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Efficacy and Safety of Transurethral Laser Surgery Versus Transurethral Resection for Non-Muscle-Invasive Bladder Cancer: A Meta-Analysis and Systematic Review

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Keywords

Bladder cancer · Laser surgery · Transurethral resection · Systematic review and meta-analysis

Abstract

Objective: To compare the efficacy and safety of transurethral laser surgery and transurethral resection of a bladder tumor (TURBT) for non-muscle-invasive bladder cancer (NMIBC). ***Material and Methods:*** A research was carried out in Medline via PubMed, EMBASE, the Cochrane Library, and Web of Science up to October 20, 2019, to identify articles related to transurethral laser surgery and TURBT for NMIBC. All analyses were done using RevMan5.3 and Stata14. ***Results:*** A total of 17 studies involving 2,439 participants were included. The analysis showed no significant difference in operation times (mean difference = –0.2; 95% CI –2.29 to 1.89; $p = 0.85$) or occurrences of urethral stricture (OR = 0.7; 95% CI 0.24–2.06; $p = 0.52$). Transurethral laser surgery was associated with a lower incidence of obturator nerve reflex (OR = 0.04; 95% CI 0.02–0.09; $p < 0.00001$) and bladder perforation (OR = 0.09; 95% CI 0.04–0.23; $p < 0.00001$), a higher rate of detrusor muscle acquisition (OR = 5.28; 95% CI 2.42–11.49; $p < 0.0001$), shorter catheterization (mean difference = –1.05; 95% CI –1.41 to –0.68; $p < 0.00001$) and hospitalization times (mean difference = –0.96; 95% CI –1.59 to –0.33; $p = 0.003$), and lower rates of bladder irrigation (OR = 0.21; 95% CI 0.13–0.35; $p < 0.00001$) and recurrence both at 12 months (OR = 0.66; 95% CI 0.48–0.9, $p = 0.008$) and at 24 months (OR = 0.6; 95% CI 0.41–0.86; $p = 0.005$). ***Conclusions:*** Transurethral laser surgery for NMIBC, as compared to TURBT, is associated with a lower incidence of complications, a lower recurrence rate, and faster postoperative recovery.

Introduction

Bladder cancer is one of the most common malignant tumors of the urinary system. The American Cancer Society estimates that there will be 80,470 new cases of bladder cancer and 17,670 cancer-related deaths in 2019 [1]. More than 95% of bladder cancers are urothelial carcinomas, and non-muscle-invasive bladder cancer (NMIBC) accounts for 75–80% of urothelial carcinomas, including bladder tumors confined to the mucosa (stage Ta, carcinoma in situ) or submucosa (stage T1) [2].

Currently, the standard treatment for NMIBC is transurethral resection of bladder tumor (TURBT) followed by

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adjuvant intravesical chemotherapy or immunotherapy [3, 4]. Although TURBT is very mature, it is still difficult to control the cutting depth when the tumor is close to the ureteral orifice; the obturator nerve reflex may occur when the tumor is located in the lateral wall, leading to bladder perforation and even iliac vascular injury [5, 6]. At the same time, piecemeal resection as an “incise and scatter” process is associated with an increased risk of tumor recurrence and difficulties accurately assessing pathological staging of tumors due to incomplete resection [7–9].

With the development of laser technology, the first transurethral NMIBC laser surgery occurred in the 1970s [10]. It was approved by the FDA in 1984 and has been widely used in recent years due to its good tissue vaporization and hemostatic effect as well as its high safety [10, 11]. In particular, the use of laser surgery for en bloc resection can provide an intact tissue specimen for accurate pathological evaluation and reduce the risk of scattering malignant cells [12]. Several kind of lasers have been found to be useful in transurethral laser therapy for NMIBC, with holmium and 2-um lasers being the most commonly used in clinical practice [13]. With the increasingly extensive application of laser surgery, whether laser surgical treatment NMIBC can replace TURBT as the gold standard for NMIBC or only as a supplement to TURBT has become a hot issue. In recent years, several studies have directly compared transurethral laser therapy with TURBT in an attempt to explore this issue and they have yielded similar, but not completely consistent, results on some oncology and perioperative indicators [14–16]. At the same time, these existing studies all have shortcomings such as a small sample size, being single center, and a lack of randomization, and some of them are only observational studies so the results obtained may exaggerate or reduce the real difference in efficacy and safety between transurethral laser surgery and TURBT. This paper shows a meta-analysis of the previous literature in order to more accurately compare the efficacy and safety of transurethral laser surgery and TURBT treatment of NMIBC and to explore whether transurethral laser surgery can replace TURBT so as to provide a reference for the selection of clinical treatment options.

Methods

Search Strategy

A systematic search was carried out in Medline via PubMed, EMBASE, the Cochrane Library, and Web of Science up to October 20, 2019, to identify published articles related to transurethral laser surgery and TURBT for NMIBC. The types of studies included randomized controlled trials (RCT), cohort studies, and clinical case-control studies. The search terms used included: (bladder cancer OR bladder tumor OR bladder carcinoma OR noninvasive bladder cancer OR urothelial carcinoma) and (transurethral resection OR resection) and (laser). We also browsed the list of references for highly relevant literature and manually searched the grey literature to ensure that no relevant literature was missing. This system review and meta-analysis is reported in accordance with the preferred reporting items of the system review and meta-analysis (PRISMA) [17] (ISSM_PRISMA_Checklist.pdf; for all online suppl. material, see www.karger.com/doi/10.1159/000506655).

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) the types of studies were RCT or cohort studies and clinical case-control studies; (2) the study subjects were primary NMIBC patients with a clear pathological diagnosis and postoperative bladder perfusion therapy, followed up for more than 1 year; (3) interventions included all laser types of transurethral laser surgery; (4) studies involved the comparison of transurethral laser surgery and TURBT; and (5) outcome indicators included at least one of the following: operation time, incidence of obturator nerve reflex, incidence of bladder perforation, detrusor muscle acquisition rate, hospitalization time, catheterization time, bladder irrigation rate, incidence of urethral stricture, and recurrence rate.

The exclusion criteria were: (a) the subjects included patients with recurrent or muscle-invasive bladder cancer; (b) ta lack of relevant outcome indicators; (c) the patient had undergone other transurethral procedures; and (d) unclear outcomes and missing data; and (e) republished literature.

Selection Process and Data Abstraction

Two reviewers reviewed the titles, abstracts, and full text independently according to the inclusion and exclusion criteria. Disputes arising during the title and abstract screening phase were directly incorporated into the full text assessment to ensure that all relevant papers were not omitted. In the full text stage, the differences were resolved by negotiation between 2 reviewers. If there was no agreement, a third reviewer is consulted.

The 2 reviewers independently extracted relevant data with a predesigned data extraction table. Baseline data extracted included: first author and publication year, country, study type, surgical methods, sample size, follow-up time, outcomes, and quality score. Outcome indexes can be divided into intraoperative indexes and postoperative indexes. Intraoperative indicators include operation time, incidence of obturator nerve reflex, incidence of perforation, and detrusor muscle acquisition rate. Postoperative outcome indicators included: hospitalization time, catheterization time, bladder irrigation rate, incidence of urethral stricture, 12-month recurrence rate, and 24-month recurrence rate. The median, range, and sample size data provided in the literature were all converted into the data types required for the statistics in this study by the method described by Hozo et al. [18].

Literature Quality and Risk of Bias Assessment

To assess the quality of the literature and the risk of bias, we used the Jadad score [19] to evaluate RCT and the Newcastle-Ottawa Scale (NOS) [20] to evaluate retrospective cohort studies. The Jadad score mainly evaluates randomization and randomization

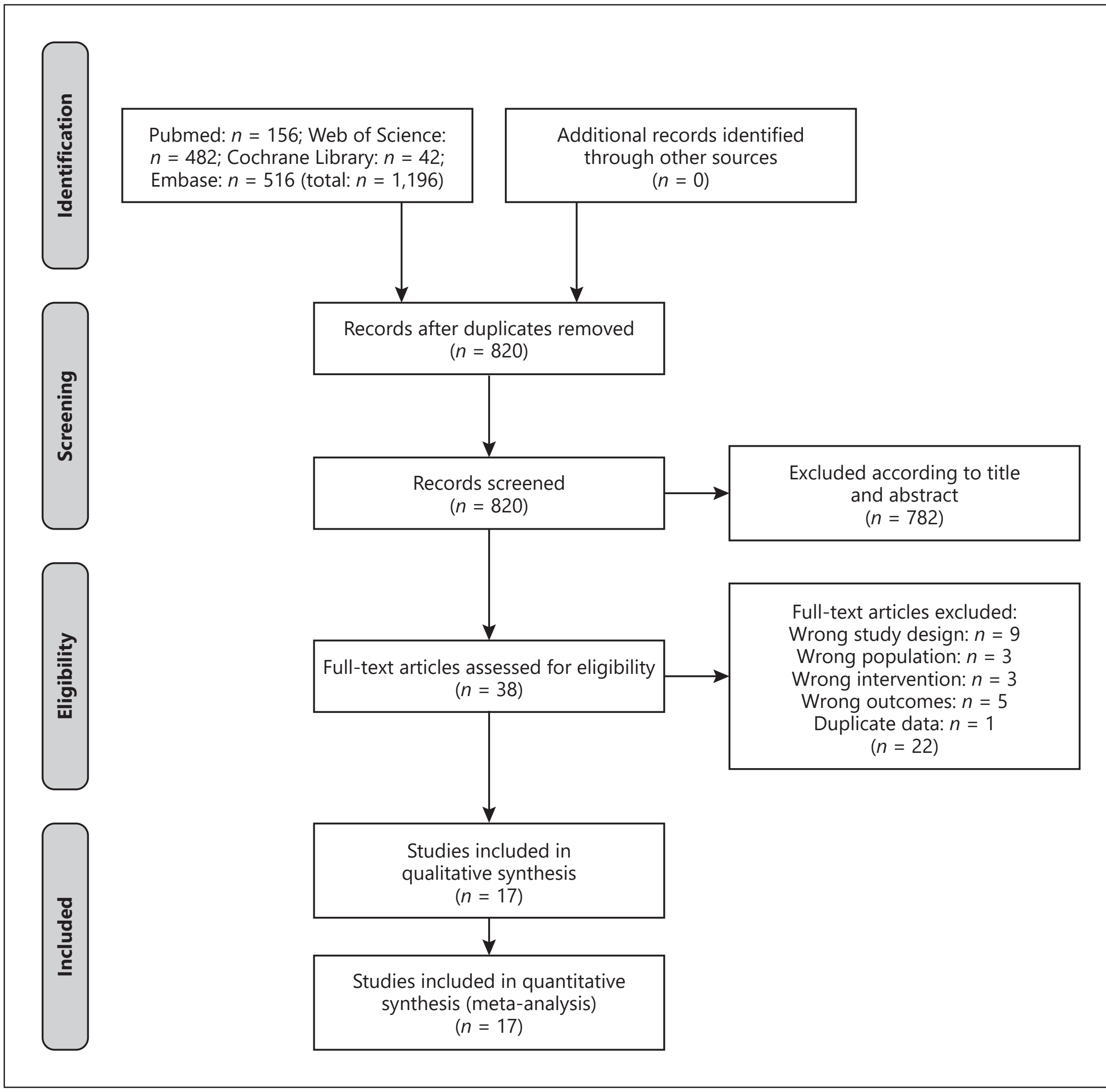


Fig. 1. Flowchart showing the selection of studies for the meta-analysis.

concealment, the blinding method, withdrawal, and loss of access [19]. NOS scores were primarily used to assess the representativeness, comparability, and follow-up integrity of exposed and non-exposed cohorts [20]. In this study, the Jadad score is considered to be greater than or equal to 4 points and the NOS score is considered to be greater than or equal to 7 points for high-quality literature.

Statistical Analysis

Cochrane Review Manager 5.3 (China) and Stata software were used for all statistical and meta-analyses, and $p < 0.05$ was considered statistically significant. The effect size of continuous variables was estimated by calculating the mean difference (MD) of the results and their 95% CI, and the combined effect was estimated. The effect size of binary variables was estimated by calculating the OR of the results and their 95% CI, and the combined effect was estimated. Heterogeneity was assessed using inconsistency (I^2) statistics. We believe that if I^2 is greater than 50% then the heterogeneity is considerable and the random-effects model should be adopted. When I^2 is less than 50%, the heterogeneity is within an acceptable range and the fixed-effects model should be adopted.

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed using Stata software to identify the source of heterogeneity. Heterogeneity and pooled effect values were recalculated after each included study was eliminated in turn. We determined the most likely source of heterogeneity by using the forest maps provided by Stata software that sequentially excluded each study. After finding the source of heterogeneity, we analyzed the experiment design, sample size, outcome evaluation criteria, and other aspects to explain the reasons for the emergence of heterogeneity and judged the reliability of statistical results.

Publication bias was quantified by the Egger method. When the p value obtained by the Egger method was > 0.05, there was no

Table 1. Literature information and quality evaluation results

Study	Study type	Surgical method		Sample size		Follow-up, months	Outcomes	Quality score	
		laser group	control group	laser group	TURBT			Jadad	NOS
Song et al. [34]	RC	holmium	TURBT	64	51	24	A, B, C, D, E, G, H, I	NA	8
Zhong et al. [33]	RC	2 μm	TURBT	30	42	24	A, D, E, F, G, H, I	NA	8
		holmium	TURBT	25	42	24	A, D, E, F, G, H, I		
Liu et al. [32]	RCT	2 μm	TURBT	64	56	36	A, B, C, D, E, F, G, H	5	NA
Tao et al. [31]	RC	KTP	TURBT	74	84	24	A, B, C, D, E, F, G, I	NA	8
Yang et al. [30]	RC	KTP	TURBT	28	32	20–64	A, B, C, D, G, I	NA	8
Chen et al. [29]	RCT	2 μm	TURBT	71	71	18	A, B, C, D, E, G	5	NA
Migliari et al. [26]	RC	Thulium	TURBT	58	61	13–25	B, C	NA	8
Xu et al. [25]	RCT	KTP	TURBT	99	94	24	A, B, C, D, E, G, I	5	NA
Zhang et al. [24]	RCT	thulium	TURBT	149	143	36	A, B, C, F	4	NA
Ma et al. [27]	RCT	holmium	TURBT	86	92	12	F	5	NA
Kramer et al. [28]	RC	holmium	TURBT	65	165	12	A, D, E, F, J	NA	7
Chen et al. [23]	RCT	LBO	TURBT	83	75	36	A, B, C, D, E, H	4	NA
D'Souza et al. [22]	RC	holmium	TURBT	23	27	36	A, B, C, D, E, H	NA	7
Cheng et al. [21]	RC	KTP	TURBT	34	30	12	A, B, D, E	NA	7
Li et al. [14]	RC	thulium	TURBT	136	120	48	A, B, C, D, E, J	NA	8
He et al. [16]	RC	holmium	TURBT	49	46	12–36	A, B, C, D, E, F, J	NA	8
Xu et al. [15]	RC	1.9-μm Vela	TURBT	26	44	24	A, B, C, D, E, G	NA	9

A, operation time; B, obturator nerve reflex; C, bladder perforation; D, catheterization time; E, hospitalization time; F, 12-month recurrence rate; G, 24-month recurrence rate; H, urethral stricture; I, bladder irrigation; J, detrusor muscle acquisition; RC, retrospective cohort; KTP, potassium-titanyl-phosphate; NA, not available.

significant publication bias. On the contrary, it indicated the existence of a publication bias. If a publication bias existed, we tested the effect of publication bias on the results by pruning and filling. If a publication bias was found to have a significant impact on the results, it is discussed in detail in the Discussion.

Results

Literature Retrieval Results and Basic Characteristics

We consulted a large amount of literature and conducted careful research and screening; the specific process is shown in Figure 1. The results showed a total of 1,196 relevant studies chiefly from electronic databases. After removing duplicates, 782 references were excluded based on the title and abstract because they were reviews or letters or irrelevant to the subject of this study. By reading the full text of 38 cations, 17 studies were eventually included [14–16, 21–34], comprising 2,439 participants. Of the 17 studies, 6 were RCT [23–25, 27, 29, 32] and the rest were retrospective cohort studies [14–16, 21, 22, 26, 28, 30, 31, 33, 34]. The included studies ranged from 2010 to 2018, with a median follow-up of 24 months (range: 12–64 months). In our meta-analysis, the main characteristics and data of each study are shown in Table 1.

Methodological Quality Assessment

We used the Jadad score [19] to evaluate the RCT and the NOS [20] to evaluate the retrospective cohort studies. Through detailed evaluation, we found that the Jadad scores of all RCT were greater than or equal to 4, and the NOS scores of all of the retrospective cohorts were greater than or equal to 7, suggesting that all of the included studies were of good quality. The scores for each study are shown in Table 1.

Meta-Analysis Results

Operation Time

Fifteen studies [14–16, 21–25, 28–34] reported the difference in operating time between transurethral laser surgery and TURBT therapy for NMIBC. The overall heterogeneity was considerable (I^2 = 82%), and meta-analysis results using the random-effects model (MD = –0.2; 95% CI –2.29 to 1.89; p = 0.85) showed no statistical significance (Fig. 2a).

Obturator Nerve Reflex

A total of 14 studies [14–16, 21–26, 29–32, 34], involving 1,847 patients, showed that the incidence of obturator nerve reflex during transurethral laser surgery was significantly lower than with TURBT through a fixed-effects model meta-analysis (OR = 0.04; 95% CI 0.02–0.09; p < 0.00001). I^2 = 0% meant that no significant heterogeneity was found (Fig. 2b).

Bladder Perforation

A total of 12 studies [14–16, 22–25, 29–32, 34] reported the rate of bladder perforation, and the fixed-effects model meta-analysis showed that the risk of bladder perforation in transurethral laser surgery was only 0.09 times that of TURBT (OR = 0.09; 95% CI 0.04–0.23; p < 0.00001). I^2 = 0 meant that no significant heterogeneity was found (Fig. 2c).

Detrusor Muscle Acquisition

A total of 3 studies [14, 16, 28] reported the rate of bladder perforation, and meta-analysis of the fixed-effects model showed that the detrusor muscle acquisition rate in transurethral laser surgery was 5.28 times higher than that of TURBT (OR = 5.28; 95% CI 2.42–11.49; p < 0.0001). I^2 = 0 meant that no significant heterogeneity was found (Fig. 2d).

Catheterization Time and Hospitalization Time

A total of 15 studies [14–16, 21–23, 25, 26, 28–34] reported the postoperative urinary catheter retention time, and 13 reported the postoperative hospitalization time [14–16, 21–23, 25, 28, 29, 31–34]. Meta-analysis of the random-effects model showed that the postoperative catheterization time (MD = –1.05; 95% CI –1.41 to –0.68; p < 0.00001) (Fig. 2e) and hospitalization time (MD = –0.96; 95% CI –1.59 to –0.33; p = 0.003) (Fig. 2f) after transurethral laser surgery were significantly shorter than with TURBT. I^2 in both cases was 97%, indicating significant heterogeneity.

Bladder Irrigation and Urethral Stricture

A meta-analysis of 5 studies [22, 29, 32–34] using fixed-effects models found no significant difference in postoperative urethral stricture rates between transurethral laser surgery and TURBT (OR = 0.7; 95% CI 0.24–2.06; p = 0.52) (Fig. 2g). Five studies [22, 29, 32–34] were meta-analyzed using fixed-effects models and found that the probability of needing bladder irrigation after transurethral laser surgery was significantly lower than with TURBT (OR = 0.21; 95% CI 0.13–0.35; p < 0.00001) (Fig. 2h). I^2 was 0 and 9%, respectively.

Postoperative Recurrence Rate

Recurrence rates at 12 months were reported in 7 articles [16, 24, 27, 28, 31–33] and recurrence rates at 24 months were reported in 8 articles [15, 25, 29–34]. A meta-analysis of fixed-effect models showed that the recurrence rates of transurethral laser surgery at 12 months (OR = 0.66; 95% CI 0.48–0.9; p = 0.008) (Fig. 2i) and 24 months (OR = 0.6; 95% CI 0.41–0.86; p = 0.005) (Fig. 2j) were significantly lower than with TURBT. I^2 = 0 meant that no significant heterogeneity was found.

Subgroup Analysis

Our study included 17 articles comprising 6 RCTS and 11 retrospective cohort studies. In order to investigate whether the study type would have a significant bias on our results, we conducted a subgroup analysis based on the study type, and the results showed that there was no significant difference in meta-analysis results between the RCT subgroup and the retrospective cohort subgroup. It is worth noting that the meta-analysis results of the 12-month recurrence rate were inversely correlated with the overall results in both subgroups, showing no statistical difference. This study mainly includes several kinds of laser, such as holmium laser, KTP, 2-micron laser, and thulium laser. In order to further clarify whether there are differences among different kinds of laser, we conducted subgroup analyses according to laser types. Subgroup analyses showed that holmium lasers appeared to have superior efficacy and safety compared to several other lasers in different outcome measures. Specific subgroup results are available in Table 2.

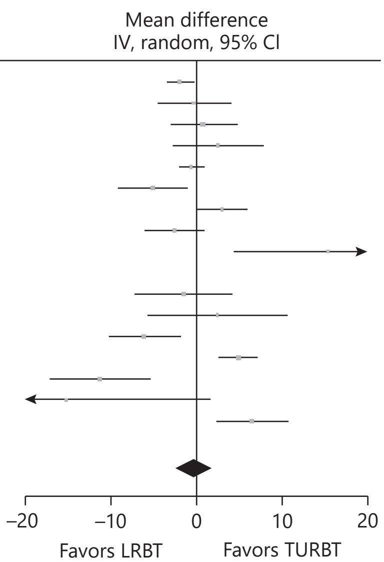
Fig. 2. Forest plot and meta-analysis of: operation time (**a**), obturator nerve reflex (**b**), bladder perforation (**c**), detrusor muscle acquisition (**d**), catheterization time (**e**), hospitalization time (**f**), bladder irrigation (**g**), urethral stricture (**h**) and 12- (**i**) and 24-month-recurrence rates (**j**) [14–16, 21–26, 28–34].

(For figure see next page.)

a

Study or subgroup	LRBT mean	LRBT SD	LRBT total	TURBT mean	TURBT SD	TURBT total	Weight, %	Mean difference IV, random, 95% CI	Year
Song, 2010	16.54	3.81	64	18.36	4.45	51	8.8	–1.82 (–3.36; –0.28)	2010
Zhong2, 2010	22.52	8.78	25	22.69	8.34	42	6.7	–0.17 (–4,44; 4.10)	2010
Zhong1, 2010	23.63	8.46	30	22.69	8.34	42	7.0	0.94 (–3.00; 4.88)	2010
Liu, 2013	48.2	15.8	64	45.6	13.5	56	5.9	2.60 (–2.64; 7.84)	2013
Tao, 2013	22.65	4.8	74	23.12	4.6	84	8.9	–0.47 (–1.94; 1.00)	2013
Yang, 2014	22	8.3	28	27	7.8	32	6.8	–5.00 (–9.09; –0.91)	2014
Zhang 2015	31.51	12.8	149	28.43	13.19	143	7.8	3.08 (0.10; 6.06)	2015
Kramer, 2015	27.19	11.96	65	29.65	12.46	165	7.4	–2.46 (–5.93; 1.01)	2015
Chen, 2015	56.5	37.4	71	41	29.4	71	2.6	15.50 [4.43; 26.57)	2015
Xu, 2015	32.17	25.1	116	33.62	18.51	113	5.5	–1.45 (–7.15; 4.25)	2015
D'Souza, 2016	58.2	15.8	23	55.6	13.5	27	3.8	2.60 (–5.62; 10.82)	2016
Chen, 2016	21.46	10.42	83	27.47	15.3	75	6.8	–6.01 (–10.13; –1.89)	2016
Cheng, 2017	35	3.75	34	30	5	30	8.4	5.00 (2.81; 7.19)	2017
Li, 2018	25.96	21.19	136	37.18	25.77	120	5.4	–11.22 (–17.05; –5.39)	2018
Xu, 2018	58.9	33.5	26	74	36.6	44	1.3	–15.10 (–31.92; 1.72)	2018
He, 2018	52.45	9.52	49	45.84	10.85	46	6.8	6.61 (2.49; 10.73)	2018
Total (95% CI)			**1,037**			**1,141**	**100.0**	**–0.20 (–2.29; 1.89)**	

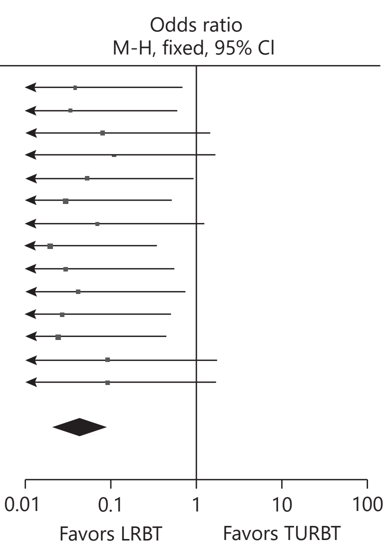
Heterogeneity: $\tau^2 = 12.24$; $\chi^2 = 82.26$, df = 15 ($p < 0.00001$); $I^2 = 82\%$
Test for overall effect: $Z = 0.19$ ($p = 0.85$)



b

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Song, 2010	0	64	8	51	7.0	0.04 (0.00; 071)	2010
Liu, 2013	0	64	10	56	8.3	0.03 (0.00; 060)	2013
Tao, 2013	0	74	6	84	4.6	0.08 (0.00; 1.46)	2013
Yang, 2014	0	28	4	32	3.1	0.11 (0.01; 2.16)	2014
Migliari, 2015	0	58	8	61	6.2	0.05 (0.00; 095)	2015
Xu, 2015	0	99	13	94	10.4	0.03 (0.00; 0.52)	2015
Zhang, 2015	0	149	6	143	5.0	0.07 (0.00; 1.27)	2015
Chen, 2015	0	71	18	71	13.8	0.02 (0.00; 034)	2015
D'Souza, 2016	0	23	11	27	7.8	0.03 (0.00; 0.56)	2016
Chen, 2016	0	83	9	75	7.5	0.04 (0.00; 073)	2016
Cheng, 2017	0	34	10	30	8.3	0.03 (0.00; 051)	2017
He, 2018	0	49	13	46	10.4	0.03 (0.00; 0.44)	2018
Li, 2018	0	136	4	120	3.6	0.09 (0.01; 1.78)	2018
Xu, 2018	0	26	7	44	4.2	0.09 (0.01; 1.72)	2018
Total (95% CI)		**958**		**934**	**100.0**	**0.04 (0.02; 0.09)**	
Total events	0		127				

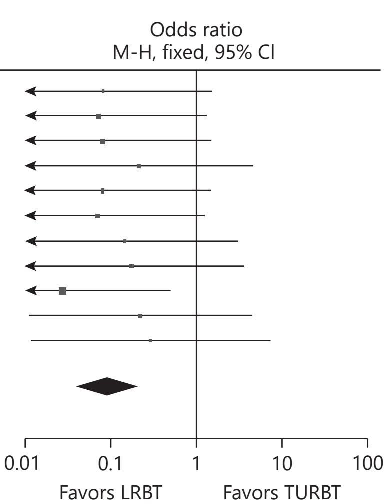
Heterogeneity: $\chi^2 = 1.90$, df = 13 ($p = 1.00$); $I^2 = 0\%$
Test for overall effect: $Z = 8.05$ ($p < 0.00001$)



c

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Song, 2010	0	64	4	51	9.2	0.08 (0.00; 1.56)	2010
Liu, 2013	0	64	5	56	10.8	0.07 (0.00; 1.34)	2013
Tao, 2013	0	74	6	84	11.2	0.08 (0.00; 1.46)	2013
Yang, 2014	0	28	2	32	4.3	0.21 (0.01; 4.65)	2014
Xu, 2015	0	99	5	94	10.4	0.08 (0.00; 1.50)	2015
Zhang, 2015	0	149	6	143	12.2	0.07 (0.00; 1.27)	2015
Chen, 2015	0	71	0	71		Not estimable	2015
D'Souza, 2016	0	23	3	27	5.9	0.15 (0.01; 3.04)	2016
Chen, 2016	0	83	2	75	4.8	0.18 (0.01; 3.73)	2016
He, 2018	0	49	12	46	23.6	0.03 (0.00; 0.49)	2018
Xu, 2018	0	26	3	44	4.8	0.22 (0.01; 4.51)	2018
Li, 2018	0	136	1	120	2.9	0.29 (0.01; 7.23)	2018
Total (95% CI)		**866**		**843**	**100.0**	**0.09 (0.04; 0.23)**	
Total events	0		49				

Heterogeneity: $\chi^2 = 2.12$, df = 10 ($p = 1.00$); $I^2 = 0\%$
Test for overall effect: $Z = 5.29$ ($p < 0.00001$)



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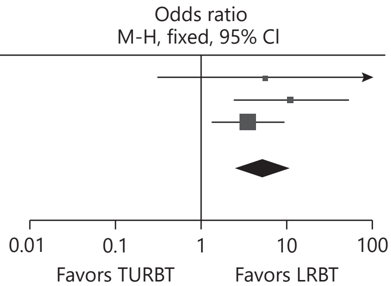
d

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Kramer, 2015	65	65	150	156	9.9	5.66 (0.31; 101.91)	2015
He, 2018	47	49	31	46	19.2	11.37 (2.43; 53.23)	2018
Li, 2018	130	136	103	120	70.9	3.58 (1.36; 9.40)	2018
Total (95% CI)		**250**		**322**	**100.0**	**5.28 (2.42; 11.49)**	
Total events	242		284				

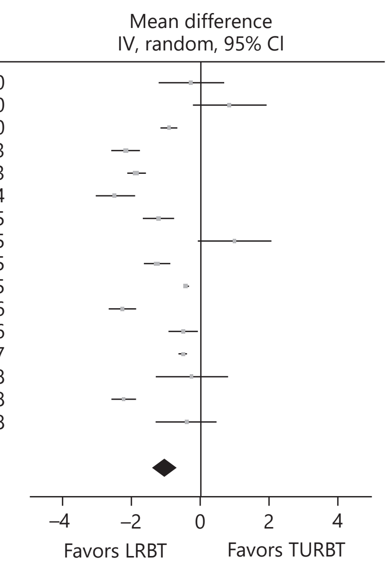
Heterogeneity: $\chi^2 = 1.58$, df = 2 ($p = 0.45$); $I^2 = 0\%$
Test for overall effect: $Z = 4.19$ ($p < 0.0001$)



e

Study or subgroup	LRBT mean	LRBT SD	LRBT total	TURBT mean	TURBT SD	TURBT total	Weight, %	Mean difference IV, random, 95% CI	Year
Zhong2, 2010	3.36	1.87	25	3.62	2.05	42	4.9	–0.26 (–1.22; 0.70)	2010
Zhong1, 2010	4.47	2.42	30	3.62	2.05	42	4.6	0.85 (–0.22; 1.92)	2010
Song, 2010	1.48	0.38	64	2.39	0.77	51	7.2	–0.91 (–1.14; –0.68)	2010
Tao, 2013	3.15	1.4	74	5.32	1.1	84	6.8	–2.17 (–2.57; –1.77)	2013
Liu, 2013	2.34	0.43	64	4.21	0.92	56	7.1	–1.87 (–2.13; –1.61)	2013
Yang, 2014	3.24	1.2	28	5.73	0.9	32	6.4	–2.49 (–3.03; –1.95)	2014
Xu, 2015	1.41	0.66	99	2.62	2.13	94	6.7	–1.21 (–1.66; –0.76)	2015
Chen, 2015	3.1	3.7	71	2.1	2.7	71	4.6	1.00 (–0.07; 2.07)	2015
Kramer, 2015	1.74	1.28	65	3.01	1.43	165	6.9	–1.27 (–1.65; –0.89)	2015
Migliari, 2015	1.17	0.08	58	1.58	0.2	61	7.4	–0.41 (–0.46; –0.36)	2015
D'Souza, 2016	2.24	0.43	23	4.51	0.92	27	6.8	–2.27 (–2.66; –1.88)	2016
Chen, 2016	1.98	1.07	83	2.49	1.55	75	6.7	–0.51 (–0.93; –0.09)	2016
Cheng, 2017	3	0.25	34	3.5	0.25	30	7.3	–0.50 (–0.62; –0.38)	2017
He, 2018	4.59	2.64	49	4.84	2.65	46	4.6	–0.25 (–1.31; 0.81)	2018
Li, 2018	2.03	1.61	136	4.27	1.17	120	7.0	–2.24 (–2.58; –1.90)	2018
Xu 2018	5.2	1.7	26	5.6	2	44	5.2	–0.40 (–1.28; 0.48)	2018
Total (95% CI)			**929**			**1,040**	**100.0**	**–1.05 (–1.41; –0.68)**	

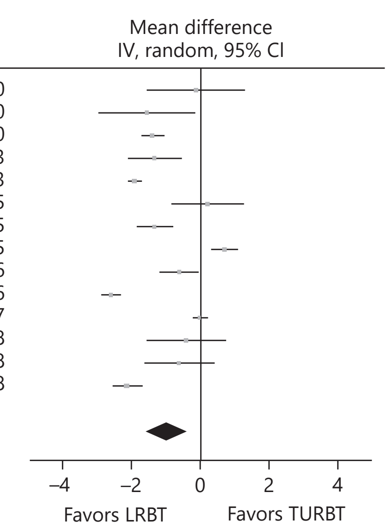
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 448.12$, df = 15 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 5.59$ ($p < 0.00001$)



f

Study or subgroup	LRBT mean	LRBT SD	LRBT total	TURBT mean	TURBT SD	TURBT total	Weight, %	Mean difference IV, random, 95% CI	Year
Zhong1, 2010	6.43	2.43	30	6.55	3.73	42	5.7	–0.12 (–1.54; 1.30)	2010
Zhong2, 2010	5	2.12	25	6.55	3.73	42	5.7	–1.55 (–2.95; –0.15)	2010
Song, 2010	2.88	0.63	64	4.27	1.01	51	7.8	–1.39 (–1.71; –1.07)	2010
Tao, 2013	5.25	2.1	74	6.56	2.9	84	7.1	–1.31 (–2.09; –0.53)	2013
Liu, 2013	3.51	0.34	64	5.42	0.65	56	7.9	–1.91 (–2.10; –1.72)	2013
Chen, 2015	6	3.6	71	5.8	2.7	71	6.5	0.20 (–0.85; 1.25)	2015
Yang, 2014	2.53	0.78	116	3.85	2.59	113	7.6	–1.32 (–1.82; –0.82)	2015
Xu, 2015	2.73	1.27	65	2.03	1.42	165	7.7	0.70 (0.32; 1.08)	2015
Kramer, 2015	3.41	2.51	83	4.03	0.94	75	7.5	–0.62 (–1.20; –0.04)	2016
D'Souza, 2016	3.21	0.34	23	5.82	0.65	27	7.8	–2.61 (–2.89; –2.33)	2016
Cheng, 2017	5	0.5	34	5	0.25	30	7.9	0.00 (–0.19; 0.19)	2017
He, 2018	5.22	2.76	49	5.63	2.91	46	6.3	–0.41 (–1.55; 0.73)	2018
Xu 2018	5.8	1.3	26	6.4	2.9	44	6.7	–0.60 (–1.59; 0.39)	2018
Li, 2018	3.11	1.05	136	5.24	2.06	120	7.7	–2.13 (–2.54; –1.72)	2018
Total (95% CI)			**860**			**966**	**100.0**	**–0.96 (–1.59; –0.33)**	

Heterogeneity: $\tau^2 = 1.30$; $\chi^2 = 437.04$, df = 13 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 2.99$ ($p = 0.003$)

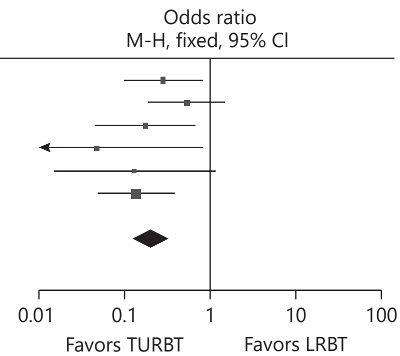


2

g

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Zhong2, 2010	12	25	32	42	16.5	0.29 (0.10; 0.83)	2010
Zhong1, 2010	19	30	32	42	13.0	0.54 (0.19; 1.51)	2010
Song, 2010	3	64	11	51	15.5	0.18 (0.05; 0.68)	2010
Tao, 2013	0	74	10	84	13.0	0.05 (0.00; 0.83)	2013
Yang, 2014	1	28	7	32	8.4	0.13 (0.02; 1.15)	2014
Xu, 2015	5	99	26	94	33.6	0.14 (0.05; 0.38)	2015
Total (95% CI)		**320**		**345**	**100.0**	**0.21 (0.13; 0.35)**	
Total events	40		118				

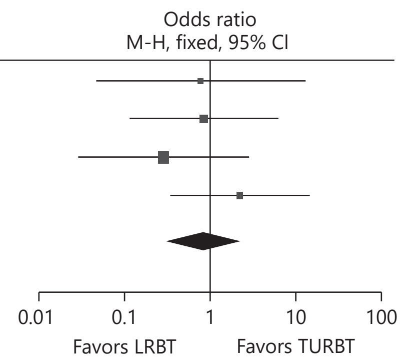
Heterogeneity: $\chi^2 = 5.51$, df = 5 ($p = 0.36$); $I^2 = 9\%$
Test for overall effect: $Z = 6.12$ ($p < 0.00001$)



h

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Zhong1, 2010	0	30	0	42		Not estimable	2010
Song, 2010	1	64	1	51	14.5	0.79 (0.05; 13.01)	2010
Zhong2, 2010	0	25	0	42		Not estimable	2010
Liu, 2013	2	64	2	56	27.3	0.87 (0.12; 6.39)	2013
Chen, 2016	1	83	3	75	41.2	0.29 (0.03; 2.88)	2016
D'Souza, 2016	2	23	3	75	17.0	2.29 (0.36; 14.60)	2016
Total (95% CI)		**289**		**341**	**100.0**	**0.86 (0.30; 2.47)**	
Total events	6		9				

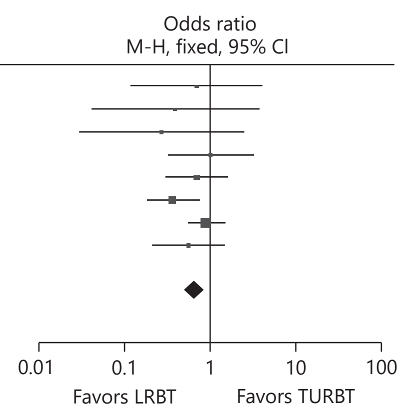
Heterogeneity: $\chi^2 = 1.92$, df = 3 ($p = 0.59$); $I^2 = 0\%$
Test for overall effect: $Z = 0.28$ ($p = 0.78$)



i

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Zhong1, 2010	2	27	4	39	3.0	0.70 (0.12; 4.12)	2010
Zhong2, 2010	1	23	4	39	2.8	0.40 (0.04; 3.79)	2010
Tao, 2013	1	74	4	84	3.7	0.27 (0.03; 2.51)	2013
Liu, 2013	7	64	6	56	5.7	1.02 (0.32; 3.25)	2013
Kramer, 2015	10	54	23	94	13.7	0.70 (0.31; 1.61)	2015
Ma, 2015	16	86	35	92	27.5	0.37 (0.19; 0.74)	2015
Zhang, 2015	45	149	46	143	32.7	0.91 (0.56; 1.50)	2015
He, 2018	9	49	13	46	10.9	0.57 (0.22; 1 50)	2018
Total (95% CI)		**526**		**593**	**100.0**	**0.66 (0.48; 0.90)**	
Total events	91		135				

Heterogeneity: $\chi^2 = 5.78$, df = 7 ($p = 0.57$); $I^2 = 0\%$
Test for overall effect: $Z = 2.64$ ($p = 0.008$)



j

Study or subgroup	LRBT events	LRBT total	TURBT events	TURBT total	Weight, %	Odds ratio M-H, fixed, 95% CI	Year
Zhong1, 2010	2	24	3	32	3.1	0.88 (0.14; 5.72)	2010
Zhong2, 2010	1	20	3	32	2.9	0.51 (0.05; 5.26)	2010
Song, 2010	20	63	23	51	22.7	0.57 (0.26; 1.22)	2010
Liu, 2013	12	64	13	56	14.7	0.76 (0.32; 1.84)	2013
Tao, 2013	1	74	6	34	7.2	0.18 (0.02; 1.52)	2013
Yang, 2014	1	28	3	32	3.5	0.36 (0.04; 3.65)	2014
Chen, 2015	4	71	7	71	8.6	0.55 (0.15; 1.95)	2015
Xu, 2015	21	99	26	94	27.4	0.70 (0.36; 1.36)	2015
Xu, 2018	4	26	12	44	9.9	0.48 (0.14; 1.70)	2018
Total (95% CI)		**469**		**496**	**100.0**	**0.60 (0.41; 0.86)**	
Total events	66		96				

Heterogeneity: $\chi^2 = 2.28$, df = 8 ($p = 0.97$); $I^2 = 0\%$
Test for overall effect: $Z = 2.79$ ($p = 0.005$)

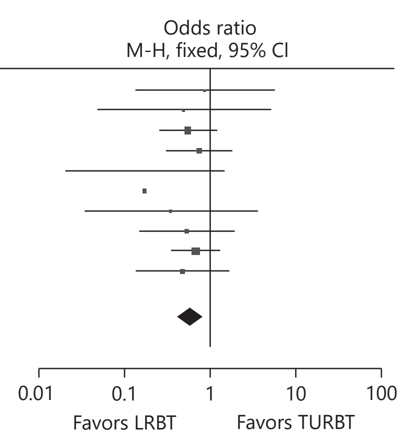


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Table 2. Subgroup analysis of study type and laser type

	Obturator nerve reflex	Bladder perforation	Catheterization time	Bladder irrigation	12-month recurrence rate	24-month recurrence rate
Study type						
RCT	0.05 (0.02 to 0.13)	0.09 (0.02 to 0.38)	–1.35 (–1.55 to –1.15)	0.14 (0.0 to 0.38)	0.70 (0.48 to 1.01)	0.69 (0.43 to 1.13)
RC	0.03 (0.01 to 0.12)	0.10 (0.03 to 0.29)	–0.55 (–0.60 to –0.51)	0.25 (0.14 to 0.44)	0.59 (0.34 to 1.02)	0.57 (0.37 to 0.87)
Laser type						
Holmium	0.03 (0.0 to 0.16)	0.06 (0.01 to 0.31)	–1.21 (–1.38 to –1.04)	0.24 (0.10 to 0.54)	0.50 (0.31 to 0.78)	0.56 (0.27 to 1.16)
KTP	0.04 (0.01 to 0.16)	0.10 (0.02 to 0.56)	–0.76 (–0.87 to –0.65)	0.12 (0.05 to 0.28)	0.27 (0.03 to 2.51)	0.57 (0.32 to 1.04)
2 μm	0.03 (0.00 to 0.19)	0.07 (0.00 to 1.34)	–0.05 (–2.270 to 2.16)	0.54 (0.19 to 1.51)	0.91 (0.35 to 2.38)	0.71 (0.36 to 1.39)
Thulium	0.07 (0.01 to 0.37)	0.11 (0.01 to 0.92)	–0.45 (–0.510 to –0.40)	–	0.91 (0.56 to 1.50)	–

RC, retrospective cohort. Values are presented as MD (95% CI).

Sensitivity Analysis

There was significant heterogeneity in the analysis of operation time, catheterization time, and hospitalization time (82, 97, and 97%, respectively). We used Stata software for sensitivity analysis and found that the results obtained after removing each study in turn were between the 2 bounds (Fig. 3). At the same time, after removing each study in turn, the I^2 of the corresponding outcome indicators did not change significantly. In the operation time group, the meta-analysis results changed from MD = –0.2 (95% CI –2.29 to 1.89; $p = 0.85$) to MD = –0.11 (95% CI –0.87 to 0.66; $p = 0.79$) after we switched the random-effects model to the fixed-effects model. In the outcome index group of catheterization time, the results of the meta-analysis changed from MD = –1.05 (95% CI –1.41 to –0.68; $p < 0.00001$) to MD = –0.6 (95% CI –0.64 to –0.55; $p < 0.00001$). In the outcome index group of hospitalization time, the results of the meta-analysis changed from MD = –0.96 (95% CI –1.59 to –0.33; $p = 0.003$) to MD = –1.15 (95% CI –1.25 to –1.05; $p < 0.00001$). The meta-analysis results of the 3 outcome indicator groups did not change after switching to the fixed-effects model. At the same time, combined with the forest map of sensitivity analysis obtained by Stata software, we found that although the 3 outcome indicator groups all had obvious heterogeneity they had no significant impact on the results, and the results we obtained are stable and credible.

Publication Bias

Publication bias was quantitatively analyzed by the Egger method. Publication bias was found in the 5 outcome indicator groups including catheterization time, obturator nerve reflex, bladder perforation, bladder perfusion, and detrusor muscle acquisition rate ($p < 0.05$) (Fig. 4). Further verification by the trim-and-fill method showed that, although publication bias may exist, our results were robust [35].

Discussion

TURBT, as the standard surgical treatment for NMIBC, has the advantages of less trauma, a faster postoperative recovery, and maintenance of the quality of life of the patient by retention of the bladder [36]. However, the commonly used transurethral resection has complications such as obturator nerve reflex and bladder perforation [5]. At the same time, as a process of "incise and scatter," the spread of bladder tumor cells and incomplete tumor resection also limit its application [37]. In addition, TURBT is not suitable for patients with anticoagulants or patients with artificial pacemakers because the anticoagulant increases the risk of bleeding and the flow of electricity in the tissues during TURBT has the potential to interfere with the pacemaker [38, 39]. Laser application is a new, safe, and efficient technology, especially in urology. Several studies have reported the advantages of transurethral laser surgery in the treatment of NMIBC, including a low incidence of intraoperative obturator nerve reflex and bladder perforation, a rapid postoperative recovery, complete pathological specimens, and a low recurrence

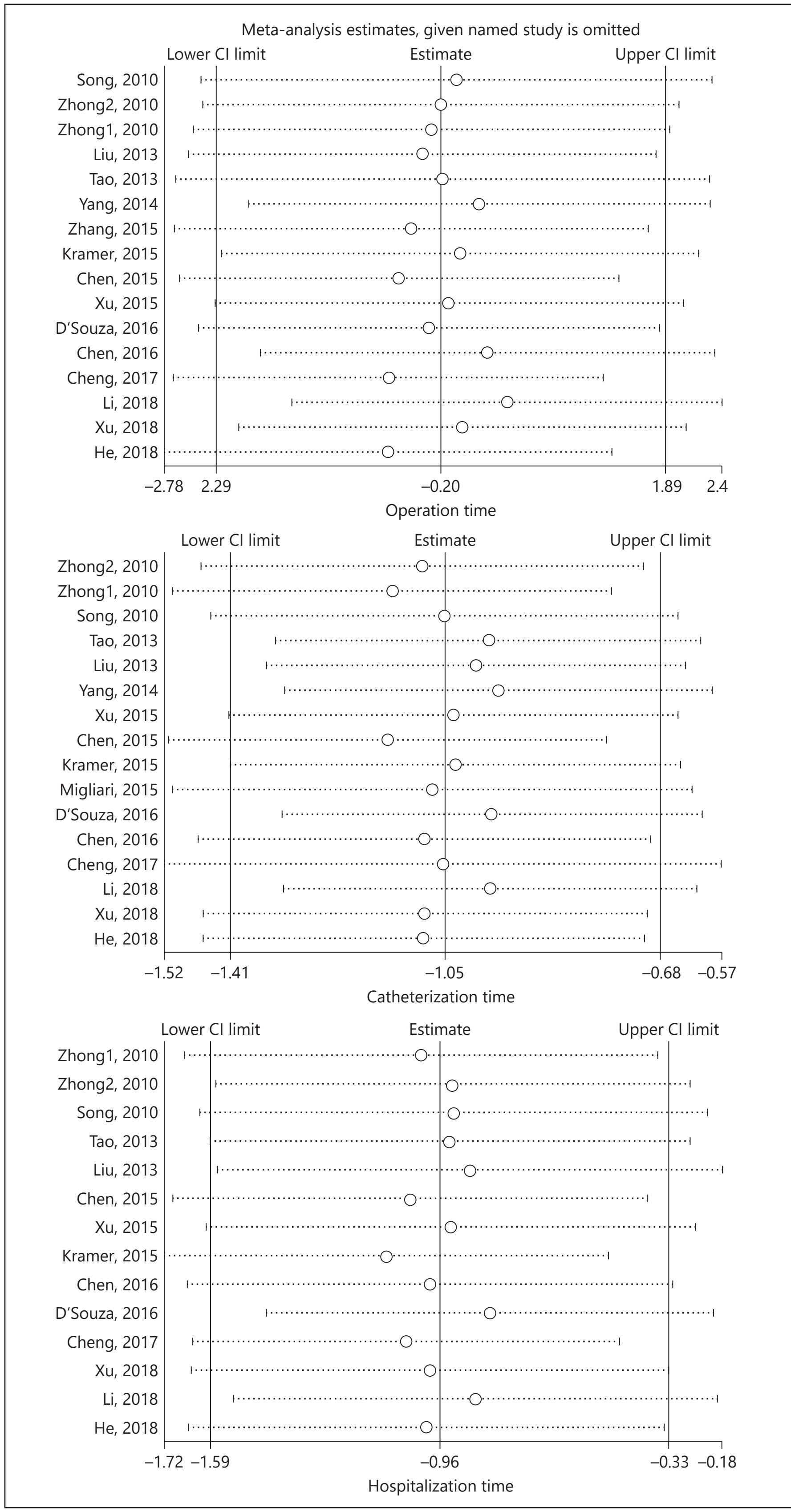

Fig. 3. Forest plots for sensitivity analysis [14–16, 21–26, 28–34].

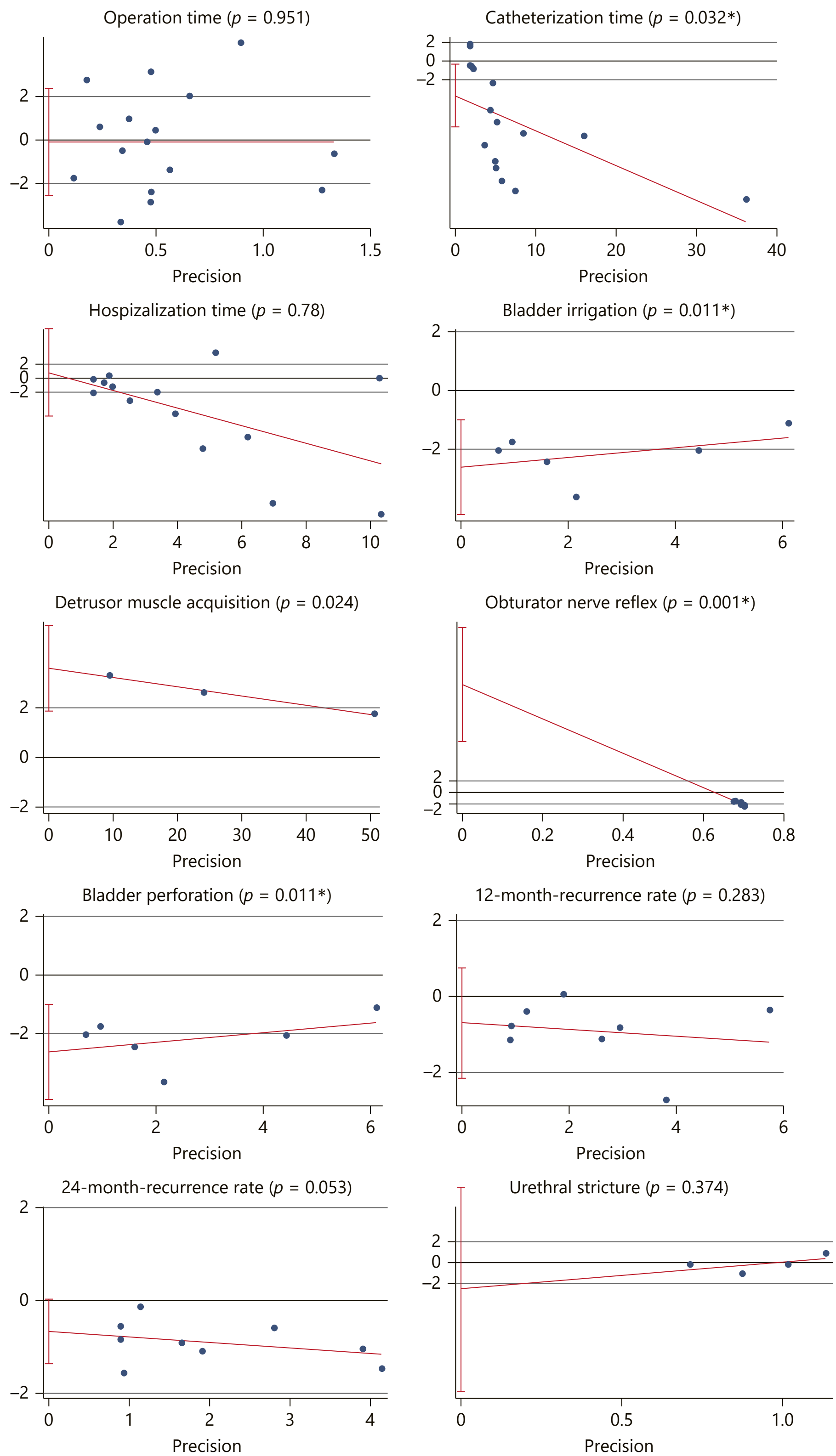

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Fig. 4. Publication bias (Egger graphs).

rate [14–16, 21–23]. Studies have also demonstrated that it can be selectively absorbed by hemoglobin and does not use an electric current, so it has a higher safety for patients using anticoagulants and patients with artificial pacemakers, which greatly expands the applicable patient population of transurethral laser surgery [22, 28]. Judging from the above research results, transurethral laser surgery compared to TURBT has great advantages, but the sample size of these studies is small and proved insufficient; there is still a lack of large-sample RCT, so we conducted the meta-analysis included 2,439 participants in order to draw strong conclusions and provide a strong basis for clinical decision making.

As far as we know, our meta-analysis is the latest and most comprehensive. Ours is the first meta-analysis to analyze the recurrence rate at 12 months and the first to conduct subgroup analysis based on research type and laser type. The results of our meta-analysis showed no statistically significant difference in operative time or postoperative incidence of urethral stricture for transurethral laser surgery showed compared to transurethral resection of bladder tumors. However, compared with TURBT, transurethral laser surgery has a lower incidence of intraoperative obturator nerve reflex and bladder perforation, a higher rate of detrusor muscle acquisition, shorter catheterization and hospitalization times, a lower probability of postoperative bladder irrigation, and lower recurrence rates at 12 and 24 months.

The reason for this result may be that during the treatment of NMIBC laser surgery and TURBT used completely different energy forms and completely different tumor removal methods. However, the basic operation techniques of transurethral surgery are similar, including endoscopic insertion through an endoscopic sheath and then insertion of the optical fiber or electric cutting ring and operation by means of swing, rotation, advance and retreat, etc. Therefore, there is no statistical difference in terms of the operation time and incidence of urethral stricture. In transurethral laser surgery, tissue is cut by laser energy. Since the surgical instrument itself is in a noncontact state with the bladder tissue and no electric current passes through the bladder tissue during the operation, no stimulation of the bladder wall nerve will be formed, thus basically eliminating the risk of obturator nerve reflex [40]. Due to the absence of current interference, transurethral laser surgery is also relatively safe for patients with pacemakers [28, 41]. The energy of a laser at a specific wavelength is not absorbed by water during propagation but can be selectively absorbed by hemoglobin to achieve the effect of coagulation and blockage of blood vessels, thus having a good hemostatic effect [30, 42]. This property reduces the probability of bladder irrigation after surgery and the duration of catheterization, and it provides a safe surgical opportunity for patients undergoing long-term anticoagulant therapy [43]. Because there is less bleeding during transurethral laser surgery, surgeons can obtain a clearer surgical field and more accurate positioning. Laser has the characteristics of high efficient tissue vaporization and good tissue solidification, and the penetration of the heat inside the tissue is shallow, so the adjacent tissue is less damaged [28, 44]. Combined with the low incidence of obturator nerve reflex, the incidence of bladder perforation was greatly reduced. To sum up, laser surgery has a lower incidence of intraoperative and postoperative complications, and some special patients do not need a longer time for preoperative preparation, so transurethral laser surgery has a shorter hospitalization time.

Due to the precise tissue cutting capability of the laser and the superior intraoperative safety, en bloc resection of NMIBC is possible. Complete resection of the tumor, lamina propria, and detrusor can reduce the residual tumor and the dissemination of tumor cells on the one hand and provide high-quality pathological specimens for further pathological diagnosis and staging on the other hand [45]. In addition, combined with the good vaporization and coagulation effect of laser, capillaries and lymphatic vessels are effectively closed, and the possibility of tumor cell dissemination is reduced [41, 45]. Accurate pathological staging based on high-quality specimens can also better guide the selection of further treatment plans. Based on the above characteristics, the tumor recurrence rate of the transurethral laser surgery group at 12 and 24 months was lower than that of the TURBT group.

According to the results of the subgroup analysis, we basically excluded the bias caused by research type. Statistical results of 12-month recurrence rates in both subgroups revealed no statistical significance, which may be because the sample size was too small to obtain accurate results. We need more relevant studies to further clarify the difference between transurethral laser surgery and TURBT in the future. When we did a subgroup analysis by laser type, holmium laser seemed to have better efficacy and safety. This may be related to the earliest use, widest application, and most mature technology of holmium laser in urology. Due to the limited amount of literature and the sample size, the results need to be further verified by head-to-head clinical control studies.

In our sensitivity analysis, we found no significant source of heterogeneity, but we found that our results were robust despite the presence of heterogeneity. As the outcome indicators of heterogeneity are all related to the statistics of time, we consider that the differences in the indicators of perioperative time may have been caused by the different surgical concepts and perioperative management concepts of different hospitals.

Limitations

It is undeniable that this study also has several limitations. First, despite the statistics on recurrence rates at 12 and 24 months, the literature volume is still small and there is a lack of long-term data. Second, due to the small amount of literature, no more-detailed subgroup analysis was performed based on laser type and TURBT type. Third, heterogeneity and publication bias may exist.

Conclusion

Transurethral laser surgery for NMIBC, as compared with TURBT, is associated with a lower incidence of intraoperative complications, a lower postoperative recurrence rate, and a faster postoperative recovery.

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Disclosure Statement

The authors have no conflict of interests to declare.

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Author Contributions

Jiangnan Xu: study design, data collection, statistical analysis, and writing and submission of this paper. Chao Wang: study design, data collection, statistical analysis, revision of this paper. Jun Ouyang: study design, writing and overall planning of this paper. JiaLe Sun: data collection and partial statistical analysis. Can Hu: data collection.

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