

A Comparative Study on the Therapeutic Effect of en Bloc Transurethral Resection of Bladder Tumors with Needle Electrode and Traditional Transurethral Resection of Bladder Tumor on Non-Muscle Invasive Bladder Tumor

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Abstract

Background:

En bloc transurethral resection of bladder tumors (ERBT) as an improved method of traditional transurethral resection of bladder tumor (TURBT), has not been standardized. The purpose of this study is to evaluate the safety and effectiveness of the technology.

Methods:

We divide non-muscle invasive bladder cancer into an experimental group receiving ERBT and a control group receiving traditional TURBT, and compared the recurrence rate by Kaplan-Meier curve adjusted by propensity score matching (PSM) analysis. In addition, we analyzed the independent risk factors affecting the recurrence rate of NMIBC by COX risk regression.

Discussion:

Compared with traditional transurethral resection of bladder tumor treatment, En bloc transurethral resection of bladder tumors has less intraoperative bleeding and high surgical safety. Moreover, this technique can obtain high-quality pathological specimens, which has obvious advantages in postoperative pathological assessment.

Background

As a common urological disease, bladder cancer is clinically guided by TNM staging. T1, Ta and carcinoma in situ are usually called non-muscle invasive bladder cancer (NMIBC). For NMIBC, current treatment aims to preserve bladder function and remove all tumor tissue¹⁻². The preferred treatment is transurethral resection of bladder tumor (TURBT), which is both a treatment method and a diagnostic method. Studies have shown that 70%-80% of patients are judged as NMIBC in the first diagnosis¹⁻². At the same time, after proper treatment of NMIBC patients, the recurrence rate within 5 years after surgery is 15-61%, and 1-45% will occur disease progression³.

However, TURBT has certain defects, including thermal damage of adjacent tissues and fragmentation of tumor tissue, which reduces the accuracy of pathological assessment and increases the risk of recurrence⁴. In order to overcome the shortcomings of traditional TURBT treatment, Japanese scholars first proposed the en bloc transurethral resection of bladder tumors (ERBT) to treat NMIBC in 1980. The report believes that this procedure can overcome the main defects of traditional TURBT⁵. ERBT is usually excised around the base of the tumor, and obvious healthy tissue is reserved around the tumor as a preventive margin. Gradually advance to the bottom of the tumor, reaching the bladder muscle layer.

However, because ERBT has not been standardized, most practitioners still prefer to use traditional TURBT to treat patients with NMIBC. Therefore, we designed this experiment. The clinical data and

follow-up data of patients with NMIBC treated in our department from February 2016 to February 2020 were collected. The patients who received ERBT were included in the experimental group, and the patients who received TURBT were included in the control group. The treatment effect and recurrence rate of the two groups were compared to evaluate the technical safety and effectiveness.

Method

Patients enrollment

From February 2016 to February 2020, clinical data of 212 patients with NMIBC who received bladder cancer treatment in the Department of Urology, Lanzhou University.

Inclusion criteria: 1) undergoing transurethral resection of bladder tumor; 2) non-muscle invasive bladder cancer (Ta-T1N0M0); pathological diagnosis of urothelial carcinoma; 3) no distant metastasis; 4) complete clinical data ; 5) No other urinary malignant tumor diseases.

Exclusion criteria: 1) The tumor has invaded the ureter, prostate, and urethra; 2) Postoperative diagnosis of muscle invasive bladder cancer and above; 3) History of chemotherapy before surgery.

In the end, a total of 212 patients who met the criteria were included in this study, including 39 in the experimental group and 173 in the control group.

Treatment

Experimental group: The patient was placed in lithotomy position after anesthesia, the irrigating solution was saline, the surgical area was disinfected, and sterile cloth were placed. Visually place the resectoscope into the bladder to determine the number, size and location of the tumor. First mark a circle with a needle electrode at the normal mucosa of 0.5 to 1 cm around the root of the tumor, and then electrocut the mucosa to the bladder muscle layer, surround the root of the tumor, and completely cut the tumor. The hemorrhage was stopped by electrocoagulation mode. If the tumor is small, it is flushed out with a irrigator. When it is difficult to flush out, it is taken out with gripping pliers. When the tumor is too large, divide the tumor body 2-3 times before rushing out of the tunnel. Finally, a part of the tissue was taken from the wound surface as a base specimen. F22 three-lumen urinary catheter was placed after operation.

Control group: The patient was placed in lithotomy position after anesthesia, the irrigating solution was saline, the surgical area was disinfected, and sterile cloth were placed. Visually place the resectoscope into the bladder to determine the number, size and location of the tumor. Use a spade electrode to remove the tumor layer by layer, cut to the muscular layer. The hemorrhage was stopped by electrocoagulation mode. Finally, a part of the tissue was taken from the wound surface as a base specimen. Use the

irrigator to flush out the tumor tissue fragments, and leave the specimens for examination. F22 three-lumen urinary catheter was placed after operation.

Postoperative bladder infusion: All patients undergo bladder instillation after operation. Infusion drugs include cytotoxic drugs and immunologic agents. Cytotoxic drugs include epirubicin, pirarubicin, gemcitabine, etc.; individual patients choose immunologic agents, such as BCG. Method: Once a week (9 times). Treatment: Initially once a week (10 times), then once a month (10 times).

Data collection

By reading the patient's medical records, we collected the following data: the patient's baseline treatment (age, sex, time of surgery), tumor characteristics (tumor size, tumor site, number of tumors), surgical data (operative time, intraoperative blood loss, surgical complications), postoperative conditions (ventilation time, bladder flushing time, urinary catheter time), clinical TNM staging (2009 TNM staging⁶), pathological grading (WHO 2004 grading⁷). The primary endpoint of this study was tumor recurrence, which was calculated from the time of patient received treatment to the time of re-diagnosis that the tumor recurred or reached the final follow-up time.

Statistical analysis

Pearson χ^2 or Fisher exact test (for categorical data) and independent sample t test (for continuous variables) were used to evaluate the association between treatment methods and patient characteristics and clinical characteristics. In order to reduce the bias of non-random treatment allocation, we used the propensity score matching (PSM) method. All baseline covariates were considered, including age, gender, tumor size, tumor number, pathological grade, tumor stage, receiving repeat TURBT, and year of diagnosis. For PSM, ERBT-treated patients were matched 1:1 with traditional TURBT-treated patients with a propensity score of 0.05 calipers.

In this model, Kaplan–Meier curves are used to calculate the overall recurrence rate. Univariate and multivariate Cox models were conducted to compare groups in PSM analysis. P value <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Product for Social Sciences (SPSS) software (version 24.0).

Result

Patients' characteristics

From 2016 to 2020, a total of 212 patients with NMIBC were included in the study, of which 39 patients received ERBT and 173 patients received traditional TURBT. The patient's baseline data is shown in Table 1. As shown in Table 1, before the PSM match, there is a significant difference between the two

groups in receiving repeat TURBT. After PSM matching, there were no significant differences between the two groups of factors.

Survival analysis

The median follow-up time for the entire study was 21 months (2–51 months). In this study, the total recurrence rates of the experimental group and the control group were 15.4% and 23.7% ($P = 0.592$), respectively. The 6-month recurrence rate was 10.3% and 8.1%, the 1-year recurrence rate was 12.8% and 13.9%, and the 3-year recurrence rate was 15.4% and 22.0%, respectively. (Fig. 1A, Table 2). The results of multivariate analysis showed that pathological grade, tumor size, and tumor number were independent risk factors affecting patients' recurrence (Table 3). In the head-to-head PSM analysis, 33 patients receiving ERBT treatment and 33 patients receiving traditional TURBT treatment were successfully matched, and the age, gender, tumor size, tumor number, pathological grade, tumor stage, receiving repeat TURBT were balanced between the two groups (Table 1). multivariate analysis results are shown in Table 4. The total recurrence rates of the experimental group and the control group were 18.2% and 24.2%, respectively ($P = 0.226$). The 6-month recurrence rate was 12.1% and 15.2%, the 1-year recurrence rate was 15.2% and 18.2%, and the 3-year recurrence rate was 18.2% and 24.2%, respectively. (Fig. 1B, Table 2).

Table 1
Patient baseline data

Variables	Before PSM (n = 212)		P value	After PSM (n = 66)		P value
	ERBT(n = 39)	TURBT(n = 173)		ERBT(n = 33)	TURBT(n = 33)	
Sex			0.904			0.523
male	31	136		26	28	
female	8	37		7	5	
Age			0.452			0.398
<70	29	118		23	26	
≥70	10	55		10	7	
Grade			0.817			0.125
low	30	136		24	18	
High	9	37		9	15	
Stage			0.880			0.720
Ta	9	38		5	4	
T1	30	135		28	29	
Tumor size			0.688			0.769
<3 cm	32	137		26	25	
≥3 cm	7	36		7	8	
Number of tumors			0.571			0.592
single	25	119		22	24	
multiple	14	54		11	9	
Repeat TURBT			0.000001			1
received	11	7		5	5	
no received	28	166		28	28	
Detrusor			0.056			0.076
yes	39	158		33	30	
no	0	15		0	3	

Table 2
Recurrence rate

Time	Unmatched(%)		PSM(%)	
	ERBT	TURBT	ERBT	TURBT
6-month	10.3%	8.1%	12.1%	15.2%
1-year	12.8%	13.9%	15.2%	18.2%
2-year	15.4%	20.8%	18.2%	24.2%
3-year	15.4%	22.0%	18.2%	24.2%
4-year	15.4%	23.7%	18.2%	24.2%

Table 3
Univariate and multivariate analysis of survival before PSM analysis

Variables	Univariate analysis		P value	Multivariate analysis		P value
	HR	95%CI		HR	95%CI	
Sex (male)	2.398	0.949–6.063	0.065			
Age (<70)	0.807	0.441–1.476	0.485			
Grade (low)	0.348	0.191–0.635	0.001	0.396	0.216–0.726	0.003
Stage (T1)	2.125	0.902–5.008	0.085			
Tumor size (<3cm)	2.563	1.407–4.668	0.002	0.472	0.257–0.868	0.016
Number of tumors (multiple)	0.475	0.268–0.841	0.011	0.547	0.307–0.975	0.041
Repeat TURBT (no received)	3.888	0.534–28.292	0.18			

Table 4
Univariate and multivariate analysis of survival in PSM analysis

Variables	Univariate analysis		P value	Multivariate analysis		P value
	HR	95%CI		HR	95%CI	
Sex (male)	1.445	0.323–6.459	0.630			
Age (<70)	0.777	0.243–2.480	0.670			
Grade (low)	0.206	0.067–0.634	0.006	0.294	0.092–0.944	0.040
Stage (T1)	3.102	0.402–23.940	0.278			
Tumor size (<3cm)	0.172	0.059–0.502	0.001	0.236	0.078–0.716	0.011
Number of tumors (multiple)	0.744	0.249–2.222	0.596			
Repeat TURBT (no received)	2.319	0.302–17.776	0.418			

Disease progression

Of the 212 patients, 15 patients had disease progression (clinical stage or pathological grade progression). Among them, 1 case was in the experimental group and 14 cases were in the control group. The progress rates were 2.6% and 8.1%, respectively ($P = 0.224$). After PSM matching, the progress rates of the two groups were 3.0% and 9.1% ($P = 0.302$). At the same time, for high-grade tumors, the progression rates of the two groups before PSM were 11.1% and 10.8% ($P = 0.979$), and the progression rates of the two groups after PSM were 11.1% and 13.3% ($P = 0.873$). As shown in Table 5.

Table 5
Disease progression

	Before PSM		χ^2	P value	After PSM		χ^2	P value
	ERBT	TURBT			ERBT	TURBT		
Total	39	173			33	33		
Progress	1	14			1	3		
Rate	2.6%	8.1%	1.479	0.224	3.0%	9.1%	1.065	0.302
High grade	9	37			9	15		
Progress	1	4			1	2		
Rate	11.1%	10.8%	0.001	0.979	11.1%	13.3%	0.025	0.873

Comparison of perioperative conditions

This study collected perioperative data of 212 patients, including operation time, intraoperative hemorrhage, intraoperative complications, postoperative fart time, bladder irrigation time, and catheterization time (Table 6). As shown in the table, the two groups differed in intraoperative blood loss and catheterization time. After PSM matching, the two groups only had statistical differences in intraoperative bleeding (P = 0.04).

Table 6
Perioperative conditions

Variables	Before PSM		P value	After PSM		P value
	ERBT	TURBT		ERBT	TURBT	
operation time (min)	50.2 ± 20.3	40.5 ± 19.8	0.185	48.8 ± 21.8	59.0 ± 22.9	0.067
intraoperative hemorrhage(ml)	12.7 ± 9.0	19.0 ± 7.7	<0.01	12.6 ± 9.4	16.7 ± 6.2	0.04
intraoperative complications	5.1%	1.2%	0.1			
Bladder perforation	0	0				
obturator reflex	2	2				
postoperative fart time(day)	1.9 ± 0.3	1.8 ± 0.4	0.547	1.9 ± 0.3	1.8 ± 0.4	0.5
bladder irrigation time(day)	2.3 ± 0.4	2.2 ± 0.5	0.686	2.2 ± 0.4	2.4 ± 0.8	0.44
catheterization time(day)	4.9 ± 1.8	3.7 ± 1.4	<0.01	4.8 ± 1.8	4.0 ± 1.7	0.097

Postoperative pathology results

In this study, 212 patients were diagnosed with non-muscle invasive urothelial carcinoma, 166 cases of low grade (30 cases in the experimental group, 136 cases in the control group), 46 cases of high grade tumors (9 cases in the experimental group, 37 cases in the control group). The detrusor muscle tissue was found in the postoperative pathology of all patients in the experimental group. In the control group, 15 patients were not found to have detrusor muscles (8.6%). After PSM matching, 3 patients in the control group had no detrusor muscles (9.1%) in their postoperative pathological tissues. Moreover, the edge of the pathological tissue in the experimental group was clear and there were few burn marks, while the edge of the pathological tissue in the control group showed more serious burn marks.

Discussion

The incidence of bladder cancer is increasing year by year, and surgery is its main treatment strategy. Until today, ERBT technology has been widely accepted by clinicians. In addition, a variety of ERBT technologies have been invented⁸⁻⁹. However, ERBT does not have a definite standard. Moreover, its efficacy with traditional TURBT is also controversial. At present, random comparison of ERBT with needle electrode and traditional TURBT is rare in clinic.

Our approach based on propensity score matching directly compared the therapeutic benefits of ERBT and traditional TURBT. After 1:1 matching, there was no statistically significant difference in the recurrence rate between the two groups ($P = 0.226$). One study suggested that ERBT can avoid tumor fragmentation, thereby minimize the floating of tumor cells, reducing the risk of recurrence of tumors⁴. However, we did not find that ERBT showed an advantage in terms of recurrence rate and progression rate. This is consistent with the results of some literature published in recent years. Zhang et al¹⁰ compared 90 patients with NMIBC treated by transurethral resection of bladder tumors (40 in the ERBT group and 50 in the traditional TURBT group), and found that there was no difference in the total recurrence rate between the two groups (20% vs 24%, $P = 0.650$). In addition, a study¹¹ compared ERBT with 1.9 microm vela laser and traditional TURBT, and there was no difference in recurrence rate between the two groups ($P > 0.05$). However, an randomized controlled trial¹² believes that although the recurrence rate at the same location is similar in the ERBT group and the TURBT group (4.9% vs 7.5%, $P > 0.05$), the ERBT group has a clear advantage in terms of overall recurrence rate (17.1% vs 27.5%, $P < 0.05$). Therefore, in terms of recurrence rate, whether ERBT can achieve better efficacy than the traditional TURBT group requires more experiments to prove. In terms of progression rate, this study found that although the results of the two groups were not statistically different, when the factor of tumor grade was limited, the difference in progression rate between the two groups was significantly reduced. It can be seen that tumor grade seems to be a factor affecting tumor progression.

In terms of surgical effect, we compared the effects of two different surgical methods on operation time, intraoperative hemorrhage, intraoperative complications, postoperative fart time, bladder irrigation time, and catheterization time, etc. The results showed that the ERBT group had an advantage in intraoperative bleeding compared with the traditional TURBT group ($P = 0.04$). We believe that during the ERBT operation, the tumor is usually removed from the surrounding tumor and advanced to the root of the tumor, so that the blood vessels around the tumor can be cut off and hemostasis can be stopped in time, which allows a better visual field during surgery and bleeding Also less. In the study by Balan et al¹², compared with the traditional TURBT group, the ERBT group had a lower drop in hemoglobin (0.28 vs 0.76 g/dL, $P < 0.05$). It can be seen that ERBT does have an advantage in improving intraoperative bleeding. Some articles reported that ERBT can effectively reduce the time of flushing, catheterization and hospitalization¹²⁻¹⁴, but in our study, no differences were found between the two groups. In terms of surgery time, some studies believe that ERBT takes less time (13.4 vs 19.7 min, $P < 0.05$)¹², and some studies find that ERBT takes longer surgery time (40.0 vs 19.5 min, $P = 0.0002$)¹³. In our opinion, the operation time is mainly related to the experience of the surgeon doctor and the surgical instruments used. In this study, the surgeon doctor has extensive experience in surgery. At the same time, we use needle electrodes as a resection tool, which has a small contact surface with the tissue, which effectively reduces the time spent adjusting the position. Of course, the small contact area will slow the rate of resection, therefore, we did not find a difference in surgical time between the two groups. After PSM matching, we found that there were no surgical complications in the two groups of patients. Analyzing the data before matching, there was no difference in obturator nerve reflex between the two groups. This

seems to be contrary to some research results^{12, 15}. However, reading of the relevant literature carefully reveals that the traditional TURBT energy source in this type of research is a plasma monopolar source, while our traditional TURBT group energy source is a plasma bipolar electrode. In theory, the use of bipolar energy can reduce the risk of obturator nerve reflexes. Avallone et al¹⁶ compared the safety and efficacy of monopolar and bipolar energy TURBT in the treatment of NMIBC, and found that the use of bipolar energy has a tendency to reduce obturator nerve reflexes (2.6% vs 5.8%).

Research suggests that the presence of detrusor muscles is an important surgical quality control indicator used to indicate complete tumor resection¹⁷. The results of Zhang et al¹⁰ showed that the presence of detrusor muscle was easier to find in the pathological tissue after ERBT (100% vs 54%, $P < 0.01$). Another study also recognized the advantages of ERBT in this regard (2.94% vs 20.0%, $P = 0.04$)¹⁸. In this study, we also found that the pathological tissue after ERBT seems to be easier to find the detrusor muscle (100% vs 90.9%), however, statistical analysis did not find a difference between the two groups. In our analysis, this may be due to the fact that the two surgical procedures in this study both excised the tissue from the surgical wound and left it as the base specimen, which can effectively find the detrusor muscle. Comparing the postoperative pathological results of the two groups, ERBT can obtain higher-quality tumor specimens, especially less burn marks on the muscle layer, which is very beneficial for postoperative evaluation of the depth of tumor invasion.

In multivariate analysis, we found that tumor grade and tumor size are risk factors affecting tumor recurrence rate, which may be due to two factors related to postoperative tumor residuals. The EAU guidelines suggest that patients with high-grade bladder cancer have a higher risk of residual tumor after surgery¹. Yuk et al¹⁹ analyzed the risk factors affecting the residual tumor after TURBT by univariate and multivariate analysis methods. The results showed that the high-grade tumors (1.925 [1.014–3.656], $P = 0.045$) and tumors ≥ 3 cm (2.56 [1.13–6.04], $P = 0.026$) were independent risk factors for tumor residuals.

In this study, when performing ERBT on a large bladder tumor, how to completely remove the tumor is a puzzling thing. Most studies currently use 3 cm as the upper limit of ERBT. For tumors that are too large, we divide them 2–3 times and then take them out. Studies have suggested that fragmentation of tumor tissue can affect the pathological results of the tumor and underestimate the stage of the tumor. and in the process of tumors cutting, cancer cells are prone to grow and metastasize, which leads to recurrence⁴. Hayashida et al²⁰ proposed a new scheme combining endoscopic mucosal resection (EMR) and ERBT. EMR is used to remove the part of the tumor that protrudes from the mucosa, and use ERBT to remove the remaining part. And compare the recurrence rate of this surgical method with traditional TURBT. The results showed that there was no difference in the recurrence rate between the two groups ($P = 0.662$). In addition, the postoperative pathology of the new surgery can determine the degree of infiltration, while 19.4% of patients in the traditional group cannot determine the degree of infiltration ($P = 0.016$). Therefore, it seems to be a feasible method to segment tumor samples properly.

Conclusion

En bloc transurethral resection of bladder tumors with needle electrode is used as a treatment method for bladder tumor. Compared with traditional TURBT treatment, it has less intraoperative bleeding and high surgical safety. Moreover, this technique can obtain high-quality pathological specimens, which has obvious advantages in postoperative pathological assessment. In terms of recurrence-free survival, there is no difference between ERBT and traditional TURBT.

Abbreviations

ERBT= En bloc transurethral resection of bladder tumors

TURBT= transurethral resection of bladder tumor

NMIBC= non-muscle invasive bladder cancer

PSM= propensity score matching

BCG= Bacillus Calmette-Guerin

Declarations

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Authors' Contributions:

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content. The authors have agreed to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JSL is the author of the article and the main collector of data. PFS as the instructor to make appropriate revisions to the article. YDH helps data collection. YCS helps data collection. XZ helps data collection.

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Availability of data and materials:

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

Ethics approval and consent to participate:

The study protocol has been approved by the Medical Ethics Committee of the Second Hospital of Lanzhou University, Lanzhou, Gansu, China.

Consent to publish:

Not applicable.

Competing interests:

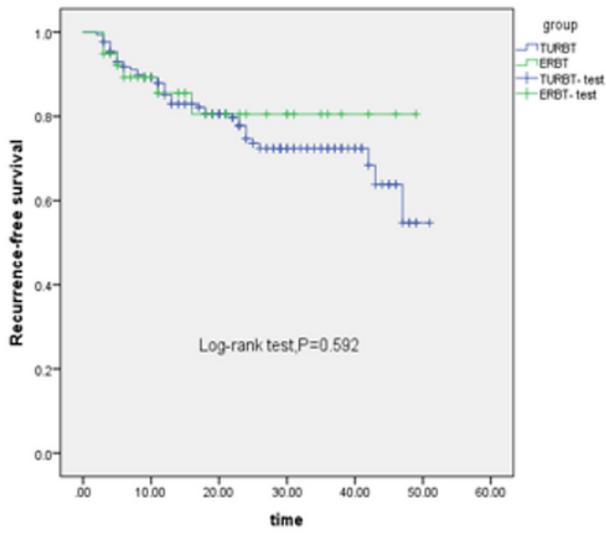
The authors declare that they have no competing interests.

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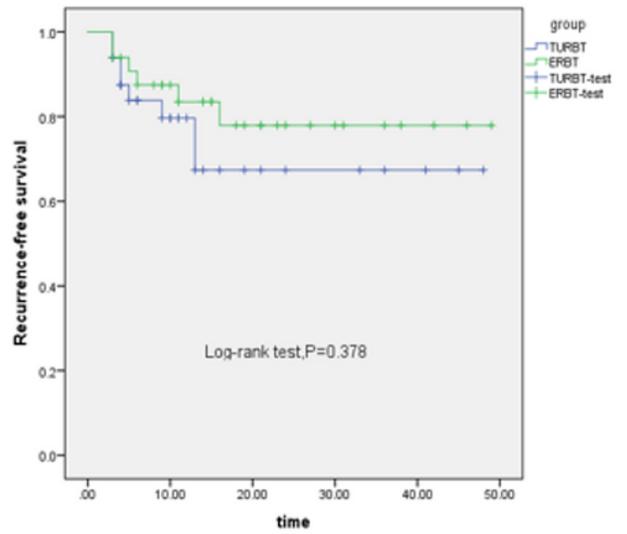
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Figures



A.



B.

Figure 1

Kaplan-Meier curve A. Kaplan-Meier curve before PSM; B. Kaplan-Meier curve after PSM