Combined use of a 980-nm diode laser and preoperative intravesical instillation of pirarubicin for the prevention of short-term recurrence of non-muscle invasive bladder cancer: A pilot study

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Abstract. At present, transurethral resection of bladder tumors (TURBT) is the main surgical method for treating non-muscle invasive bladder cancer (NMIBC), but its postoperative recurrence needs to be prevented. The aim of the present study was to investigate the efficacy of a 980-nm diode laser combined with preoperative intravesical instillation of pirarubicin (THP) for the prevention of NMIBC recurrence. The data of 120 patients with NMIBC who underwent transurethral resection between May 2021 and July 2022 were retrospectively collected, and these patients were followed up. The patients were divided into four groups based on the surgical method used and preoperative intravesical instillation of THP as follows: i) 980-nm diode laser with THP (LaT); ii) 980-nm diode laser alone (La); iii) TURBT with THP (TUT); and iv) TURBT alone (TU). Clinicopathological variables, postoperative complications and short-term outcomes among the aforementioned groups were analyzed. The blood loss volume and the incidence of perforation and delayed bleeding were significantly lower in the LaT and La groups compared with those in the TUT and TU groups. The days of bladder irrigation, catheter extubation and postoperative hospitalization were significantly shorter in the LaT and La groups compared with the TUT and TU groups. The detection rate of suspicious lesions was significantly higher in the THP irrigation groups (LaT and TUT) compared with that in the saline irrigation groups (La and TU). Tumor diameter and number, 980-nm laser and THP irrigation were shown to be independent risk factors in the Cox regression analysis. In addition, the recurrence-free survival (RFS) rate of the LaT group was significantly higher than that of the other three groups. In conclusion, a 980-nm diode laser can effectively reduce intraoperative blood loss and the incidence of perforation, and accelerate postoperative recovery. Preoperative intravesical instillation of THP is conducive to identifying suspicious lesions. The combination of a 980-nm laser with preoperative THP intravesical instillation can significantly prolong RFS time.

Introduction

Bladder cancer is one of the most common malignancies worldwide (1). In total, ~70% of patients with bladder cancer are initially diagnosed with non-muscle invasive bladder cancer (NMIBC), which is confined to the muscular layer and submucosa (2,3). Transurethral resection of bladder tumors (TURBT) is the primary surgical procedure for NMIBC (4,5), but >50% of patients experience recurrence within 1 to 2 years. Therefore, there is an urgent need to find novel treatments to reduce the rate of postoperative recurrence of NMIBC.

After recurrence of bladder cancer, progression to MIBC is likely (6), and radical resection of bladder cancer is needed at a later stage, which is associated with increased pain and a worse prognosis. Currently, TURBT combined with adjuvant therapy is considered to be effective in reducing the incidence of postoperative recurrence (7,8). Adjuvant therapy drugs, such as mitomycin C (MMC) (9,10), epirubicin (EPI) (11) and pirarubicin (THP) (12), have increased benefits due to their ability to be used in intravesical instillation. Due to its safety, low number of toxic side effects and price, THP has been widely used in the clinic. However, it is mainly used for postoperative adjuvant therapy, and there is still a lack of relevant studies

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Abbreviations: NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumors; THP, pirarubicin; LaT, laser with THP; La, laser alone; TUT, TURBT with THP; TU, TURBT alone; RFS, recurrence-free survival; MMC, mitomycin C; EPI, epirubicin; ASA, American Society of Anesthesiologists; ONR, obturator nerve reflex; BI, bladder irrigation; CE, catheter extubation; PH, postoperative hospitalization

Key words: NMIBC, THP, 980-nm diode laser

proving the efficacy of preoperative intravesical instillation for the prevention of bladder cancer recurrence.

In recent years, laser en bloc resection with a 980-nm diode laser has been shown to exhibit a notably reduced incidence of complications and recurrence compared with conventional TURBT surgery (13). For diode lasers at a 980-nm wavelength, a new generation of laser technology, their energy can be absorbed by both water and hemoglobin. Compared with conventional transurethral electric resection, due to the tissue vaporization and cutting ability, coagulation characteristics and controllable penetration depth of 980-nm diode laser, this technique has shown increased efficacy and safety, and can markedly reduce the amount of bleeding and the risk of bladder perforation (13,14). However, the efficacy of the combination of 980-nm diode laser en bloc resection and preoperative THP intravesical instillation for the treatment of patients with NMIBC remains unclear. In the present study, the aim was to investigate the effect of combining 980-nm diode laser en bloc resection with preoperative intravesical instillation of THP on the rates of postoperative recurrence and complications of NMIBC.

Materials and methods

Patients. A total of 120 patients who were diagnosed with NMIBC at the Department of Urology, The Fourth Affiliated Hospital of Guangxi Medical University (Liuzhou, China) between May 2021 and July 2022 were retrospectively included in the present study. Patients with Ta-T1N0M0 (8th American Joint Committee on Cancer TNM staging system) (15) bladder tumors that were diagnosed by preoperative magnetic resonance imaging examination and who underwent surgery were included in the current study. Exclusion criteria included: i) Patients with recurrent or muscle-invasive bladder tumors; ii) patients with other tumors; and iii) patients with distant metastasis. The patients were treated using either a 980-nm diode laser combined with preoperative intravesical instillation of THP (LaT), a 980-nm laser alone (La), TURBT combined with preoperative intravesical instillation of THP (TUT) or TURBT alone (TU). In the laser surgery group, the low-power 980-nm diode laser was used to free the tumor in the submucosa, and then the tumor was completely removed. Subsequently, the high-power 980-nm diode laser was used to vaporize the edge and base of the tumor to further ensure negative margins.

The patients in the LaT and TUT groups received preoperative intravesical instillation of 30 mg THP/30 ml saline for 15 min. The patients in the La and TU groups received preoperative intravesical instillation of 30 ml saline for 15 min. During the operation, a biopsy was performed at the THP staining sites (orange staining) in the LaT and TUT groups. For those patients with ≤3 stained sites, a biopsy was taken within 2 cm of the tumor to supplement the remaining number. In the La and TU groups, a biopsy was performed at three random sites within 2 cm of the tumor. Intravesical instillation chemotherapy with 50 ml gemcitabine (20 mg/ml) was performed for 1 year after surgery. The first chemotherapy session started within 24 h after surgery, once a week for the first 2 months and once a month after 2 months. Each patient was followed up and underwent cystoscopy every 3 months.

Data collection. Clinicopathological data were also collected and evaluated, including sex, age, American Society of Anesthesiologists (ASA) grade (16), tumor location, maximum tumor diameter, tumor multiplicity, grade (17), tumor (T) stage (15), operation time, blood loss volume, perforation, obturator nerve reflex (ONR), days of bladder irrigation (BI), days of catheter extubation (CE), days of postoperative hospitalization (PH) and delayed bleeding.

Statistical analysis. All statistical analyses were performed using SPSS (version 23.0; IBM Corp.). One-way analysis of variance was performed to analyze the difference in continuous variables among the four groups, followed by the Bonferroni post hoc test. Continuous variables are presented as the mean ± SD. χ^2 or Fisher's exact test was employed to evaluate categorical variables. Univariate and multivariate Cox regression analyses were applied to identify independent risk factors. Kaplan-Meier analysis was used to compare the survival differences among the four groups, with statistical analysis using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics of patients. The clinicopathological characteristics of patients with NMIBC in the four different groups, namely, the LaT group (n=32), the La group (n=30), the TUT group (n=29) and the TU group (n=29), are shown in Table I. There was no significant difference with regard to sex, age, ASA, tumor location, tumor diameter, multiplicity of tumor, T stage and grade among the four groups.

Perioperative surgical outcomes and detection of lesions. The perioperative surgical outcomes among the four different groups are listed in Table II. No significant differences in operation time or ONR were observed among the four groups. However, ONR did not occur in the two 980-nm laser groups but it did occur in the two TURBT groups, with a single case in the TUT group (3.4%) and two cases in the TU group (6.9%). There were significant differences among the four groups in terms of blood loss, perforation, days of BI, CE and PH, and delayed bleeding ($P<0.05$). Among the four groups, the blood loss in the two 980-nm laser groups (LaT group, 8.8±2.6 ml; La group, 8.8±2.3 ml) was significantly lower than that in the two TURBT groups (TUT group, 17.1±5.3 ml; TU group, 15.7±6.2 ml; $P<0.001$). For perforation, the incidence was similar to ONR, but statistically significant, with no perforation events occurring in the two laser groups but four cases in the TUT group (13.8%) and three cases in the TU group (10.3%). Similarly, the days of BI, CE and PH were observed to be significantly shorter in the two laser groups than in the two TURBT groups, and the time was shortened by ~2 days ($P<0.001$). In addition, there was a significant difference in delayed bleeding among the four groups, with no delayed bleeding in the two laser groups but seven cases of delayed bleeding in the TURBT groups; three in the TUT group (10.3%) and four in the TU group (13.8%). As illustrated in Table III, the detection rate of suspicious lesions in the preoperative intravesical instillation of THP (LaT and TUT) groups was significantly higher than that in the other two (La and TU) groups without THP ($P<0.001$).

Table I. Clinicopathological characteristics of patients with non-muscle invasive bladder cancer in the LaT (n=32), La (n=30), TUT (n=29) and TU (n=29) groups.

Clinicopathological characteristics	LaT group	La group	TUT group	TU group	P-value
Sex, n (%)					0.936
Male	26 (81.3)	24 (80.0)	22 (75.9)	22 (75.9)	
Female	6 (18.7)	6 (20.0)	7 (24.1)	7 (24.1)	
Age, years[a]	64.7±7.5	64.9±5.7	65.1±8.1	65.2±9.3	0.995
ASA, n (%)					0.985
I	17 (53.1)	14 (46.7)	14 (48.3)	12 (41.4)	
II	14 (43.8)	15 (50.0)	14 (48.3)	16 (55.2)	
III	1 (3.1)	1 (3.3)	1 (3.4)	1 (3.4)	
Tumor location, n (%)					0.274
Lateral	19 (59.4)	14 (46.7)	14 (48.3)	20 (69.0)	
Others	13 (40.6)	16 (53.3)	15 (51.7)	9 (31.0)	
Tumor diameter, cm[a]	2.6±0.8	2.4±0.9	2.8±1.0	2.3±0.6	0.090
Multiplicity of tumor, n (%)					0.800
Single	28 (87.5)	24 (80.0)	23 (79.3)	23 (79.3)	
Multiple	4 (12.5)	6 (20.0)	6 (20.7)	6 (20.7)	
T stage, n (%)					0.688
Ta	24 (75.0)	19 (63.3)	20 (69.0)	18 (62.1)	
T1	8 (25.0)	11 (36.7)	9 (31.0)	11 (37.9)	
WHO 2004 grade, n (%)					
PUNLMP	17 (53.1)	10 (33.3)	9 (31.0)	6 (20.7)	0.206
Low	10 (31.3)	10 (33.3)	12 (41.4)	14 (48.3)	
High	5 (15.6)	10 (33.3)	8 (27.6)	9 (31.0)	

[a]Data are presented as the mean ± SD. PUNLMP, papillary urothelial neoplasm of low malignant potential; ASA, American Society of Anesthesiologists; T, tumor; LaT, 980-nm diode laser with pirarubicin; La, 980-nm diode laser alone; TUT, transurethral resection of bladder tumors with pirarubicin; TU, transurethral resection of bladder tumors alone.

Table II. Comparison of perioperative surgical outcomes in patients with non-muscle invasive bladder cancer in the LaT (n=32), La (n=30), TUT (n=29) and TU (n=29) groups.

Perioperative surgical outcomes	LaT group	La group	TUT group	TU group	P-value
Operation time, min[a]	45.6±8.2	43.8±9.4	44.2±8.4	47.4±8.5	0.377
Blood loss, ml[a]	8.8±2.6	8.8±2.3	17.1±5.3	15.7±6.2	<0.001
Perforation, n (%)	0 (0.0)	0 (0.0)	4 (13.8)	3 (10.3)	<0.05
ONR, n (%)	0 (0.0)	0 (0.0)	1 (3.4)	2 (6.9)	0.142
Days of BI[a]	1.4±0.5	1.6±0.5	3.3±1.0	3.4±1.2	<0.001
Days of CE[a]	2.4±0.5	2.6±0.5	4.3±1.0	4.4±1.2	<0.001
Days of PH[a]	3.7±0.7	3.9±0.7	5.7±1.0	5.7±1.0	<0.001
Delayed bleeding, n (%)	0 (0.0)	0 (0.0)	3 (10.3)	4 (13.8)	<0.05

[a]Data are presented as the mean ± SD. BI, bladder irrigation; CE, catheter extubation; PH, postoperative hospitalization; LaT, 980-nm diode laser with pirarubicin; La, 980-nm diode laser alone; TUT, transurethral resection of bladder tumors with pirarubicin; TU, transurethral resection of bladder tumors alone; ONR, obturator nerve reflex.

Cox regression analysis and survival analysis. To further identify independent risk factors for NMIBC recurrence, both univariate and multivariate Cox regression analyses were employed. As shown in Table IV, the univariate and multivariate Cox regression analyses revealed that maximum tumor diameter ≥3 cm, tumor multiplicity, 980-nm laser surgery and preoperative intravesical instillation of THP were independent risk factors for recurrence of NMIBC. Among

Table III. Difference in the detection rate of suspected lesions by preoperative intravesical instillation of THP in groups with no irrigation with THP (La and TU) (n=177) and irrigation with THP (LaT and TUT) (n=183)[a].

Groups	No irrigation with THP	Irrigation with THP	P-value
Lesions, n (%)	6 (3.4)	24 (13.1)	<0.001

[a]Three biopsy samples were taken per patient. THP, pirarubicin.

Table IV. Results of univariate and multivariate Cox regression analyses.

	Univariate			Multivariate		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Sex	1.679	0.487-5.781	0.412			
Age, years	1.034	0.972-1.100	0.283			
ASA	1.334	0.565-3.147	0.511			
Lateral	1.778	0.713-4.429	0.217			
Diameter, >3 cm	6.140	2.032-18.554	<0.01	6.155	1.716-22.083	<0.01
Multiplicity	5.134	2.073-12.715	<0.001	4.819	1.778-13.059	<0.01
Operation time	1.017	0.960-1.078	0.558			
Blood loss, ml	1.023	0.955-1.097	0.515			
Grade	1.822	1.030-3.224	<0.05	1.180	0.558-2.494	0.665
T stage	2.656	1.077-6.552	<0.05	1.652	0.560-4.872	0.363
980-nm laser	0.364	0.138-0.959	<0.05	0.266	0.088-0.803	<0.05
Irrigation with THP	0.394	0.149-1.036	0.059	0.195	0.065-0.584	<0.01

HR, hazard ratio; CI, confidence interval; T, tumor; ASA, American Society of Anesthesiologists; THP, pirarubicin.

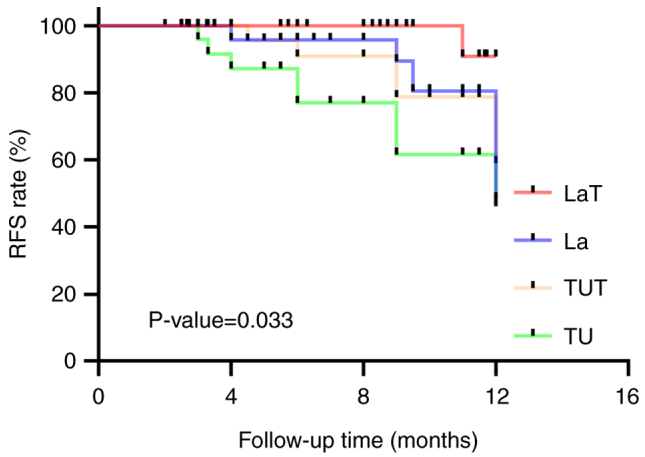

Figure 1. Comparison of RFS in patients with non-muscle invasive bladder cancer divided into the four treatment groups. The RFS rate of the LaT group was higher than that of the other three groups, including the La, TUT and TU groups. RFS, recurrence-free survival; LaT, 980-nm diode laser combined with preoperative intravesical instillation of pirarubicin; La, 980-nm diode laser alone; TUT, transurethral resection of bladder tumors combined with preoperative intravesical instillation of pirarubicin; TU, transurethral resection of bladder tumors alone.

them, the maximum tumor diameter ≥3 cm [hazard ratio (HR), 6.155; 95% confidence interval (CI), 1.716-22.083; P<0.01] and tumor multiplicity (HR, 4.819; 95% CI, 1.778-13.059; P<0.01) were adverse risk factors, while 980-nm laser surgery (HR, 0.266; 95% CI, 0.088-0.803; P<0.05) and irrigation with THP (HR, 0.195; 95% CI, 0.065-0.584; P<0.01) were protective risk factors. Moreover, a survival analysis was conducted to further investigate the effect of combining the 980-nm laser with preoperative intravesical instillation of THP on the recurrence-free survival (RFS) rate of patients with NMIBC. The Kaplan-Meier survival curves are plotted in Fig. 1. The results indicated that the RFS rate of the LaT group was significantly higher than that of the other three groups (P=0.033).

Discussion

To date, traditional TURBT is the standard surgical treatment for NMIBC, but it has some intraoperative complications, including bleeding, bladder perforation and ONR (18), which are closely associated with the surgical experience and skill of surgeons. Meanwhile, due to the segmented resection method of TURBT surgery, tumor cells may be shed during the operation to some extent, thereby increasing the risks of recurrence and metastasis (19,20). To reduce the occurrence of these complications, surgeons have conducted additional research on new approaches. In 1978, Staehler *et al* (21) first explored the use of laser surgery for bladder neoplasms. Studies have shown that compared with TURBT surgery, laser procedures

such as holmium (22-24), 2-μm (25-27), 1.9-μm Vela (28) and potassium-titanyl-phosphate (29,30) lasers used to treat NMIBC can not only reduce the incidence of complications, but can also reduce the postoperative recurrence rate when used with en bloc resection. However, studies on en bloc resection of NMIBC with a 980-nm diode laser have rarely been reported (13,31).

In the present study, the intraoperative and postoperative characteristics, and the recurrence status of patients with NMIBC were retrospectively compared in the LaT, La, TUT and TU groups. It was shown that 980-nm diode laser en bloc resection was more effective at reducing intraoperative blood loss than TURBT surgery. Furthermore, intraoperative perforation and ONR did not occur in the two 980-nm diode laser surgery groups, while four cases of perforation and a single case of ONR occurred in the TUT group, and three cases of perforation and two cases of ONR occurred in the TU group. Due to its improved hemostatic effect, the number of days of PI, CE and PH was significantly decreased compared with that in the TURBT group. In addition, no delayed bleeding was observed in the two 980-nm laser groups. According to the aforementioned results, compared with TURBT surgery, the 980-nm diode laser has similar advantages to other lasers (27,28,32-34), and the treatment of NMIBC with a 980-nm diode laser can not only decrease the incidence of intraoperative and postoperative complications, but can also accelerate postoperative recovery. More importantly, the laser groups had a lower 1-year recurrence rate, which significantly improved RFS time in the patients with NMIBC.

To prevent recurrence in patients with NMIBC, transurethral resection is usually followed by adjuvant therapy. Postoperative intravesical instillation of chemotherapeutic agents, such as MMC, EPI and THP, can effectively improve prognosis and prolong RFS time in patients with NMIBC (7). On the one hand, it has been reported that THP can be rapidly absorbed by tumor cells, and enter the nucleus to inhibit DNA synthesis (35). A meta-analysis study showed that intravesical instillation of THP significantly reduced the risk of tumor recurrence and was superior to MMC and EPI (8). On the other hand, according to the characteristics of the THP solution, preoperative intravesical instillation of THP can stain tumors orange, which may be conducive to the detection of small lesions and reduce the risk of missed detection. However, the effect of preoperative intravesical instillation of THP on postoperative recurrence in patients with NMIBC remains unclear. Considering the advantages of both the 980-nm diode laser and the intravesical instillation of THP solution, the combined effect of preoperative intravesical instillation of THP and the 980-nm diode laser was investigated on the postoperative recurrence of NMIBC in the present study.

In the present study, the proportion of suspicious lesions detected in the two THP groups, LaT and TUT, was significantly higher than that in the random sampling groups, La and TU, suggesting that preoperative intravesical instillation of THP was beneficial for detecting suspicious and unobtrusive lesions. Furthermore, Cox regression analysis showed that both the preoperative intravesical instillation of THP and 980-nm diode laser surgery were protective factors for the recurrence of NMIBC, which significantly reduced the risk of tumor recurrence. In addition, the survival analysis showed that among the four groups, the LaT group exhibited a significantly higher 1-year RFS rate for patients with NMIBC compared with that in the other three groups, followed by the La, TUT and TU groups. The results indicated that preoperative THP intravesical instillation or en bloc resection with a 980-nm diode laser could effectively prolong RFS time in patients with NMIBC and reduce the postoperative recurrence rate.

However, there are some limitations to the current study. The study is retrospective rather than a double-blind prospective randomized controlled study, which may have led to selection bias to some extent. Additionally, the small sample size of this study may also have led to the deviation of results. In the future, a randomized controlled study will be performed to draw more rigorous conclusions.

In summary, compared with TURBT surgery alone, 980-nm diode laser en bloc resection combined with preoperative intravesical instillation of THP not only assists in reducing the incidence of intraoperative and postoperative complications, but also accelerates postoperative recovery in patients and reduces the risk of recurrence of NMIBC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZT prepared the manuscript and performed the statistical analysis. JP performed the data analysis. SW and FZ contributed to the data acquisition, analysis and interpretation. MW presented the concept of the study and designed the study. ZT and PJ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of Guangxi Medical University (Liuzhou, China) (approval no. KY2021053) and written informed consent was obtained from all patients.

Patient consent for publication

Written informed consent was obtained from the patients to publish this paper.

Competing interests

The authors declare that they have no competing interests.

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