

Efficacy and safety of *en bloc* resection versus transurethral resection for ureteral orifice-invasive bladder tumors

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Abstract

Background: Surgical treatment for ureteral orifice-invasive bladder tumors is tricky and remains controversial. **Objective:** This study compared the efficacy and safety of thulium laser *en bloc* resection of bladder tumor (ERBT) and transurethral resection of bladder tumor (TURBT) for ureteral orifice-invasive tumors. **Methods:** Clinical data of patients with non-muscle invasive bladder tumors close to or invading the ureteral orifice from March 2016 to October 2023 were retrospectively analyzed. Pre-operative imaging confirmed no ureteral dilation or hydronephrosis. Bladder instillation chemotherapy was administered based on the pathological findings. Follow-up with cystoscopy and imaging was conducted every 3 months for 1–2 year(s), and then every 6 months thereafter. **Results:** Forty-two patients were included (25 ERBT, 17 TURBT). All surgeries were completed without intraoperative complications. Median follow-up lasted for 22 months. Baseline median age (65 vs. 63 years, $p=0.27$), tumor number (all solitary), and size (2.85 ± 1.06 cm vs. 3.14 ± 0.82 cm, $p=0.37$) were comparable between the TURBT and ERBT groups. Mean operative time was shorter with ERBT (16.08 ± 3.26 min) than with TURBT (30.00 ± 3.53 min; $p=0.01$). Post-operative hematuria occurred in two TURBT cases and none in ERBT ($p=0.006$). Detrusor muscle sampling was missed in seven TURBT cases and none with ERBT ($p=0.003$). Hospitalization was shorter for ERBT (3.12 ± 0.73 days) than with TURBT (4.53 ± 0.80 days; $p=0.04$). No short-term ureteral stenosis or hydronephrosis developed in either group. **Conclusion:** ERBT safely resects ureteral orifice-invasive tumors, avoids double-J stenting, and protects the ureteral orifice, rendering it preferable to TURBT in this setting.

Keywords: Bladder cancer, Transurethral resection of bladder tumor, Ureteral orifice, *En bloc* resection

1. Introduction

Bladder cancer is a common malignant urinary tumor with high morbidity and mortality rates,¹ with 75% of patients initially diagnosed with non-muscle invasive bladder cancer (NMIBC).² Currently, the primary diagnostic and therapeutic option for NMIBC is the transurethral resection of bladder tumor (TURBT).^{3,4} In cases where tumors are adjacent to or invading the ureteral orifice without upper urinary tract hydronephrosis, the electrocautery range of TURBT often involves the removal of the ureteral orifice, incurring complications such as distal ureteral stenosis and post-surgical hydronephrosis, which may require reoperation.⁵ It is proposed that placing a ureteral stent following TURBT for ureteral orifice-invasive tumors could effectively prevent distal ureteral stenosis and support favorable post-surgical recovery.⁶ However, controversy remains as to whether this approach can prevent long-term distal ureteral stenosis or influence tumor recurrence. Notably, bladder tumors invading or adjacent to the ureteral orifice often disrupt the anti-reflux mechanism of the ureteral orifice after TURBT, potentially facilitating tumor metastasis along the ureteral stent.

In recent years, thulium laser *en bloc* resection of bladder tumor (ERBT)⁷ has been widely applied in treating NMIBC.⁸ In this approach, a circular incision along the edge of the bladder tumor is made along the superficial muscle layer, allowing for *en bloc* resection.⁹ The thulium laser has demonstrated superiority in tissue cutting, vaporization, and hemostasis for bladder tumors. Clinical studies also showed

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that, compared to TURBT, thulium laser surgery is associated with lower tumor recurrence rates, fewer complications such as obturator nerve reflex and bladder perforation, shorter surgical time, and faster post-operative recovery.^{10,11} With high water-absorbing efficiency, the thulium laser enables precise control of tissue damage depth, while its continuous wave output gives smooth incision and vaporization, resulting in ideal cutting and hemostatic effects.¹¹ Moreover, the adjustable power settings allow flexible control of the cutting energy, making it particularly valuable for resection of tumors near the ureteral orifice, where TURBT poses technical challenges.

In this study, we retrospectively analyzed the clinical data of NMIBC patients with tumors invading or adjacent to the ureteral orifice. We aimed to explore the efficacy and safety of thulium laser ERBT without ureteral stent placement in treating bladder tumors invading or adjacent to the ureteral orifice.

2. Methodology

2.1. Patients' data

This study retrospectively analyzed the clinical data of NMIBC patients with tumors invading or adjacent to the ureteral orifice, treated at Shanghai General Hospital between March 2016 and October 2023. Pre-operative B-mode ultrasound or computerized tomography urography confirmed the absence of ureteral dilation, hydronephrosis, or primary tumor in the upper urinary tract. Patients with cystitis glandularis, bladder carcinoma *in situ*, tumors extending beyond the ureteral orifice, or myometrial invasive bladder cancer confirmed by post-operative pathology were excluded.

2.2. Surgical methods

All patients received surgery under general anesthesia. For the TURBT group, the tumor was completely removed using a circular electrode, with the cutting base reaching the deep muscle layer and the ureteral orifice completely resected. The smooth mucosa of the internal segment of the ureteral wall was mildly everted and exposed to the electrocautery wound. The base was routinely biopsied for pathological analysis. Electrocoagulation was used for hemostasis, except for the ureteral section and intramural segment, where electrocoagulation should be avoided. In 17 cases requiring extensive resection of the bladder mucosa around the ureteral orifice or significant retraction of the ureteral stump beyond the bladder, a double-J (D-J) tube (F 4.7) was placed in the affected ureter after thoroughly flushing away the tumor tissue fragments and floating debris within the bladder. For the thulium laser ERBT group, a thulium-doped fiber laser treatment machine (Raykeen T120F Thulium Fiber Laser, Shanghai Raykeen Co., China) was used (Figure 1).

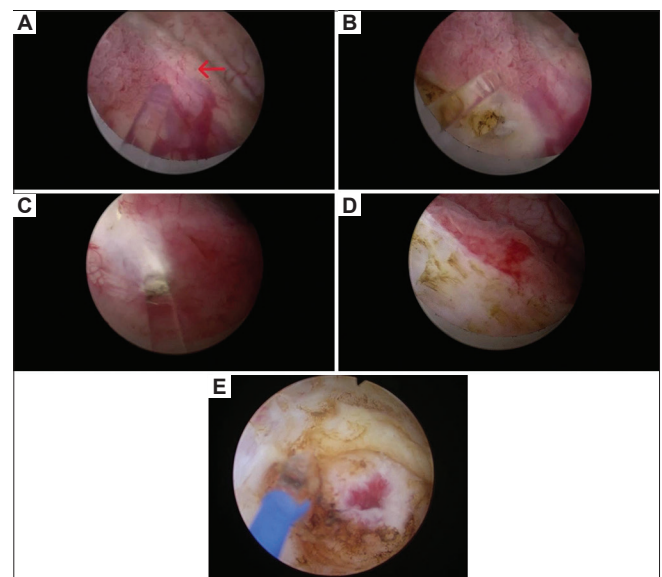


Figure 1. Intraoperative images illustrating key steps during thulium laser *en bloc* resection of bladder tumor. (A) A tumor adjacent to the right ureter (pointed by the red arrow). (B) A 30 W thulium laser (Shanghai Raykeen Co., China) was used to excise the muscular layer away from the ureteral orifice. (C) At the ureteral orifice side, the laser power was switched to 5 W to incise the mucosa, separating the tumor from the ureteral orifice. (D) The ureteral orifice was completely preserved. (E) The tumor covering the ureteral orifice and the ureteral orifice were completely removed using a 30 W thulium laser.

For a bladder tumor adjacent to the ureteral orifice, a circular incision was made about 5–10 mm around the periphery of the tumor through to the detrusor muscle layer. Together with the ureteral orifice, the tumor was completely removed through the detrusor muscle layer using a 30 W thulium laser. Then, a complete tumor specimen was flushed out through the urethra without a ureteral stent.

For a tumor located over 5 mm away from the ureteral orifice, a 5–10 W thulium laser was used to cut the mucosa along the edge of the tumor near the ureteral orifice. The tumor was then lifted away from the ureteral orifice. Then, the laser power was switched to 30 W for routine resection. Bladder instillation chemotherapy was implemented based on the pathological results. Follow-up for cystoscopy and imaging examinations was performed every 3 months within 1–2 years after surgery and every 6 months thereafter according to the pathological results. This study was approved by the Ethics Committee of Shanghai General Hospital, and informed consent to participate was obtained from all patients included in the study.

2.3. Statistical analysis

The collected data were recorded into Microsoft Excel and analyzed using the Statistical Package for Social Sciences software (version 30.0) and GraphPad Prism version 5. Numerical variables, such as tumor size, hospitalization

time, and operative time, were presented as mean ± standard deviation, whereas age and follow-up time were expressed as median (interquartile range). Categorical variables were reported as counts and percentages. Unpaired differences in proportions were compared using the Chi-square test or Fisher’s exact probability test, depending on the specific circumstances. The Z-test (standard normal deviation) was used to calculate significant differences in proportions. A $p<0.05$ was considered statistically significant.

3. Results

All 42 surgeries, performed by the same surgeon, were completed without intraoperative complications or the need for blood transfusions. In the TURBT group, D-J tubes were successfully placed in all 17 patients during surgery, which took 3–15 min, with an average of 6 min. Electrocautery wound base biopsies confirmed the absence of residual tumors. All patients received immediate post-surgical bladder instillation chemotherapy. Only high-risk NMIBC patients were subjected to Bacillus Calmette–Guérin instillation starting 1 month after surgery, whereas the remaining patients underwent post-surgical intravesical chemotherapy alone. The post-operative pathological diagnosis in the TURBT group included one case of papilloma, four cases of low-grade malignant potential urothelial papilloma, seven cases of low-grade papillary urothelial carcinoma, and five cases of high-grade papillary urothelial carcinoma. In the ERBT group, there was one case of papilloma, two cases of low-grade malignant potential urothelial papilloma, 13 cases of low-grade papillary urothelial carcinoma, and nine cases of high-grade papillary urothelial carcinoma. Histopathological staging showed 12 Ta and 5 T1 cases in the TURBT group, compared with 15 Ta and 10 T1 cases in the ERBT group ($p=0.87$). Tumor grade distribution included 7 low-grade and 5 high-grade tumors in the TURBT group, and 13 low-grade and 9 high-grade tumors in the ERBT group ($p=0.64$). According to the American Urological Association risk classification, five patients were at low-risk, six at intermediate-risk, and five at high-risk in the TURBT group. In contrast, seven patients were at low-risk, eight at intermediate-risk, and nine at high-risk in the thulium laser ERBT group ($p=0.74$) (Table 1). No adverse events such as fever, lower back pain, or bone marrow suppression occurred during immediate post-surgical or subsequent bladder instillation chemotherapy. Around 4–8 weeks after TURBT surgery, the D-J tube was removed under cystoscopy. During catheterization, no persistent or refractory urinary frequency, pain, or adverse events requiring early tube removal were observed.

The median follow-up time lasted for 22 (9–46) months. Median age was 65 (61–77) years for the TURBT group and 63 (60–75) years for the thulium laser ERBT group ($p=0.27$). All patients had solitary urinary bladder tumors. The mean

Table 1. Clinical characteristics of patients

Parameters	TURBT	Thulium laser ERBT	<i>p</i>
Median age, years (mean [interquartile range])	65 (61–77)	63 (60–75)	0.27
Mean tumor size, cm (mean±SD)	2.85±1.06	3.14±0.82	0.37
Tumor location			0.86
Beside the left ureteral orifice	8	10	
Beside the right ureteral orifice	9	15	
Tumor stage			0.87
Ta	12	15	
T1	5	10	
Tumor grade			0.64
Low	7	13	
High	5	9	
AUA risk category			0.74
Low	5	7	
Intermediate	6	8	
High	5	9	

Note: Data presented as frequencies, unless stated otherwise. Statistical significance determined at $p<0.05$. Abbreviations: AUA: American Urological Association; ERBT: *En bloc* resection of bladder tumor; TURBT: Transurethral resection of bladder tumor.

tumor size in contrast-enhanced computed tomography in the TURBT group measured 2.85 ± 1.06 cm and 3.14 ± 0.82 cm in the thulium laser ERBT group ($p=0.37$). The size of all the tumors was within 5 cm. Regarding tumor locations, tumors were beside the left ureteral orifice in eight cases and beside the right ureteral orifice in nine cases in the TURBT group. In the ERBT group, the tumors were beside the left ureteral orifice in 10 cases and beside the right ureteral orifice in 15 cases ($p=0.86$) (Table 1). Mean operative time was 30.00 ± 3.53 min in the TURBT group and 16.08 ± 3.26 min in the thulium laser ERBT group ($p=0.01$). Post-operative hematuria developed in two TURBT cases and none in the thulium laser ERBT group ($p=0.006$). Detrusor muscle biopsy was missed in seven TURBT cases and none in the ERBT group ($p=0.003$). Mean hospitalization time was 4.53 ± 0.80 days in the TURBT group and 3.12 ± 0.73 days in the thulium laser ERBT group ($p=0.04$) (Table 2). No short-term ureteral stenosis or hydronephrosis occurred in the thulium laser ERBT group. One patient from the TURBT group developed upper urinary tract hydronephrosis caused by ureteral stenosis after removal of the D-J tube and underwent ureteral reimplantation surgery. No tumor recurrence was found in the upper urinary tract of the affected ureter in either group. Cystoscopy showed normal urine emanating from the ureteral orifice. Cystoscopy showed normal urine emanating from the ureteral orifice, and no orifice stenosis was spotted. Recurrence took place in three TURBT cases and none in the thulium laser ERBT group ($p=0.01$). None of the recurrent tumors in the patients from the TURBT group were located in the previous surgical area.

Table 2. Pre-operative characteristics of patients

Parameters	TURBT	Thulium laser ERBT	p
Mean operative time, mins (mean±SD)	30.00±3.53	16.08±3.26	0.01
Delayed post-operation hematuria	2	0	0.006
Missing the detrusor muscle during biopsy	7	0	0.003
Mean hospitalization time, days (mean±SD)	4.53±0.80	3.12±0.73	0.04
Recurrence	3	1	0.01
Hydronephrosis	1	0	0.02

Note: Data presented as frequencies, unless stated otherwise. Statistical significance determined at $p<0.05$.
Abbreviations: AUA: American Urological Association; ERBT: *En bloc* resection of bladder tumor; SD: Standard deviation; TURBT: Transurethral resection of bladder tumor.

4. Discussion

Transurethral resection of bladder tumor is the gold standard for treating NMIBC, aiming at completely removing the tumor and providing specimens for definitive diagnosis and post-operative treatment guidance.³ However, conventional TURBT using devices such as plasma electrocautery has many potential drawbacks. For example, the thermal damage to the adjacent soft tissues, such as the muscle layer, during TURBT can cause difficulties during the pathological examination of the fragmented tissue, whereas compression and fragmentation of the tumor tissue may lead to shedding of considerable tumor cells, increasing the risk of tumor bladder implantation and hematogenous spread.^{8,12,13} Due to the shallow resection depth, incomplete resection may occur during TURBT, and residual tumor tissue may need to be removed through re-TURBT. Moreover, a deeper resection may increase the risk of complications such as bladder perforation and bleeding, making it difficult to balance the safety and effectiveness of TURBT. In addition, the electric current can stimulate the obturator nerve, causing muscle contraction and bladder perforation in some cases, especially for tumors situated on the lateral wall. When managing bladder tumors near the ureteral orifice, the tissue damage caused by the TURBT may injure the ureteral orifice, often necessitating ureteral stent placement. These drawbacks limit the application of TURBT, prompting alternative solutions. The application of lasers in urology provides another option for bladder tumor resection. Many laser treatments for NMIBC, including potassium titanium phosphate laser, holmium laser, and a 120 W high-performance system green laser, have been proven to be safe and effective.¹⁴⁻¹⁶ As the latest innovation in surgical lasers, the thulium laser exhibits higher absorption rates, a stronger cutting capacity, and less thermal damage in water.^{17,18} Several studies have reported its association with a higher detrusor recognition rate and fewer complications.^{17,18} The tissue penetration depth of the thulium

laser is only 0.2 mm due to its short wavelength, which enables precise dissection. Accurate cutting can reduce damage to the surrounding mucosa and enable surgical procedures closer to the ureteral orifice.

Bladder tumor invading the ureteral orifice accounts for 5.4–13.3% of bladder tumors.^{6,19} For NMIBC invading the ureteral orifice, partial cystectomy combined with ureterovesical replantation is routinely performed. Radical cystectomy is recommended for high-grade stage T1 cancer with hydronephrosis. In addition, bladder tumors that do not invade but are adjacent to the ureteral orifice are also commonly encountered in clinical practice. Although TURBT remains the gold standard for bladder tumor management, it poses significant risks when tumors are close to, but not invading, the ureteral orifice. The procedure often fails to preserve the integrity of the ureteral orifice and may even lead to post-operative scar contraction and ureteral orifice constriction. TURBT relies on pure electrocautery for tumor resection and spot electrocoagulation for hemostasis in active bleeding areas. While this technique can reduce the incidence of ureteral stricture, the reported incidence of distal ureteral stricture after ureteral orifice resection can be as high as 16%.²⁰ Mano *et al.*¹⁹ reported the results of 79 patients who underwent TURBT, with 84 ureteral orifices removed without placing ureteral tubes. The median follow-up time was 15 months, and a total of 11 cases (13%) developed hydronephrosis. Among them, 3 cases (4%) required endoscopic treatment due to ureteral bladder junction stenosis, and 5 cases (6%) had hydronephrosis secondary to muscle-infiltrating tumors and required radical cystectomy. The remaining 3 cases (4%) had temporary hydronephrosis that resolved spontaneously.¹⁹

Once scar stenosis occurs after ureteral orifice resection, subsequent treatment is challenging and almost always requires secondary laparoscopic surgery. Placement of a D-J tube may theoretically reduce the incidence of stenosis after ureteral orifice resection and is therefore commonly used in clinical practice. However, few studies have reported the effects and adverse events of this method. Some researchers believe that, although ureteral tubes can lower the risk of acute obstruction and lower back pain caused by ureteral edema or spasm, they do not achieve a significant preventive effect on ureteral fibrosis, which typically begins 3–4 weeks after surgery.¹⁹ In this study, the D-J tube in the TURBT group was placed for 4–8 weeks, with follow-up spanning from 9 to 46 months. Notably, one patient who retained the D-J tube for 8 weeks developed ureteral stenosis 2 months after stent removal, which progressed to renal hydronephrosis and was subsequently managed by ureteral reimplantation surgery. Although the sample size of this study is relatively small, the absence of ureteral stenosis in all 25 patients treated with thulium laser ERBT without stent placement supports its

significant advantage in treating bladder tumors invading or adjacent to the ureteral orifice.

In addition, traditional TURBT surgery with ureteral D-J tubes may cause tumor cell reflux into the upper urinary tract, inducing tube syndrome such as urinary frequency, urgency, and pain.²¹ It may also cause chemotherapy drugs to reflux into the kidneys, increasing the adverse reactions of post-operative bladder instillation chemotherapy.²¹ These concerns can restrict the application of ureteral tubes. In this study, no adverse reactions, such as fever, lower back pain, or bone marrow suppression, were observed during the immediate post-TURBT instillation of epirubicin or subsequent bladder instillation chemotherapy. The D-J tube was retained for 4–8 weeks without severe urinary frequency, and the implementation of the instillation chemotherapy was not affected. However, seven patients still experienced mild back pain after the D-J tube placement. In contrast, no cases of lower back pain were found in the thulium laser ERBT group. Considering that both surgical wounds and bladder instillation chemotherapy can cause lower urinary tract symptoms, and the severity of symptoms could substantially vary, this study did not use the bladder overactivity rating scale to conduct a detailed evaluation of lower urinary tract symptoms caused by ureteral tubes. For NMIBC patients at intermediate and high risk of recurrence and progression, Chinese guidelines recommend post-operative bladder instillation of Bacillus Calmette–Guérin.²² However, whether ureteral tube placement increases the incidence of Bacillus Calmette–Guérin-related adverse events has not yet been reported.

The proposed theory that ureteral tube placement may cause reflux of tumor cells into the upper urinary tract and subsequent implantation metastasis is mainly supported by two reasons. First, the ureteral orifice is armed with an anti-reflux mechanism, which would disappear after removal of the ureteral orifice or placement of the D-J tube. The residual tumor cells in the post-operative urine can reflux into the upper urinary tract and cause implantation metastasis in high-malignancy tumor cases. Second, the risk of tumor ascending would increase due to the D-J tube placement. However, this theory has not been validated in large-scale evidence-based studies. In clinical practice, the authors have treated cases of ureteral implant metastasis caused by D-J tube placement after TURBT, underscoring the need to further investigate strategies to prevent such events. We propose the following precautions. First, the use of D-J tubes should be avoided whenever possible. For bladder tumors invading the ureteral orifice, using thulium laser ERBT to remove the ureteral orifice can preclude short-term and long-term ureteral stenosis after surgery. Therefore, using the thulium laser ERBT to remove tumors at a standard depth can reduce the risk of tumor residue. Second, in cases where the tumor is close to but has not yet completely invaded the ureteral

orifice, low-power thulium laser in continuous wave can be used to excise the mucosa along the gap between the tumor and the ureteral orifice. With its precise tissue-cutting capabilities, the low-power thulium laser minimizes collateral injury to adjacent mucosa and submucosal structures. This technique preserves the structural and functional integrity of the ureteral orifice, thereby maintaining its anti-reflux mechanism and reducing the risk of fibrosis-related long-term stenosis, which is more common after TURBT. Third, several mechanisms have been proposed to explain the recurrence of bladder tumors after TURBT, including tumor polycentricity, incomplete resection, and tumor cell implantation. In traditional TURBT, tumors are removed in a piecemeal manner, increasing the chance of tumor cells entering the bladder mucosa, especially on the surface of the burned urinary epithelium. By contrast, thulium laser ERBT surgery generates a “coagulation layer” beneath the evaporated tissue, minimizing the risk of seeding tumor cells into the mucosa. Moreover, complete tumor *en bloc* removal further reduces the potential for tumor dissemination.^{12,23,24} Compared with D-J tube placement after TURBT, thulium laser ERBT can minimize tumor debris production. Continuous bladder irrigation and immediate bladder instillation chemotherapy after surgery may also help reduce the likelihood of retrograde implantation of exfoliated tumor cells into the upper urinary tract.

This study has several limitations. First, the sample size was relatively small, and the retrospective design restricted the evidence level of the results to some extent. Prospective trials with a large sample can be conducted to further support the findings of this study.

5. Conclusion

Thulium laser ERBT for NMIBC that invade or are close to the ureteral orifice can obviate the need for ureteral stent placement while effectively preventing post-operative ureteral stenosis and hydronephrosis. For bladder tumors close to the ureteral opening, where TURBT may cause damage to the ureteral orifice, low-power thulium laser ERBT represents an optimal alternative for preserving the structural and functional integrity of the ureteral orifice.

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Conflict of interest

The authors declare they have no competing interests.

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Writing—review & editing: All authors

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai General Hospital, and all patients provided informed consent to participate.

Consent for publication

Not applicable, as this study received ethical exemption.

Data availability statement

Not applicable.

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