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Original Article

Comparative study of 2 um laser versus Holmium laser for the resection of non-muscle invasive bladder cancer

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Abstract: Objectives: To compare the safety and efficacy of conventional monopolar transurethral resection of bladder tumor (TURBT), 2-micron continuous-wave laser and holmium laser resection techniques in the management of primary non-muscle invasive bladder tumor (NMIBT). Methods: From January 2009 to January 2013, 210 patients newly diagnosed primary NMIBC were enrolled randomly in this study, including conventional TURBT group (n=70), holmium laser group (n=70) and 2-micron laser group (n=70). We retrospectively analyze and record operative time, postoperative bladder irrigation, catheterization time, hospitalization time, complications included obturator nerve reflex, bladder perforation, blood transfusion, and 2-year tumor recurrence rate in all patients. Results: Characteristics of patients and tumors in all three groups were compared before surgery. There was no significant difference in operative time among the three groups. Compared with the conventional TURBT group, both 2-micron and holmium groups had less intraoperative and postoperative complications, including obturator nerve reflex, bladder perforation, and postoperative bladder irritation. There were no significant differences among the three groups in the blood transfusion rate and incidence of urethral stricture. Patients in the 2-micron and holmium groups had less catheterization and hospitalization time than those in the conventional TURBT group. There was no significant difference in the 2-year tumor recurrence rate among the three groups. Conclusion: Our results demonstrated that the use of 2-micron (thulium) laser and holmium laser in the management of NMIBT were superior to conventional monopolar TURBT, while there were no significant differences between 2-micron laser and holmium laser. However, 2-micron laser and holmium laser did not have an obvious advantage over conventional TURBT in 2-year tumor recurrence rate. A longer follow-up period and larger numbers of patients are necessary to demonstrate the present result in the future.

Keywords: Non-muscle invasive bladder tumor, holmium laser, 2-micron laser, transurethral resection of the bladder tumor

Introduction

The incidence of bladder cancer ranks first among all urinary tract tumors [1]. The majority of the newly diagnosed bladder cancers are of the non-muscle invasive bladder tumor (NMIBT), which are confined to the mucosa and staged as Ta, T1, or carcinoma in situ (CIS) [2]. Currently, the standard surgical treatment of NMIBT is transurethral resection of the bladder tumor (TURBT) [3]. Back in 1976, lasers were added to the endourological armamentarium for the treatment of bladder cancer [4]. Despite the standard procedure for staging and treating non-muscle invasive bladder tumor by TURBT via a wire loop at present, laser resection techniques for bladder tumor came back into focus with the introduction of Holmium yttrium aluminum garnet laser (Ho: YAG) [5] and Thulium yttrium aluminum garnet laser (Tm: YAG) [6]. Today, Ho: YAG and Tm: YAG seem to offer alternatives in the treatment of bladder cancer, but still to prove their potential in larger prospective randomized controlled studies with long-term follow-up [7].

In this study, we compared the safety and efficiency of conventional TURBT, 2-micron (thulium) continuous-wave laser, and holmium laser in the treatment for patients with non-muscle invasive bladder tumor.

Patients and methods

Patients

From January 2009 to January 2013, 210 patients (see Supplementary Table) newly diagnosed primary NMIBC were enrolled randomly in this study, including conventional TURBT group (n=70), holmium laser group (n=70) and 2-micron laser group (n=70). We retrospectively analyze and record operative time, postoperative bladder irrigation, catheterization time, hospitalization time, complications included obturator nerve reflex, bladder perforation, blood transfusion, and 2-year tumor recurrence rate in all patients. Patients were excluded if they had muscle invasive bladder tumors, recurrent tumors, distant metastases, or upper urinary tract tumors. CT and cystoscopy with biopsy were chosen to diagnose bladder cancer and evaluate the clinical stage preoperatively. CIS was detected by using urine exfoliative cytology and random bladder biopsies. Patients were randomly assigned to the conventional TURBT, 2-micron laser or holmium laser group using computer-generated random numbers. Each patient was unaware of which surgery applied. Preoperative evaluations included the clinical history, physical examination, routine blood/urine examination, urine cytology, CT scan of the abdomen and pelvis, cystoscopy and a biopsy of the tumor. The experimental process was approved by the Ethics Committee of our hospital. All the patients were provided written informed consent to participate in the study.

Operation procedures

All operations were performed by one experienced surgeon. Patients were placed in the lithotomy position with epidural anesthesia. Normal saline was used for continuous irrigation during the 2-micron laser and holmium laser operation, and glycine solution was used for conventional TURBT.

The RevoLix 2-micron laser system (LISA Laser products OHG, Germany), and a 550-mm end-firing PercuFib fiber (LISA laser products OHG, Germany) introduced via a 26-F continuous flow resectoscope (Karl Storz, Germany), were used in the continuous wave mode. The entire bladder was carefully examined to determine the tumors location, size, number and presence or absence of tumor pedicle. Approximately 30-50 W of power was chosen during the operation. The tumor was vaporized by the laser beam with a fiber-tissue distance of about 2 mm. A circular incision was made around the tumor, followed by level incisions beneath it with subsequent tumor retrieval. The circular incision connected marks made about 1-2 cm away from the tumor edge and continued until the deep muscular layer was exposed. When the tumor was relatively large, it was necessary to incise longitudinally. In most patients, the complete tumor tissue with basal layers was obtained after several rounds of laser incision and blunt peeling. The hemostasis was achieved by using laser light spots. An extractor was used to wash out these tumor specimens.

Holmium laser system (Raykeen DHL-1, maximum output 60W, maximum ureter frequency 30 Hz, wave length 2.1 um, China) and a 26 F reflux plasma prostate resectoscope (Olympus, Japan) were used in holmium laser operation. Laser output power (30-60 W) was tailored according to the characteristics of the tumor. The fiber was held 2 to 3 mm away from the tissue. When the vaporization reached the tumor base, the vaporization continued until the deep muscular layer was exposed. The other operation procedure was similar to the 2-micron laser.

For the conventional TURBT procedure, a Wolf 26-F continuous flow resectoscope with loop electrode (Richard Wolf, Germany) was used in operation. The cutting and coagulation power was set at 120 W and 60 W respectively.

Regardless of the technique applied, the bladder mucosa was coagulated 2 cm away from the tumor base. The tumor specimens were sent for histopathologic examination after operation to determine the tumor stage and grade. An 18-22 three-way Foley urethral catheter was placed after operation for all patients. We removed the catheter when the patient's urine was normal.

The intravesical chemotherapy for bladder cancer with 40 mg/40 ml epirubicin was conducted immediately 1 week after the operation, applying weekly for 8 weeks, followed by monthly maintenance to 12 months.

Outcome measures

Operative time, postoperative bladder irrigation, catheterization time, hospitalization time, and complications included obturator nerve

Table 1. Characteristics of patients and tumors

Variable	TURBT (n=70)	2-micron laser (n=70)	Holmium laser (n=70)	F/χ^2 value	*P* value
Sex				0.83	>0.05
Male	48	50	45		
Female	22	20	25		
Age (y)	57.87±4.99	58.31±6.13	59.97±5.75	2.69	>0.05
Tumor number (n)	2.53±1.21	2.74±1.52	2.43±1.33	0.98	>0.05
Tumor size (cm)	1.53±0.20	1.63±0.32	1.58±0.51	1.25	>0.05
Tumor location				0.784	>0.05
Lateral	25	23	28		
Other	45	47	42		
Stage				1.58	>0.05
Ta	35	40	37		
T1	27	23	28		
CIS	8	7	5		
Grade				2.62	>0.05
PUNLMP	18	20	15		
Low	46	40	48		
High	6	10	7		

TURBT = transurethral resection of bladder tumor; PUNLMP = papillary urothelial neoplasms of low malignant potential.

reflex, bladder perforation, blood transfusion, were documented in all groups. A 2 years follow-up study was performed postoperatively for all patients: cystoscopy and ultrasonography were performed every 3 months for the 2 years and followed by every 6 months to monitor the recurrence of bladder cancer.

Statistical analysis

Statistical analysis was done by using SPSS I7.0 software (Chicago, IL, USA). All numerical results are presented as mean ± SD, one-way analysis of variance was used for continuous variables and the chi-square test was used for categoric variables. Tumor recurrence was calculated and compared using the Kaplan-Meier curve analysis and Log-rank test. P<0.05 was considered to be statistically significant.

Results

A total of 210 patients were enrolled in our study, and they were randomly assigned to the conventional TURBT group (n=70), 2-micron laser group (n=70) and holmium laser group (n=70). The baseline characteristics in patients with NMIBT had no significant difference in three groups and were presented in **Table 1**. All cases had sufficient specimens for pathologic diagnosis, including tumor staging and grading.

Intraoperative and postoperative outcomes of the three groups were compared in **Table 2**. There was no statistically significant difference among the three groups for the mean operative time and incidence of blood transfusion. Eleven patients experienced obturator nerve reflex in the conventional TURBT group, while none of patients experienced obturator nerve reflex in 2-micron laser and holmium groups. Bladder perforation did not occur in the 2-micron laser and holmium groups, but it occurred in five patients in the conventional TURBT group. No patient died during the operation in three groups. Postoperative bladder irrigation performed in the conventional TURBT (14 patients) because of postoperative bleeding was more than in the 2-micron laser group (5 patients) and holmium laser group (6 patients). No significant difference was found in postoperative catheterization time and hospitalization time between 2-micron laser group and holmium laser group, but in conventional TURBT group the catheterization and hospitalization time were significantly longer.

During the 2-year follow-up study postoperatively, 24 patients (10 patients from conventional TURBT group, 6 patients from the 2-micron laser group, and 8 patients from the holmium laser group) lost to follow-up, while no recurrence or progression was detected in these patients. The tumor recurrence rate were analyzed at the end of study. The Kaplan-Meier survival curves are shown in **Figure 1**. There were 8 patients experienced tumor recurrence in conventional TURBT group within 24 months with a 2-year tumor recurrence rate of 15.0% (9/60), while 8 patients in 2-micron laser group with a 2-year tumor recurrence rate of 10.9% (7/64) and 9 patients in holmium laser group with a 2-year tumor recurrence rate of 12.9% (8/62). There was no significant difference in the 2-year recurrence rate among the three groups.

Table 2. Intraoperative and postoperative outcomes of conventional TURBT, 2-micron laser and holmium laser group

Variable	TURBT	2-micron laser	Holmium laser	F/χ^2 value	*P* value
Operative time	27.33±6.62	25.50±4.23	26.24±7.20	1.56	>0.05
Blood transfusion (NNT)	2	0	0	4.04	>0.05
Obturator nerve reflex	11	0	0	23.22	<0.00*
Bladder perforation	5	0	0	10.24	<0.01*
Catheterization time (d)	3.29±0.46[a,b]	2.47±0.42	2.36±0.51	74.60	<0.00*
Hospitalization time (d)	4.43±0.55[a,b]	3.41±0.45	3.26±0.44	113.75	<0.00*
Bladder irrigation	14	5	6	6.63	<0.05*
Urethral stricture	4	2	3	0.70	>0.05

TURBT = transurethral resection of bladder tomor, NNT=number need to treat; *Statistically significant. [a]P<0.05 (TURBT VS 2-micron laser), [b]P<0.05 (TURBT VS Holmium laser).

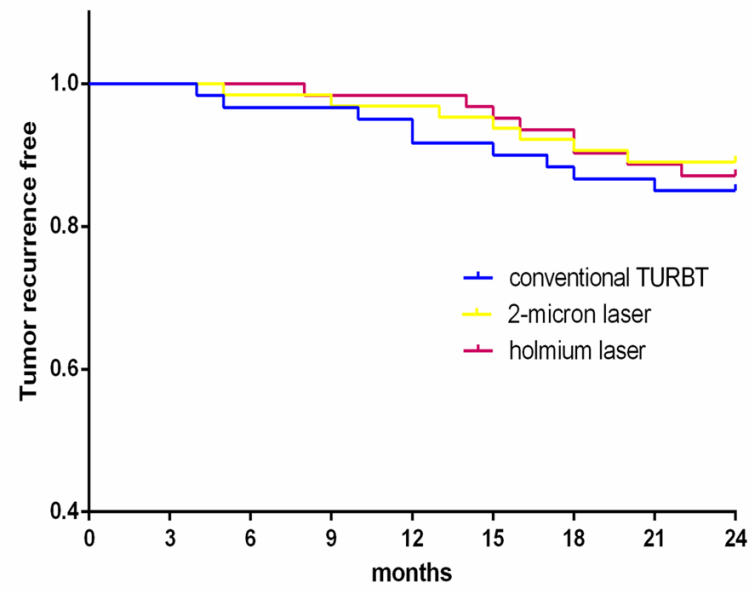

Figure 1. Kaplan-Meier survival curves of tumor recurrence time (PPS, per protocol set). No statistical difference was observed among the three groups (P>0.05).

Discussion

TURBT is considered as the gold standard for the treatment of NMIBC [1]. However, the complications associated with conventional monopolar TURBT limit the application of this procedure, included Intraoperative bleeding, blood transfusion, bladder perforation, and obturator nerve reflex. To overcome these limitations of TURBT, several new resection techniques have been introduced for the management of NMIBT in recent years. The 2-micron laser and holmium laser are two of the most commonly used techniques, while laser surgery was first regarded as the treatment for benign prostate hyperplasia [8]. Several researches have reported the satisfactory outcomes of 2-micron laser and holmium laser resection for primary non-muscle invasive bladder [9, 10]. In our study, we compared the 2 years follow-up results among 2-micron laser, holmium laser, and conventional TURBT in the management of NMIBT.

Bladder perforation is one of the most serious complications during conventional TURBT, especially for the tumors located in the lateral bladder wall. The main reasons for bladder perforation are thermal injury and obturator nerve reflex [11]. The conventional TURBT procedure was performed by using a monopolar electrode, thereby the current flow passed through the patient's body. During the operation, the high temperature generated by the electrode lead to thermal injury of the treatment site. When the current flow passed through the obturator nerve might cause obturator nerve reflex, which resulted in sudden muscle contractions and bladder perforation [12]. However, bladder perforation and obturator nerve reflex were rarely happened during the laser surgeries according to the meta-analysis about the safety and efficacy of transurethral laser therapy for bladder cancer recently [13]. When 2-micron laser and holmium laser were applied to tumor resection, no current flow was produced during the procedure. This

procedure could not stimulate the obturator nerve, and the temperature of the treatment site by laser energy was lower resulted in minimal thermal injury. Therefore, obturator nerve reflex and bladder perforation could be avoided by using laser techniques [14, 15]. In this study, none of patients in 2-micron laser group and holmium group suffered bladder perforation and obturator nerve reflex.

Intraoperative bleeding is another important complication in TURBT. The energies from 2-micron laser and holmium laser were both highly confined within less than 5-mm depth of the contact bladder surface [14, 16]. Furthermore the vaporization and coagulation can be achieved simultaneously during the laser surgical procedure, leading to an excellent hemostatic property. However, the cutting and coagulation were separated in conventional TURBT. The control of intraoperative bleeding was not as good as the laser techniques, providing a poor visibility during the procedure, which might increase the difficultly of surgery and prolong operative time. In addition, postoperative bladder irrigation, catheterization time and hospitalization time are associated with postoperative bleeding and surgical damage. In our study, there were no significant differences in operative time and the incidence of blood transfusion among the conventional TURBT, 2-micron laser and holmium laser. However, more patients in conventional TURBT group need postoperative bladder irrigation, while no significant difference were found between 2-micron laser and holmium laser group. Moreover, catheterization time and hospitalization time in conventional TURBT were longer than in 2-micron laser and holmium laser, and there was no significant difference between 2-micron laser and holmium laser. These results revealed that 2-micron laser and holmium laser were superior to conventional TURBT in aspects of safety and recovery with less invasive and more satisfactory hemostatic.

No matter which technique is applied, the tumor recurrence rate was one of the most concerns from patients and surgeons postoperatively. The reduction of tumor recurrence rate remains a great challenge to the surgeon in the treatment of non-muscle invasive bladder cancer [17]. Tumor multicentricity, incomplete tumor resection, and intraoperative dissemination of tumor cells are considered possible incentives for high recurrence rate of NMIBC following transurethral resection [18]. During laser procedure, the tumors are vaporized by a high power laser beam, which might reduce residual tumor cells to some extent. So in theory, the tumor recurrence rate should be higher in patients underwent the conventional TURBT compared with patients underwent 2-micron laser and holmium laser resection of NMIBT. However, in our present study, there was no significant difference in the 2-year tumor recurrence rate among the conventional TURBT, 2-micron laser and holmium laser. Furthermore, several previous randomized controlled trials also demonstrated that there was no significant difference in tumor recurrence rate between laser operation and conventional TURBT [9, 10, 14, 19]. A longer follow-up period and larger numbers of patients are necessary to demonstrate the present result.

Conclusions

Our results demonstrated that the use of 2-micron (thulium) laser and holmium laser in the management of NMIBT were superior to conventional monopolar TURBT with reducing perioperative complications and minimizing postoperative bladder irritation, catheterization time and hospitalization time, while there were no significant differences between 2-micron laser and holmium laser. Therefore, the 2-micron laser and holmium laser may be an effective and safe alternative techniques to conventional TURBT. However, 2-micron laser and holmium laser did not demonstrate an obvious advantage over conventional TURBT in 2-year tumor recurrence rate. A longer follow-up period and larger numbers of patients are necessary to demonstrate the present result in the future.

Disclosure of conflict of interest

None.

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