurrence at the 18-month follow-up ($p = 0.383$). Zhang et al. [11] found that overall recurrence rate was 14.7%, 42.1%, and 62.5% in low risk, intermediate-low risk, and intermediate-high risk subgroups, respectively. However, none of these studies used a systematic classification system for assessing recurrence and progression, especially with long-term follow-up. Hence, future studies should use a standard classification scheme and gather results from long-term follow-up periods.

3.4. Second resection

The risk of residual tumor and frequent under-staging after initial TURBT has been demonstrated. A second TURBT, usually performed within 2—6 weeks of the primary procedure, is always recommended in certain cases such as T1 bladder tumors. The potential advantages of thulium laser treatment, as previously mentioned, include accurate reporting of the depth of invasion, which serves for determining the correct diagnosis. This opens away to re-evaluate the need for a second resection or for the restaging of bladder tumors in the short term. Migliari et al. [12] found that re-resection and cold cup biopsy of the tumor base at 90 days postoperatively was negative for bladder tumor persistence or recurrence in all 58 patients who had received thulium laser treatment; however, seven of 61 patients who had undergone TURBT were found to be tumor-positive, and 3 of these patients were upstaged. These results support the conclusion that employing thulium laser treatment has the potential of avoiding a second resection for 90 days postoperatively. However, further studies with long-term follow-up are warranted in order to thoroughly support these findings.

4. Conclusion

Newly developed, high-performance techniques based on thulium laser represent safe and efficient procedures for treating bladder cancer. There was no significant difference between ThuLEBT and TURBT with respect to tumor recurrence and progression rates. Furthermore, ThuLEBT is advantageous because it allows complete tumor resection and straight forward histological evaluation of specimens, enabling to re-evaluate the need for a second resection or for restaging the bladder tumor in the short term. Large, prospective, multicentre studies with longer follow-up periods should be performed to systematically confirm the advantages of thulium laser applications for treating bladder cancer.

Conflicts of interest

The authors declare no conflict of interest.

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