# Influences of Different Operative Methods on the Recurrence Rate of Non-Muscle-Invasive Bladder Cancer

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## ABSTRACT

**Purpose:** To compare the influence of three operative approaches [transurethral en bloc resection of bladder tumor by pin-shaped electrode (pin-ERBT), transurethral resection of bladder tumor (TURBT) and transurethral holmium laser resection of bladder tumor (HoLRBT)] on the recurrence rate of non-muscle-invasive bladder cancer (NMIBC) at low dimension (i.e. diameter below 3 cm).

**Materials and Methods:** A retrospective analysis was conducted for a total of 115 patients affected by solitary NMIBC, with a diameter <3 cm, who were submitted to operation between March 2013 to May 2017. The patients were divided according to the operative method applied (pin-ERBT, TURBT and HoLRBT groups, respectively). The 2-year recurrence rate was compared among the three groups, and multivariat Cox hazard model analysis was applied to analyze the influencing factor(s) for postoperative recurrence.

**Results:** The 2-year recurrence rate was 10.0% in ERBT, 38.5% in TURBT and 40.0% in HoLRBT group, with a significant difference ($P$ =0.014). According to the Cox hazard model analysis, age(HR=1.058, 95% CI: 1.019~1.098，$P$=0.003), operative method(HR=2.974,6.508,

95% CI: 0.862~10.255,1.657~25.566, *P*=0.023), smoking(HR=2.399, 95% CI: 1.147~5.017, *P*=0.020) and pathological grade(HR=2.012,95% CI: 1.279~3.165, *P*=0.002) were risk factors for postoperative recurrence of bladder cancer.

**Conclusion**: Pin-ERBT can prominently decrease the postoperative recurrence rate of solitary NMIBC with a diameter <3 cm.

**Key words:** ERBT, pin-shaped electrode, NMIBC, recurrence rate, TURBT, HoLRBT

## INTRODUCTION

Bladder cancer (BC) is considered one of the common malignant tumors of the urinary system. BC can be classified in non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Transurethral resection of bladder tumor (TURBT) is the most typical treatment for this pathological condition. Still, TURBT has certain disadvantages, such as dissemination and seeding as well as incomplete resection due to fragmentation of tumor tissues, which can potentially lead to a higher postoperative recurrence rate. Maurice and colleagues have shown that the postoperative recurrence rate of TURBT can be as high as 30-50%[(1)] As a novel operative methodology, en bloc resection of bladder tumor by pin-shaped electrode (pin-ERBT) can entirely promote the resection of the bladder tumor utilizing the distinctive features of a pin-shaped electrode, which possesses advantages such as clear layer, precise cleavage and accurate pathological stage after operation transurethral holmium laser resection of bladder tumor (HoLRBT) is another new procedure that enables a gradual or entire excision of the bladder tumor by laser-based energy.[(2)]

Therefore, here we investigated the impact of these three operative methods on the postoperative recurrence rate of BC. For this, their recurrence rates were retrospectively reviewed, and Cox hazard model analysis was performed to analyze the risk factors linked to the recurrence of solitary NMIBC, at the dimension of less than 3 cm.

## PATIENTS AND METHODS

### *1. Study Population*

A total of 115 NMIBC patients who were treated with transurethral surgery for the first time in our hospital, between March 2013 and May 2017, were selected.

### *2. Inclusion and exclusion criteria*

Inclusion criteria: ① Primary, solitary and Ta stage bladder tumor with the maximum diameter less than 3cm. ② Treated by one of the three transurethral surgeries; ③ Recieved 1 year of standardized bladder perfusion treatment after operation, and regular reexamination of cystoscopy. ④ The surgens have experience of TURBT over 10 years. Exclusion criteria: ① Recurrent bladder tumor. ②Benign or non urothelial tumor pathological diagnosis. ③ Tumors were multiple or with diameter greater than or equal to 3cm; ④ patients with other tumors. The operation was performed by 3 senior consultants with rich experience in TURBT.

### *3. Surgical technique*

The enrolled patients were divided into 3 groups according to the operative methods, namely pin-ERBT (n=30), TURBT (n=65) and HoLRBT (n=20) groups. Based on the WHO 2004 classification[3], tumors were classified into grade I (papillary urothelial neoplasm of low malignant potential), II (low-grade urothelial carcinoma) and III (high-grade urothelial carcinoma). The baseline data of the patients are shown in Tables 1. Their diagnosis was confirmed by ultrasonography, CT plain scan and contrast-enhanced scan of the urinary system, as well as cystoscopy and tissue biopsy. The local Ethics Committee approved the use of patient data, and consent was obtained from all patients involved.

### *3.1. Pin-ERBT group*

A tissue range of ~1 cm away from the basilar part of the tumor was initially marked with the pin-shaped electrode. Mucous, submucosa and superficial muscular layers were then cut open and gradually separated towards the basilar part of the bladder tumor, along the superficial

muscular layer, using the electrode. Thereafter, the whole tumor and basilar parts were fully dissociated and the supply vessels of the tumor were concomitantly coagulated. Isolated tumor tissues were further washed out using an irrigator or taken out with a retrieval basket.

### *3.2. TURBT group*

The operation range was labeled at ~1 cm away from the tumor area using a looped electrode. Subsequently, both tumor and peripheral mucosa were electrically resected from the crown of tumor to the superficial muscular layer of the bladder. The resected tissues were then washed out using an irrigator.

### *3.3. HoLRBT group*

An optical fiber (diameter =550 μm, laser energy =1.0-2.0 J, frequency =15-20 Hz) was selected for a circular cutting of the muscular layer, along the periphery, at 1 cm away from the basilar region of the tumor. Cutting was done towards the tumor root until the intact tumor was excised. This procedure was performed under a direct light source. Tumor tissues were further washed out using an irrigator. Alternatively, tumors were removed using a retrieval basket.

After each operative procedure, patients were given persistent bladder washout and postoperative indwelling of urethral catheter. Thereafter, intravesical instillation of pirarubicin or gemcitabine was performed. Patients were reexamined by cystoscopy once every 3 months after operation, when the time to recurrence was eventually recorded. Each patient was followed up to 2 years or recurrence. Median follow up duration in each group was 24 months.

### *3. Statistical Analysis*

SPSS 21.0 was adopted for statistical data analysis. Data measurement were expressed as mean ± standard deviation ( ±s). Independent sample's t-test was used for comparison between two groups. Alternatively, one-way analysis of variance was performed for comparison among multiple groups. Categorical and count data were presented as n (%). The comparison of unordered categorical data between groups was subjected to $\chi 2$ test, while the comparison of

ordered categorical data between two groups was examined by Mann-Whitney U test Kruskal-Wallis H test was utilized for comparison among multiple groups. The cumulative recurrence rate at each time point was compared, among different operative approaches, using Kaplan-Meier method. Cox hazard model analysis was applied to screen the risk factors for tumor recurrence. Statistically significant was defined by $p<0.05$.

## RESULTS

### *1. Clinical features of selected NMIBC patients( Table 1)*

### *2. Comparison of surgery information among distinct patient groups*

As indicated in Table 2, no significant differences were observed, in regard to sex, age, diabetes mellitus and smoking, among the patient groups. And the differences in the lesion size, pathological grade and bladder lesion position were not statistically significant when comparing each group of patients. Also,We observed that the operation time was longer in pin-ERBT group than that in TURBT and HoLRBT groups. This difference was statistically significant ($P$ =0.007). According to the results of $\chi 2$ test, however, no statistically significant differences among the groups were observed in the type of anesthesia used ($P$ =0.888) and the category of perfused drug ($P$ =0.991).

### *3. Comparison of recurrence rate in patients from distinct groups*

The pin-ERBT group had a remarkably lower recurrence rate than TURBT and HoLRBT groups after 24 months of operation ($P$ =0.014) (Table 3).

### *4. Analysis of risk factors for recurrence in distinct patient groups*

Based on the results of univariate analysis, the recurrence was not correlated with the perfused drug （$P$ = 0.544） and lesion position ($P$ =0.723). Nevertheless, the reccurence rate had associations with factors including sex ($P$ =0.024), age ($P$ =0.723), smoking ($P$ ＜0.001), pathological grade ($P$ ＜0.001), type of anesthesia ($P$ =0.018) and operative method ($P$ =0.044) (Table 4).

In the multivariate Cox hazard model analysis, the recurrence was taken as the dependent variable, the follow-up time was taken as the time variable, and the indexes with statistical significance in the univariate analysis, including gender, age, anesthesia mode, pathological level, smoking, operation mode were regarded as independent variables. The assignment of each variable is shown in Table 4. The results indicated that age(*P*=0.003), operative method(*P*=0.023), smoking *P*=0.020) and pathological grade(*P*=0.002) were the risk factors for the recurrence among the patients.(Table 4)

***5. Comparison of cumulative recurrence rate among groups***

The 24-month cumulative recurrence rates in the TURBT and HoLRBT groups were similarly higher than that in the pin-ERBT group, and this difference was statistically significant (*P* =0.021) (Figure 1).

**DISCUSSION**

Bladder cancer is a relatively high incidence rate of cancer. Accurate diagnosis requires cystoscopy and pathological diagnosis. Special types of bladder tumors, such as bladder small cell carcinoma, are difficult to diagnose and need to be confirmed by immunohistochemistry [(4)]. TURBT is a commonly used operative method for bladder cancer. Still, 36-51% of the TURBT-derived specimens lack muscular layer tissues[(5)], limiting the determination of the pathological stage [13]. Besides, the tumor residual rate along the basilar region can be up to 30-44% after TURBT [(6)]. Second transurethral resection may remove the tumor more thoroughly, but there are also controversies. Some scholars think that in patients with single, small T1 and / or high-grade tumor, secondary TURBT is not closely related to tumor residual and disease deterioration [(7)]. At the same time, the incidence of obturator reflex in TURBT is high, and there is a risk of bladder perforation [(8)]. It has been denoted that, in TURBT group,~70% specimens contain muscular layer tissues, while entire tumor specimens containing muscular layer tissues can be obtained in both HoLRBT and ERBT groups[(9)]. The cauterization of the tumor tissues

by TURBT can alter the tissue morphology, so that intact specimens containing a muscular layer cannot be acquired. Some studies have indicated that tumor staging can be clinically underestimated up to 49% of the patients[10]. Engilbertsson and colleagues[11] have identified the conditions of tumor cells in the circulating blood of 16 patients before and during TURBT. In this case, tumor cells could be observed in 7 patients, from which 6 (86%) had an much higher number of tumor cells during operation, suggesting that tumor cells may enter the circulation system during TURBT, therefore increasing the risk of tumor metastasis and tumor recurrence.

The recurrence rate of BC is typically high, but related data can vary in the current literature. For instance, Hurle and colleagues have reported that the recurrence rate of BC is 15% by a 2-year follow-up after en bloc resection by pin-shaped electrode[12]. Based on laser en bloc resection, Muto and colleagues have found a recurrence rate of~14.5% at 16 months after postoperative follow-up[13]. Liu and colleagues also compared the postoperative recurrence rate between patients who were submitted to laser en bloc resection (n=64) versus traditional TURBT (n= 56)[14]. According to their results, the recurrence rates were 10.9%, 19.5% and 31.3% after 1, 2 and 3 years of en bloc resection, versus 10.7%, 22.9% and 33.9%, after traditional electro resection, respectively. Still, no significant differences were detected between the two groups.

In terms of the risk factors related to the recurrence of BC, Rink and colleagues revealed that an active smoking history was an independent risk factor for recurrence after BC surgery in males[15]. Lu and colleagues found that the recurrence rate was positively correlated with the pathological grade of the tumor[16]. Moreover, Koumpan and colleagues have shown that patients undergoing combined spinal-epidural analgesia have a lower recurrence rate than those undergoing general anesthesia[17]. In this case, it appears that the volatile anesthetics used during general anesthesia may stimulate the production of hypoxia-inducible factor 1 (HIF-1),

thus activating the proliferation of tumor cells. In this study, we did not find that the choice of intravesical instillation drugs is related to tumor recurrence, and the relevant literature also shows that the difference between the choice of pirarubicin and gemcitabine is not a risk factor for tumor recurrence, but the incidence of bladder irritation symptoms after gemcitabine selection is slightly lower than that of pirarubicin [18] .

In the present study, the recurrence rate in the pin-ERBT group after 2 years of operation was markedly lower than in the TURBT and HoLRBT groups, which is consistent with some previous studies[19,20].Intriguingly, Chen'[21] s reports have shown similar postoperative recurrence rates on both ERBT and HoLRBT but, in the present study, the HoLRBT group exhibited a distinctly higher long-term (2-year) recurrence rate than pin-ERBT group. There are some possible explanations for this kind of contradicting result. First, the holmium laser may simultaneously cleave and vaporize properties, so it cannot clearly recognize anatomical layers when compared with the pin-shaped electrode. Second, the holmium laser does not generally achieve a satisfactory resection effect on tumors located in sharp angles, such as the bladder dome and the anterior bladder wall, due to the straight optical fibers. Third, it is difficult to control the depth of cutting promoted by the holmium laser, which can easily cause bladder perforation[22].

According to the results of multivariate Cox hazard model regression analysis, clinical features including age, operative method, smoking and pathological grade were the risk factors for the recurrence of BC. The operative method served as an influencing factor with statistical significance, indicating that operative factors can affect the recurrence rate, besides the biological characteristics of the tumor.

The pin-shaped electrode is typically slim in shape and able to flexibly rotate and to bluntly dissect, allowing a precise cleavage of the tissue. Therefore, it can accurately resect tumors at distinct sites of the bladder by means of 360° rotation of endoscopic sheath. Some advantages

can be highlighted for this kind of operation: (i) tumors can be cut and isolated along the muscular layer, so the resection is more precise and the exact pathological stage can be defined; (ii)labeling of the cutting range before cleavage as well as partial block age of blood supply can decrease the probability of metastasis and recurrence induced by blood-borne dissemination; (iii) specimens can be removed entirely, reducing the implantation and recurrence rates of BC. In contrast, pin-ERBT also have a few limitations. This technique, for instance, is not suitable for extensive NMIBC tumors. Indeed, in the case of tumors larger than 3 cm in diameter, the resected specimens cannot be removed completely. Therefore, some in-depth optimization for en bloc resection of larger tumors(i.e. diameter less than 3 cm) will be further required.

Compared with TURBT and HoLRBT, pin-ERBT is characterized by fewer complications, higher efficiency, thorough tumor enucleation, lower recurrence rate and easier handling. As such, this operative method is worthy of clinical popularization and application. Nevertheless, there were some limitations in this study. Firstly, the sample size for this research was small, so the elaboration of more long-term, large-sample and multi-center prospective studies will be needed to confirm our data. Secondly, only the patients with solitary tumors with a diameter over 3 cm were analyzed, so the operative efficacy using a multiple range of large tumors should be further verified.

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**STATEMENT OF ETHICS**

All patients have given their written informed consent.This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki,and the use of patient data was approved by the ethics committee of Hebei General Hospital(No.202005).

## AUTHOR CONTRIBUTIONS

J.L. and S.L.designed clinical studies. Y.J. and S.L. analyzed the data and wrote the manuscript. S.L. and F.S.and W.W.and H.X. performed the surgery.C.Y. and J.L.and P.Z followed up patients. J.L. and S.L.andY.J. reviewed, revised,and approved the final paper.

## CONFLICT OF INTEREST

The authors report no conflict of interest.

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**Figure legends**

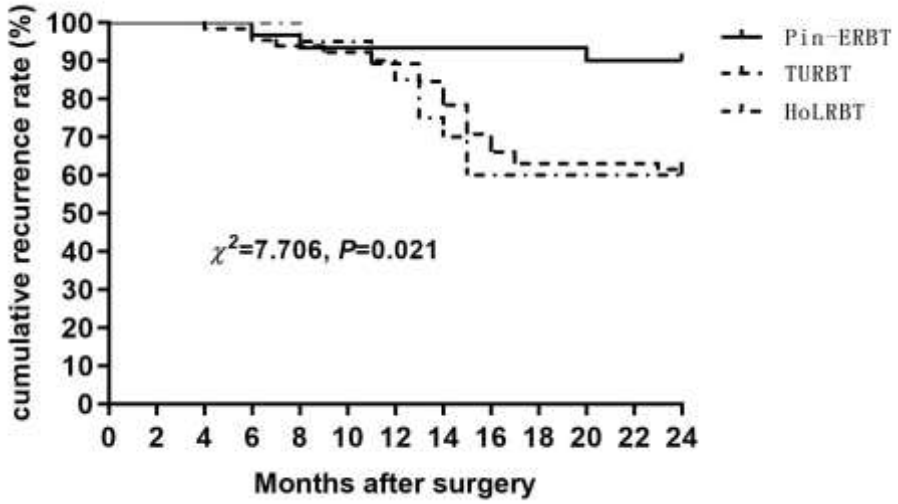


**Figure 1: Comparison of cumulative recurrence rate at 24 months after operation among groups**

**Table 1: Statistics of clinical features among the BC patient population**

| CLINICAL FEATURE | STATISTICAL RESULT |
|---|---|
| **Sex** | |
| Male | 93 (80.9) |
| Female | 22 (19.1) |
| **Age (years old)** | 64.46±11.91 (33.0-88.0) |
| **Lesion size (cm)** | 1.86±0.73 (0.2-3.0) |
| **Type of anesthesia** | |
| General anesthesia | 74 (64.3) |
| Spinal anesthesia | 41 (35.7) |
| **Operation time (hrs)** | 1.53±0.31 (0.8-3.0) |
| **Pathological grade** | |
| Papillary urothelial neoplasms of low malignant potential | 43 (37.4) |
| Low-grade urothelial carcinoma | 37 (32.2) |
| High-grade urothelial carcinoma | 35 (30.4) |
| **Perfused drug** | |
| Pirarubicin | 103 (89.6) |
| Gemcitabine | 12 (10.4) |
| **Diabetes mellitus** | 20 (17.4) |
| **Smoking** | 35 (30.4) |
| **Recurrence rate at 12 months** | 11 (9.6) |
| **Recurrence rate at 24 months** | 36 (31.3) |
| **Operative method** | |
| Pin-ERBT | 30 (26.1) |
| TURBT | 65 (56.5) |
| HoLRBT | 20 (17.4) |
| **Lesion position** | |
| Lateral wall | 72 (62.6) |
| Neck | 8 (7.0) |
| Anterior wall | 25 (21.7) |
| Trigone | 10 (8.7) |

**Table 2: Comparison of clinically features of three groups**

| | | Pin-ERBT n=30 | TURBT n=65 | HoLRBT n=20 | *P*- value |
|---|---|---|---|---|---|
| Sex | Male | 24 (80.0) | 55 (84.6) | 14 (70.0) | 0.344 |
| | Female | 6 (20.0) | 10 (15.4) | 6 (30.0) | |
| Age; Mean±SD, year | | 63.23±10.39 | 66.23±11.86 | 60.55±13.51 | 0.141 |
| Diabetes | | 4 (13.3) | 14 (21.5) | 2 (10.0) | 0.390 |
| Smoking | | 9 (30.0) | 20 (30.8) | 6 (30.0) | 0.996 |
| Lesion size (cm) Mean±SD, | | 1.94±0.64 | 1.88±0.75 | 1.66±0.76 | 0.374 |
| Pathological grade (%)[a] | I | 13 (43.3) | 21 (32.3) | 9 (45.0) | 0.680 |
| | II | 9 (30.0) | 24 (36.9) | 4 (20.0) | |
| | III | 8 (26.7) | 20 (30.8) | 7 (35.0) | |
| Lesion position(%) | Lateral wall | 23 (76.7) | 38 (58.5) | 11 (55.0) | 0.555 |
| | Neck | 1 (3.3) | 5 (7.7) | 2 (10.0) | |
| | Anterior wall | 4 (13.3) | 17 (26.2) | 4 (20.0) | |
| | Trigone | 2 (6.7) | 5 (7.7) | 3 (15.0) | |
| Operation time (h) | | 1.68±0.32 | 1.49±0.27[b] | 1.44±0.34 | 0.007 |
| Type of anesthesia (%) | General anesthesia | 20 (66.7) | 42 (64.6) | 12 (60.0) | 0.888 |
| | Spinal anesthesia | 10 (33.3) | 23 (35.4) | 8 (40.0) | |
| Perfused drug (%) | Pirarubicin | 27 (90.0) | 58 (89.2) | 18 (90.0) | 0.991 |
| | Gemcitabine | 3 (10.0) | 7 (10.8) | 2 (10.0) | |

Note[a]: I: papillary urothelial neoplasm of low malignant potential, II: low-grade urothelial carcinoma, III: high-grade urothelial carcinoma.

*Note[b]: [b]$p<0.05$ vs. pin-ERBT group.*

**Table 3: Comparison of recurrence rate among patients receiving different operative methods**

| Group | n | Recurrence rate at 24 months |
|---|---|---|
| Pin-ERBT | 30 | 3 (10.0) |
| TURBT | 65 | 25 (38.5)[a] |
| HoLRBT | 20 | 8 (40.0)[a] |
| $\chi^2$ | - | 8.583 |
| *p* | - | 0.014 |

Note: [a]$p<0.05$ vs. pin-ERBT group.

**Table 4** Univariate COX analysis and Multivariate COX regression analysis results

| Factor | un-adjusted effect size（Univariate） | | | | adjusted effect size（Multivariate） | | | |
|---|---|---|---|---|---|---|---|---|
| | *Wald*$\chi^2$ | *P* | *HR(95% CI)* | | Variable | *Wald*$\chi^2$ | *P* | *HR(95% CI)* |
| Recurrence | | | | | Yes=1, No=0 | | | |
| Gender | 5.107 | 0.024 | 2.228(1.112~4.464) | | Male=1, female=2 | 0.006 | 0.937 | 1.031(0.486~2.189) |
| Age | 12.382 | 0.000 | 1.064(1.028~1.101) | | Numerical type | 8.864 | 0.003 | 1.058(1.019~1.098) |
| Lesion size | 0.118 | 0.731 | 0.922(0.580~1.465) | | | - | - | - |
| Anesthesia method | 5.598 | 0.018 | 2.206(1.145~4.248) | | Spinal anesthesia =1, general anesthesia =2 | 0.778 | 0.378 | 1.404(0.661~2.98) |
| Operation time | 0.962 | 0.327 | 0.562(0.178~1.778) | | | - | - | - |
| Pathological grade[a] | 15.259 | 0.000 | 2.417(1.552~3.764) | | Grade I =1, grade II =2, grade III =3 | 9.152 | 0.002 | 2.012(1.279~3.165) |
| Perfused drug | 0.367 | 0.544 | 0.694(0.213~2.262) | | | - | - | - |
| Diabetes | 0.515 | 0.473 | 0.708(0.275~1.820) | | | - | - | - |
| Smoking | 8.508 | 0.004 | 2.648(1.376~5.095) | | Yes=1, No=0 | 5.407 | 0.02 | 2.399(1.147~5.017) |
| Operative method | | | | | | | | |
| Pin-ERBT | 6.227 | 0.044 | 1 | | Pin-shaped electrode =1 | 7.533 | 0.023 | 1 |
| TURBT | 5.828 | 0.016 | 4.375(1.320~14.499) | | electric resection =2 | 2.977 | 0.084 | 2.974(0.862~10.255) |
| HoLRBT | 5.381 | 0.020 | 4.816(1.276~18.173) | | holmium laser =3 | 7.199 | 0.007 | 6.508(1.657~25.566) |
| Lesion position | | | | | | | | |
| Lateral wall | 1.326 | 0.723 | | | | - | - | - |
| Neck | 0.353 | 0.552 | 1.445(0.429~4.868) | | | - | - | - |
| Anterior wall | 1.128 | 0.288 | 1.509(0.706~3.225) | | | - | - | - |
| Trigone | 0.001 | 0.976 | 1.019(0.303~3.430) | | | | - | - | - |

Note[a]: I: papillary urothelial neoplasm of low malignant potential, II: low-grade urothelial carcinoma, III: high-grade urothelial carcinoma.