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ORIGINAL ARTICLE

A retrospective comparison of thulium laser en bloc resection of bladder tumor and plasmakinetic transurethral resection of bladder tumor in primary non-muscle invasive bladder cancer

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Abstract

Bladder cancer is currently considered the most common malignancy of the urinary tract. Thulium laser en bloc resection of bladder tumor (TmLRBT) and plasmakinetic transurethral resection of bladder tumor (PK-TURBT) are two alternative common procedures used in our department to manage patients with primary non-muscle invasive bladder cancer (NMIBC) over the past decade. In this work, the safety and efficacy of TmLRBT were retrospectively compared to those of PK-TURBT in patients with primary NMIBC. From January 2013 to December 2015, 256 patients diagnosed with primary NMIBC were selected for this retrospective study. A total of 136 consecutive patients diagnosed with primary NMIBC were enrolled in the TmLRBT group. A similar historical cohort of 120 consecutive patients who underwent PK-TURBT was used to compare the two procedures. Clinical data, including age, gender, tumor characteristics, operation duration, hospitalization, irrigation, catheterization, and intraoperative and postoperative complications, were recorded. There were no significant differences in age, gender, mean tumor size, mean tumor number, tumor location, or risk between the TmLRBT and PK-TURBT groups. The TmLRBT group was associated with a significantly shorter operation duration (25.96 ± 21.19 min vs 37.18 ± 25.77 min, $P = 0.018$) and a shorter hospitalization time (3.11 ± 1.05 days vs 5.24 ± 2.06 days, $P = 0.036$). The postoperative irrigation time (6.33 ± 4.05 h vs 14.76 ± 6.28 h, $P = 0.027$) and catheterization time (2.03 ± 1.61 days vs 4.27 ± 1.17 days, $P = 0.035$) in the TmLRBT group were lower than those in the PK-TURBT group. No significant differences in fever and rebleeding were found in the TmLRBT and PK-TURBT groups. There were no significant differences in the overall, low-risk, intermediate-risk, and high-risk recurrence-free rates between the two groups ($P = 0.43$, $P = 0.68$, $P = 0.71$, and $P = 0.24$, respectively). The proportion of bladder detrusor muscle (BDM) identified in pathologic specimens of the TmLRBT group was higher than that in the PK-TURBT group ($P = 0.006$). TmLRBT may reduce operation duration time, hospitalization time, postoperative irrigation time, and catheterization time. TmLRBT is considered safer and more effective in treating primary NMIBC. Recurrence-free rates did not differ between groups.

Keywords Thulium laser · PK-TURBT · En bloc resection · Bladder cancer

Introduction

Bladder cancer is currently considered the most common malignancy of the urinary tract. The global incidence rate is 9.0 per 100,000 among men and 2.2 per 100,000 among women. The worldwide mortality according to the age-standardized rate (ASR) is 2.2 per 100,000 for men and 0.9 per 100,000 for women. The global world 5-year prevalence rate is 39.3

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per 100,000 among men and 11.6 per 100,000 among women [1]. Transurethral resection of bladder tumor (TURBT) is still considered the gold standard treatment for primary non-muscle invasive bladder cancer (NMIBC). However, surgeons have reported several drawbacks of the TURBT procedure, such as the deficiency of the bladder detrusor muscle (BDM), the obturator nerve reflex (ONR), thermal damage to surrounding tissues, and the technique of "incise and scatter". These drawbacks may lead to difficulty in performing an accurate pathological evaluation of fragment tissue and increase the risk of recurrence [2]. To overcome these problems, thulium laser en bloc resection of bladder tumor (TmLRBT) and plasmakinetic transurethral resection of bladder tumor (PK-TURBT) are two alternative common procedures that have been used in our department to manage patients with primary NMIBC over the past decade. In this work, the safety and efficacy of TmLRBT were retrospectively compared with those of PK-TURBT in patients with primary NMIBC.

Material and methods

Patients and groups

From January 2013 to December 2015, 256 patients diagnosed with primary NMIBC were selected for this retrospective study. A total of 136 patients underwent TmLRBT (TmLRBT group), and 120 patients underwent PK-TURBT (PK-TURBT group). TmLRBT and PK-TURBT were performed by the same surgeon, Dr. *X*. All patients were stratified into three risk groups (low-risk, intermediate-risk, and high-risk tumor group) according to the prognostic factors for recurrence using the latest European Association of Urology (EAU) guidelines [3].

The exclusion criteria were age > 85 years, American Society of Anesthesiologists (ASA) physical status classification system (ASA IV or higher), carcinoma in situ (CIS), suspected locally advanced bladder cancer (stage 2 or higher tumors) on computed tomographic (CT) scan, distant metastases, and recurrent NMIBC. All patients signed an informed consent form.

For the TmLRBT group, a two-micrometer continuous-wave thulium laser (XL Vela, Germany StarMedTec, wavelength 1.9 μm, power 30–50 W) was used. TmLRBT was performed with the patient in a lithotomic position under intravertebral anesthesia, with 0.9% sodium chloride as continuous irrigation. TmLRBT was performed through a 550-μm fiber with a 26F continuous thulium resectoscope (LISA Laser products, Lindau-Katlenburg, Germany). The parameter settings were as follows: an energy of 1.5 J, pulses of 20 Hz, and a resultant power of 30 W. The distal tip of the laser fiber and the aiming beam spot were visible. A circular incision border was drawn around the base of the tumor with a safety distance of approximately 1.5–2 cm (Fig. 1a, (B1)), and the exposed blood vessels were then precoagulated (Fig. 1(B2)). A vertical incision was made from the mucosa into the deep detrusor muscle layer by layer. After the mucosa was cut off, the tip of the resectoscope sheath and the vaporization of the thulium laser were used to push the tumor base until the submucosa was exposed, while the fibrous connective tissue between the mucosa layer and the detrusor muscle was identified. By using a layer-by-layer resection procedure (Fig. 1c, d), the detrusor muscle fiber was removed, and the

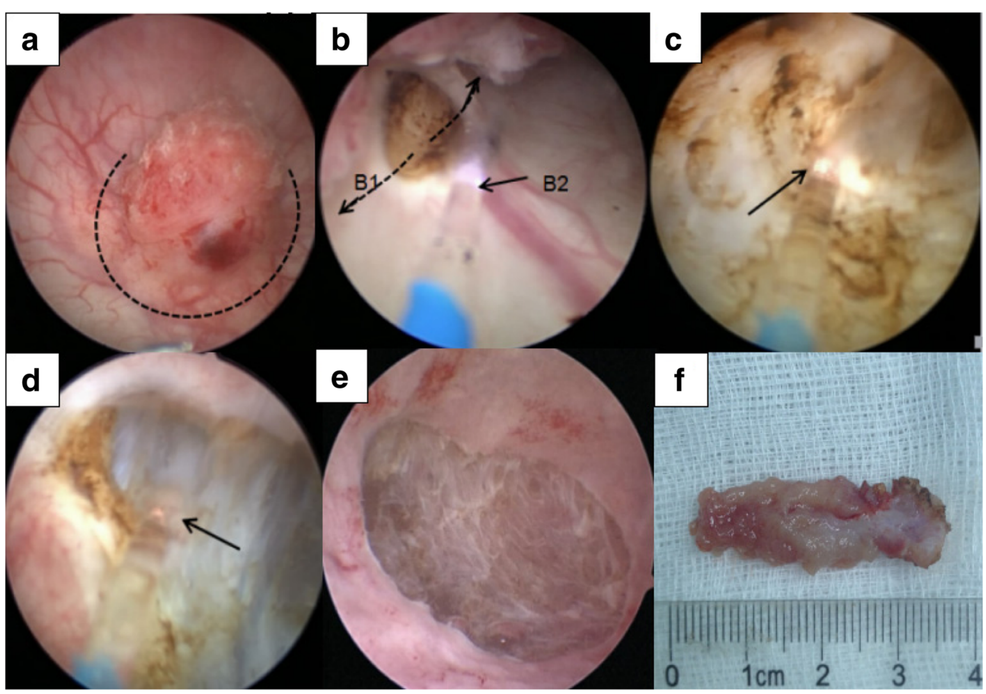

Fig. 1 **a**, (B1) A circumferential border was made around the base of the tumor with a safety distance of approximately 1.5 cm ~ 2.0 cm. (B2) Precoagulation of the exposed blood vessels. **c** Superficial muscular layer. **d** Deep muscular layer. **e** The change in the bladder wall after the tumor was en bloc resected, showing the incision margin and the smooth base. **f** Pathological specimen

structure of the transparent membranous substance was exposed (serosa, fat particles, and capillaries could be observed). At the end of the procedure, the tumor base was adequately coagulated using the thulium laser with the pulsed-wave setting at 20 W. The bladder tumor was removed en bloc at the anatomical level (Fig. 1e, f), and a complete pathological specimen was obtained (Fig. 2). The specimens were sent to the pathological department for diagnoses. The tumors < 3 cm could be extracted using an Elik's evacuator. A 22F Foley catheter was inserted after the procedure. Postoperative bladder irrigation ceased immediately after hematuria disappeared.

PK-TURBT was performed using a WOLF 26F continuous flow resectoscope with a plasmakinetic loop electrode (Gyrus Group PLC, Reading, UK) and the coagulation and cutting power sets to 100 W and 160 W, respectively. Piece-by-piece resection was performed until the detrusor muscle layer was reached. It is important to treat the entire tumor bed and a 1.5–2 cm margin around the tumor.

The patients were monitored via follow-ups every 3 months for the first year and every 6 months thereafter. The recurrence-free survival was compared within each risk subgroup. According to the EAU guidelines, a "second-look" and re-transurethral resection (re-TUR), which included checking the residual tumor or visibly recurred tumor and muscular tissue around the scar of the initial surgery, were performed within 2–6 weeks in 21 PK-TURBT patients and in 23 TmLRBT patients with high-risk NMIBC. Random biopsy was performed if necessary [4]. The International Bladder Cancer Group (IBCG) proposed the following practical definitions of high risk based on a review of current clinical practice guidelines for NMIBC [5]: any T1 and/or high grade/G3 and/or CIS (these tumors are at high risk of recurrence and progression, with progression being the primary concern).

All procedures (TmLRBT, PK-TURBT, follow-up, and re-TUR) were performed by the same surgeon (Dr. *X*).

Postoperative treatment and follow-up

Pirarubicin was instilled for intravesical therapy in the operating room after surgical treatment. Patients with severe hematuria were infused with pirarubicin in the ward after the urine became clear. One immediate postoperative intravesical chemotherapy session was adopted in patients with low-risk tumors, yet continuous postoperative intravesical instillation chemotherapy was adopted in intermediate- and high-risk NMIBC [6]. The intravesical instillation regimen was 50 mg pirarubicin weekly for 8 weeks and then once a month for 1 year. All patients were followed for cystoscopy every 3 months of the first year and then every 6 months afterwards. At the same time, urine analysis, urine cytology, blood routine, and blood biochemistry examinations were conducted. The primary endpoint of this study was the tumor recurrence rate.

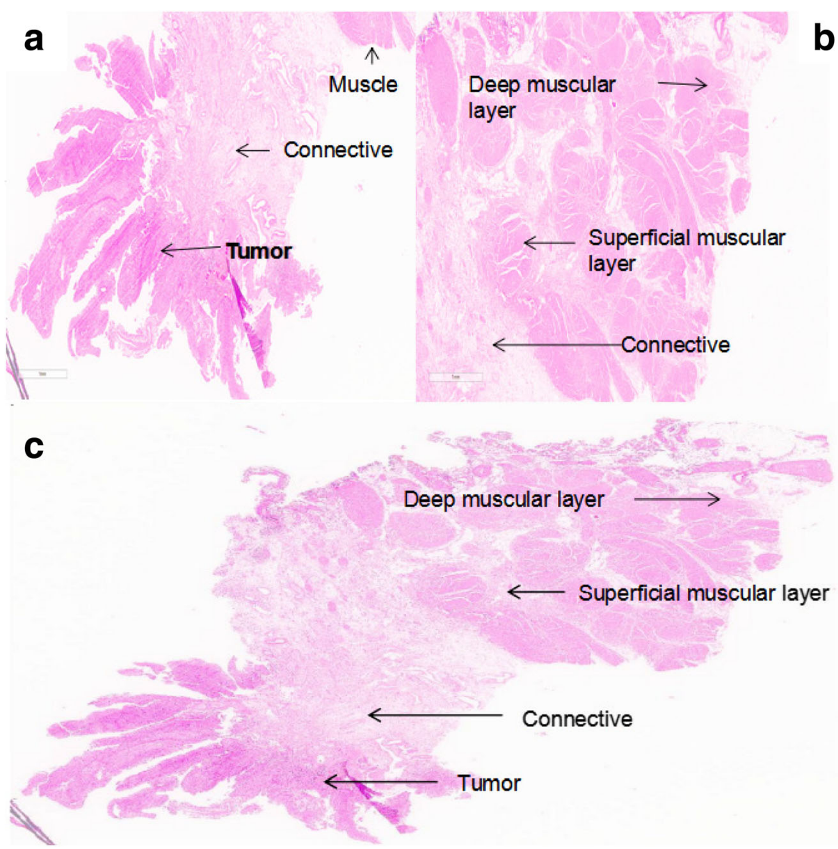

Fig. 2 H&E staining of a specimen after en bloc resection. **a**, **b** Tumor, connective, superficial, and deep muscular layers are present. The magnification is 2.0 times the original size. **c** The architectures of the tumor and bladder are preserved. Reduced from × 1.0

Statistical analysis

The statistical analysis was performed with SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were summarized as the mean ± SD.

The patient characteristics were compared between the TmLRBT group and the PK-TURBT group using independent-samples Student's *t* test for continuous parameters and the chi-squared test for categorical parameters. Recurrence-free survival was calculated using the Kaplan-Meier method and the log-rank test. *P* values < 0.05 were considered statistically significant.

Results

The patient characteristics and tumor characteristics in the two groups are listed in Table 1. There were no significant differences in age, gender, mean tumor size, mean tumor number, tumor location, or risk between the two groups.

The operative and postoperative characteristics in the two groups are shown in Table 2. TmLRBT was associated with a significantly shorter operation duration (25.96 ± 21.19 min vs 37.18 ± 25.77 min, *P* = 0.018) and a shorter hospitalization time (3.11 ± 1.05 days vs 5.24 ± 2.06 days, *P* = 0.036). The postoperative irrigation time (6.33 ± 4.05 h vs 14.76 ± 6.28 h, *P* = 0.027) and catheterization time (2.03 ± 1.61 days vs 4.27 ± 1.17 days, *P* = 0.035) in the TmLRBT group were lower than those in the PK-TURBT group. No obturator nerve reflex occurred in the TmLRBT group. In contrast, four of 120 patients in the PK-TURBT group developed this complication, including resultant bladder perforation in one patient. In both groups, two patients developed a fever. Rebleeding occurred in two of the 120 patients in the PK-TURBT group, which was stopped with continuous bladder irrigation and injection of hemocoagulase. Thus, no significant differences in fever and rebleeding were found in the TmLRBT and PK-TURBT groups. The proportion of BDM identified in the pathologic specimens of the TmLRBT group was higher than that in the PK-TURBT group (130/136 vs 103/120, *P* = 0.006). Follow-up and re-TUR were negative in all high-risk TmLRBT patients newly diagnosed with NMIBC. In one high-risk PK-TURBT patient newly diagnosed with NMIBC, re-TUR showed focal infiltration of the bladder detrusor, and then, the patient underwent radical cystectomy.

In the present study, complication rates were assessed by the classification of surgical complications [7]. (Daniel Dindo's complication classification). Although TmLRBT may have some advantages with respect to the classification of surgical complications, there was no significant difference between the two groups.

The mean follow-up period after surgery was 41 (range, 9–48) and 40.6 (range, 9–42) months in the TmLRBT and PK-TURBT groups, respectively. Comparing the two groups, four Kaplan-Meier survival curves were obtained: overall recurrence-free survival and recurrence-free survival of the low-risk, intermediate-risk, and high-risk subgroups (Fig. 3). The recurrence-free survival and 95% confidence interval (CI) are shown in Table 3. There were no significant differences in the overall, low-risk, intermediate-risk, and high-risk recurrence-free rates between the two groups (*P* = 0.43, *P* = 0.68, *P* = 0.71, and *P* = 0.24, respectively).

Table 1 Patient and tumor characteristics

Variable	TmLRBT group (*n* = 136)	PK-TURBT group (*n* = 120)	*P* value
Age (year)			0.796
< 65	80 (58.8%)	72 (60.0%)	
≥ 65	56 (41.2%)	48 (40.0%)	
Gender (male/female)	110/26	98/22	0.873
Tumor size (cm)	2.39 ± 1.09	2.15 ± 0.92	0.781
Tumor multiplicity			0.796
Single	114	102	
Multiple	22	18	
Summation	158	144	
Tumor location			0.903
Outlet	12 (7.6%)	10 (6.9%)	
Trigone	22 (13.9%)	20 (13.9%)	
Left lateral wall	54 (34.2%)	44 (30.6%)	
Right lateral wall	36 (22.8%)	42 (29.2%)	
Dome	6 (3.8%)	5 (3.5%)	
Front wall	24 (15.2%)	18 (12.5%)	
Posterior wall	4 (2.5%)	5 (3.5%)	
Risk groups (EAU, 2002)			0.992
Low	31 (22.8%)	27 (22.5%)	
Intermediate	82 (60.3%)	72 (60.0%)	
High	23 (16.9%)	21 (17.5%)	

Discussion

TURBT is considered the gold standard treatment for NMIBC. This technique, however, has many apparent drawbacks. Obturator nerve reflex and bleeding can often make the surgery difficult. In addition, deeper tissue thermal damage and ureteral orifice injury make the procedure dangerous. The absence of a muscle layer in the specimen and a positive margin are also shortcomings of TURBT [8–13]. Because these shortcomings have been widely recognized, clinicians and scientific researchers have sought to explore new cutting energies and have been continually devoted to innovating the procedure to ensure efficacy and reduce the incidence of complications.

Song et al. [14] compared the efficacy and safety of PK-TURBT, conventional monopolar transurethral resection of

Table 2 Intraoperative and postoperative characteristics of TmLRBT and PK-TURBT patients

Variable	TmLRBT group ($n = 136$)	PK-TURBT group ($n = 120$)	P value
Operation duration (min)	25.96 ± 21.19	37.18 ± 25.77	0.018
Hospitalization time (day)	3.11 ± 1.05	5.24 ± 2.06	0.036
Postoperative irrigation time (h)	6.33 ± 4.05	14.76 ± 6.28	0.027
Catheterization time (day)	2.03 ± 1.61	4.27 ± 1.17	0.035
Bladder detrusor muscle	130	103	0.006
Intraoperative complications			
Obturator nerve reflex	0	4	0.032
Bladder perforation	0	1	0.286
Postoperative complications			
Acute rebleeding	0	1	0.286
Fever (> 38.5 °C)	2	2	0.900
Classification of surgical complications			
Grade I	2	3	
≥ Grade II	0	0	0.553

bladder tumor (CM-TURBT) and holmium laser transurethral resection of bladder tumor (HoL-TURBT) in terms of their performance in patients with NMIBC. According to these previously reported results, there was no significant difference in operative duration among PK-TURBT, CM-TURBT, and HoL-TURBT, and there was no significant difference in recurrence rate among the three groups. Matthew J et al. [15] proposed the concept of endoscopic snare. However, the small number of patients (just nine patients were chosen to be reviewed retrospectively) was a limitation of the study. Tao et al. [16] reported that 120-W green light laser was a reliable therapeutic alternative for NMIBC and was superior to TURBT. Studies have suggested that green light laser endoscopic en bloc photoselective vapo-enucleation of non-muscle invasive bladder cancer is a safe and effective treatment for NMIBC [17].

TmLRBT has been widely performed in recent years. The thulium laser is a diode pumped solid-state laser with a tunable wavelength of 1.75–2.22 μm, which is much closer to the water absorption peak value (1.94 μm) with only a 0.2-mm theoretical depth of thermal damage. Due to the slightly shorter wavelength, the depth of penetration in water decreases to 250 μm. The continuous energy output leads to a higher vaporization and cutting efficiency with excellent hemostasis. Our present clinical results indicated some superiority to PK-TURBT in terms of operation duration, postoperative irrigation time, catheterization time, and hospitalization time ($P = 0.018$, 0.027, 0.035, and 0.036, respectively). The higher vaporization and cutting efficiency with excellent hemostasis can shorten the time of operation and postoperative irrigation. The time of catheterization can also be shortened when the urine color clears; thus, the time of hospitalization can be shortened. When thulium laser was used in the operation, the vaporization and cutting effects led to a smoother wound surface. A thin layer of eschar can be formed on the surface of the wound while the cutting depth can be clearly identified. Mario W. et al. [18] considered that thulium laser en bloc has the potential to lower the chance of second transurethral resection of bladder cancer. Roberto et al. [19] compared thulium laser endoscopic en bloc enucleation of bladder tumor (ThuLEBT) with monopolar resection of NMIBC. A better depth of tumor invasion was found in the ThuLEBT group, and the follow-up 3 months after the surgery may be avoided. Others reported that energy methods such as neodymium laser and green laser [20–22] could not be extensively applied to bladder tumor surgery. En bloc resection of the bladder tumor has been widely reported in the literature. Although the energy methods differed, ThuLEBT was proposed to overcome the challenges of PK-TURBT [23–30].

A European multicenter study in 2015 confirmed that en bloc resection of bladder tumor is a feasible surgical method that provides excellent pathological staging. The trend toward fewer complications and fewer recurrent rates in the resection area was concluded [31]. The specimens were sent to the pathological department for diagnoses. The proportion of BDM identified in pathologic specimens was higher for the TmLRBT group than for the PK-TURBT group ($P = 0.006$), representing an advantage of TmLRBT over PK-TURBT that provides pathologists with a better opportunity for correct and precise staging. Our data also indicated a significant difference in the obturator nerve reflex between the two groups ($P = 0.032$).

In PK-TURBT, the current flow passes from an active electrode to an adjacent return electrode. Plasmakinetic resection benefits from the generation of plasma to achieve outstanding cutting power instead of the vaporization of tissue. The tissue surface temperature was only 40 to 70 °C. Song [14] reported that as the current flow did not pass through the patient, there was no ONR during PK-TURBT. However, ONR was found

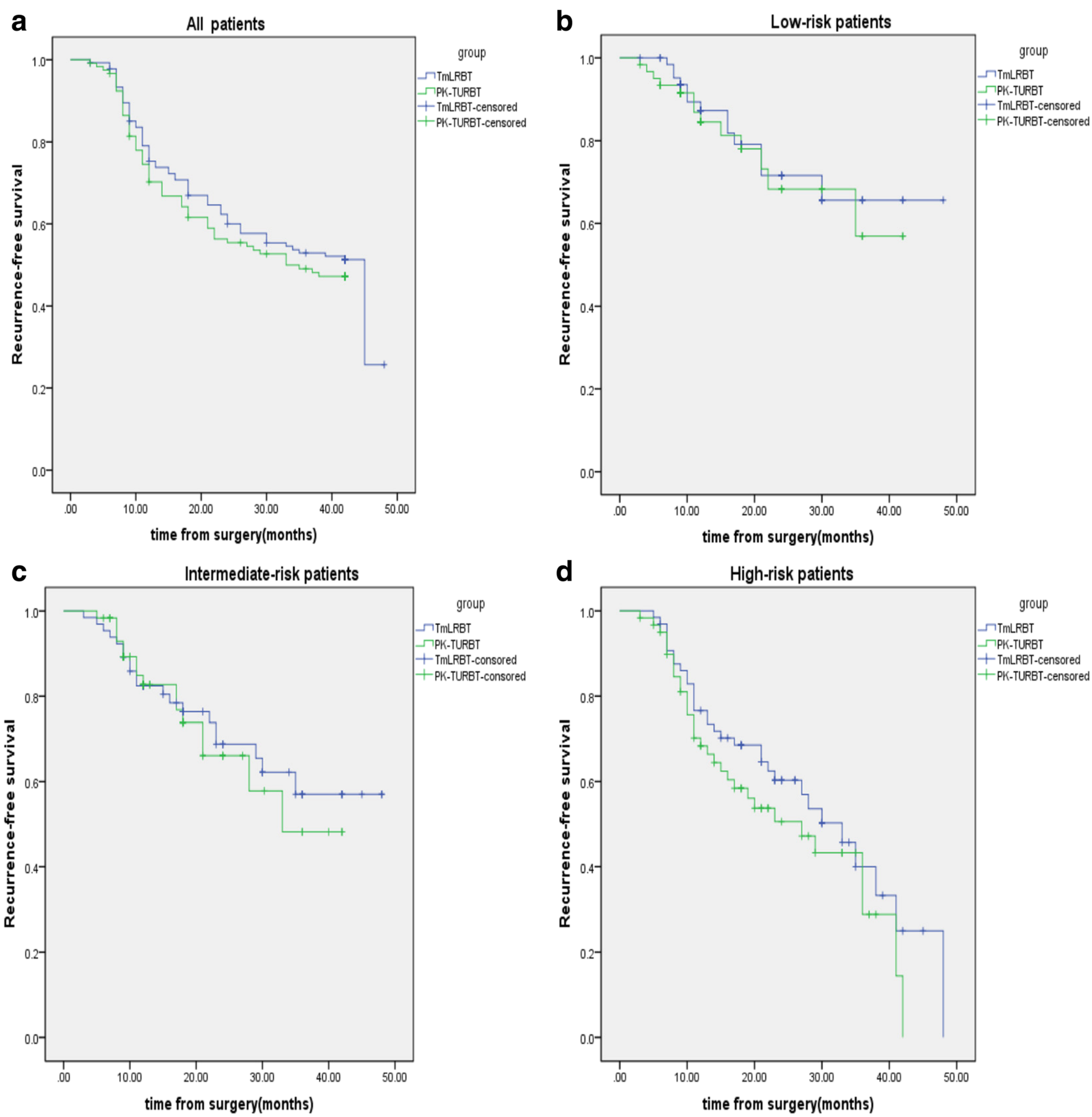

Fig. 3 Kaplan-Meier estimated overall recurrence-free survival (**a**) and recurrence-free survival for the low-risk (**b**), intermediate-risk (**c**) and high-risk (**d**) subgroups

in four patients in our study, which may have been caused by thermal injury. In TmLRBT, the tissue was cut by laser energy with minimal thermal injury, and there was no current flow during the procedure, leading to no ONR.

When evaluating the advantages and disadvantages of the two operative methods, more attention is generally paid to the incidence of complications, but the severity of the complications is frequently ignored. Based on an analysis of the incidence of complications in each group, Dindo's Daniel surgical complication scoring system [7] was used to re-evaluate the severity of the complications. The results of our research showed no differences in the incidence and degree of complications between the TmLRBT group and the PK-TURBT group.

TmLRBT offers theoretical advantages of preserving tumor architecture and limiting tumor dispersal. We suspected that TmLRBT may lower recurrence rates. However, the results of the present study do not support this claim.

Recurrence-free survival generally refers to the time between the operation date and the date of metastasis, recurrence

Table 3 The median and 95% CI of recurrence-free survival

	TmLRBT (months)			PK-TURBT (months)		
	Median	95% CI		Median	95% CI	
		Superior limit	Inferior limit		Superior limit	Inferior limit
Low-risk	37.39	32.43	42.35	32.31	27.87	36.75
Intermediate-risk	35.27	30.80	39.75	30.49	26.03	34.95
High-risk	29.25	24.89	33.61	25.04	21.04	29.04
Overall	31.79	28.81	34.78	27.86	25.16	30.56

or death, i.e., the interval until the first tumor recurrence, metastasis, or death. The observation endpoint was the earliest time interval. In our study, recurrence-free survival was similar in the two groups, and there were no significant differences in the overall, low-risk, intermediate-risk, and high-risk recurrence-free rates between the two groups, indicating that TmLRBT provided similar treatment effects to PK-TURBT for NMIBC. The pathological specimens of 1209 cases of TURBT were analyzed by Rasha Gendy [32], who reported that the recurrence rate for T1 high-grade tumors with re-TUR was 39.6%, whereas while the recurrence rate was 34.8% for TmLRBT and 33.3% for PK-TURBT in our study. This study proves that skillfully executed surgical techniques and re-TUR play important roles in reducing the recurrence rate of tumors. This study reveals that re-TUR can be avoided and that the prognosis can be guaranteed for TmLRBT.

A limitation of the current study is that longer follow-up data need to be incorporated. Zhu [33] reported that laser en bloc resection was difficult to perform in the anterior and dome wall, but there were no significant difficulties in dealing with the location of the tumor. Moreover, tumor size was another drawback. Tumors < 3 cm in size were extracted using an Elik evacuator in our study. Tumors ≥ 3 cm in size were difficult to retrieve, especially tumors with a wide base or a cauliflower appearance. In such cases, it was often difficult to retrieve the specimens after en bloc resection. To remove the tumor specimens and to minimize the impact on staging, the en bloc had to be bisected until en bloc resection could be performed. However, the "incise and scatter" method could potentially increase the risk of tumor out-of-field recurrence because of the large amount of floating tumor cells. Although there are reports that larger tumors can be retrieved with an endoscopic mesh net or with a mesh net retrieval system [15], it is not advised to apply TmLRBT to tumors ≥ 3 cm. Another limitation of the current study is the small number of patients who were analyzed, and due to the retrospective study design, including the same number of patients in both groups would have been ideal. Further research is needed to address this limitation. Furthermore, larger prospective randomized controlled trials with long-term follow-up should be devised to confirm the efficacy of TmLRBT. We will focus on these drawbacks in future research work.

In summary, TmLRBT reduces operation duration, hospitalization time, postoperative irrigation time, and catheterization time. TmLRBT can also achieve the same clinical effect as PK-TUBBT in primary non-muscle invasive bladder cancer. TmLRBT could be considered a safe and effective surgical operation method.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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