Systematic Review and Meta-Analysis

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Comparison of the efficacy and feasibility of en bloc transurethral resection of bladder tumor versus conventional transurethral resection of bladder tumor

A meta-analysis

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Abstract

Background: The aim of this meta-analysis was to compare the feasibility of en bloc transurethral resection of bladder tumor (ETURBT) versus conventional transurethral resection of bladder tumor (CTURBT).

Methods: Relevant trials were identified in a literature search of MEDLINE, EMBASE, Cochrane Library, Web of Science, and Google Scholar using appropriate search terms. All comparative studies reporting participant demographics, tumor characteristics, study characteristics, and outcome data were included.

Results: Seven trials with 886 participants were included, 438 underwent ETURBT and 448 underwent CTURBT. There was no significant difference in operation time between 2 groups ($P=0.38$). The hospitalization time (HT) and catheterization time (CT) were shorter in ETURBT group (mean difference[MD] −1.22, 95% confidence interval [CI] −1.63 to −0.80, $P<0.01$; MD −0.61, 95% CI −1.11 to −0.11, $P<0.01$). There was significant difference in 24-month recurrence rate (24-month RR) (odds ratio [OR] 0.66, 95% CI 0.47–0.92, $P=0.02$). The rate of complication with respect to bladder perforation ($P=0.004$), bladder irritation ($P<0.01$), and obturator nerve reflex ($P<0.01$) was lower in ETURBT. The postoperative adjuvant intravesical chemotherapy was evaluated by subgroup analysis, and 24-month RR in CTURBT is higher than that in ETURBT in mitomycin intravesical irrigation group ($P=0.02$).

Conclusion: The first meta-analysis indicates that ETURBT might prove to be preferable alternative to CTURBT management of nonmuscle invasive bladder carcinoma. ETURBT is associated with shorter HT and CT, less complication rate, and lower recurrence-free rate. Moreover, it can provide high-qualified specimen for the pathologic diagnosis. Well designed randomized controlled trials are needed to make results comparable.

Abbreviations: 24-month RR = 24-month recurrence rate, CI = confidence interval, CT = catheterization time, CTURBT = conventional transurethral resection of bladder tumor, EAU = European association of urology, ETURBT = en bloc transurethral resection of bladder tumor, HRs = hazard ratios, HT = hospitalization time, MD = mean difference, NMIBC = nonmuscle invasive bladder carcinoma, OR = odds ratio, OT = operation time, RFS = recurrence-free survival, SD = standard deviation, TURBT = transurethral resection of bladder tumor.

Keywords: bladder tumor, CTURBT, en bloc, ETURBT, transurethral

1. Introduction

Bladder tumor is the second most common urological malignancy and has been a growing healthcare problem all over the world.[1–4] To date, radical surgery was the most effective treatment.[5,6] For nonmuscle invasive bladder carcinoma (NMIBC), transurethral resection of bladder tumor (TURBT) remains the standard treatment.[7] Unfortunately, bladder tumor is bound up with high recurrence rates (50%–70%) after transurethral resection management, and tumor cell implantation is deemed to be a major cause of early recurrence.[8,9] Thus, it is reasonable to modify TURBT to provide en bloc transurethral resection of bladder tumor (ETURBT) of the specimen, based on the established oncological principle of dissecting through normal tissue.[10] Several studies have examined the efficacy and feasibility of en bloc TURBT.[11–16] In this study, a meta-analysis was performed to evaluate the efficacy and feasibility of ETURBT for the participants with NMIBC compared with conventional TURBT.

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2. Materials and methods

2.1. Ethics statement

Ethical approval was not required for this meta-analysis. It is a meta-analysis which has not affected participants directly.

2.2. Study selection

We searched MEDLINE, EMBASE, Cochrane Library, Web of Science, and Google scholar databases for articles published before September 12, 2016. A combination of search terms was used including "en bloc resection", "transurethral resection", "bladder tumor", "bladder cancer", "TURBT", and "cystectomy". The search was conducted with a language restricted to English publication.

2.3. Selection criteria

The inclusion criteria were as follows: original articles in English publication; trials reporting individual demographic, survival information, and clinical follow-up data; and trials comparing the efficacy and feasibility of ETURBT versus conventional transurethral resection of bladder tumor (CTURBT) in NMIBC. Single-arm trials, case reports, and systematic reviews were excluded.

2.4. Data extraction

Two investigators (Y-PW and S-HC) extracted data, respectively, employing a predefined data extraction form. Subsequent full-text record screening was fulfilled independently by 2 investigators (Y-PW and S-HC). Disagreements were resolved by a third reviewer (NX). All of the included trials in our meta-analysis contain data as follows: first author's name, published year, surgical method, number of patients, median age, operation time (OT), hospitalization time (HT), catheterization time (CT), 24-month recurrence rate (24-month RR), recurrence-free survival (RFS), and complications. We made several attempts to contact the corresponding authors to obtain the necessary data to meet inclusion criteria, when their studies did not meet inclusion requirements. At least 3 follow-up attempts were made for queries sent; unfortunately, these attempts were unsuccessful.

2.5. Statistical analysis

Statistical analysis was conducted utilizing RevMan5.3 (Cochrane Collaboration, Oxford, UK). Chi-square and I^2 tests were employed to test the heterogeneity of different trials[17,18]; no heterogeneity existed when $P>0.1$ and $I^2<50\%$, a fixed-effects model was applied to pool the trial results. Significant heterogeneity was identified if $P<0.1$ and $I^2>50\%$, and a random-effects model was employed.[19] OT, HT, and CT were determined applying continuous variables. Complications and 24-month RR were determined applying dichotomous variables. Subgroup analysis of postoperative adjuvant intravesical chemotherapy was also determined applying dichotomous variables. RFS was calculated using effect variables. Hazard ratios (HRs) with 95% confidence interval (CI) were extracted from the survival curves when HRs were unavailable for RFS.[20] Sensitivity analysis and publication bias analysis were conducted utilizing Stata 12.0 (Stata-Corp, College Station, TX). Begg funnel plot and Egger test were used to identify whether publication bias existed.

3. Results

3.1. Workflow of literature research

There were 304 potential relevant studies in the primary literature search, and 22 duplicate studies existed. After removing the duplicate studies, 258 studies were further excluded by reading the title and abstract. Then, a total of 17 additional studies were removed by 2 authors (Y-PW and S-HC) independently reading the full text. Therefore, 7 studies were included in this meta-analysis.[11–16] We described study procedure's details in Fig. 1. Two authors (Y-PW and S-HC) independently completed this work, and any disagreements were dealt with by discussion.

3.2. Study characteristics

These included studies recruited 886 participants with various stages of bladder cancer comprising 438 cases that underwent ETURBT and 448 with CTURBT. The demographics of enrolled individuals and tumor characteristics are presented in Tables 1 and 2, respectively. All of the cases applied postoperative installation therapy, mitomycin was used in 3 trials,[11,15,16] and epirubicin was used in 4 trials.[12–14]

3.3. Operation time, hospitalization time, and catheterization time

OT was available for 6 trials[11–14,16] (Fig. 2A). The pooled weight mean difference (MD) was 1.92 (95% CI $=-2.33$ to 6.18; $I^2=79\%$; $P=0.38$), indicating that there was no significant difference between ETURBT and CTURBT. HT and CT was available for all 7 trials[11–16] (Fig. 2B and C). The pooled weight MD was -1.22 (95% CI $=-1.63$ to -0.80; $I^2=82\%$; $P<0.01$) and MD was -0.61 (95% CI $=-1.11$ to -0.11; $I^2=92\%$; $P=0.02$), indicating that ETURBT yielded a shorter HT and CT over CTURBT. However, there was a significant heterogeneity existing ($I^2=82\%$ and 92%). Thus, a random model was applied, and further discussion was made to explain the heterogeneity.

3.4. 24-month recurrence rate and recurrence-free survival

Analysis showed that there was a significant difference in 24-month RR reported by 6 trials.[11,13–16] The pooled odds ratio (OR) was 0.66 (95% CI $=0.47$–0.92; $I^2=0$; $P=0.02$) (Fig. 2D). Three trials[11,12,16] reported RFS, and there was no significant difference between two arms, the pooled OR was 0.81 (95% CI $=$ 0.53–1.25; $I^2=0$; $P=0.34$) (Fig. 2E).

3.5. Complications

Four trials[13–15] reported obturator nerve reflex, and 4 trials[11,13–15] reported bladder perforation, respectively. The pooled OR was 0.04 (95% CI $=0.01$–0.15; $I^2=0$; $P<0.01$) and 0.14 (95% CI $=0.04$–0.54; $I^2=0$; $P=0.004$) (Fig. 3A and B), respectively, which indicated that ETURBT may cause less bladder perforation than CTURBT. Four trials[13–15] reported bladder irritation and 3 trials[11,13,15] reported urethral stricture, respectively. The pooled OR was 0.22 (95% CI $=0.11$–0.43; $I^2=$ 55%; $P<0.01$) and 0.57 (95% CI $=0.16$–2.06; $I^2=0$; $P=0.39$) (Fig. 3C and D), respectively, which indicated that ETURBT may cause less obturator nerve reflex and bladder irritation than CTURBT.

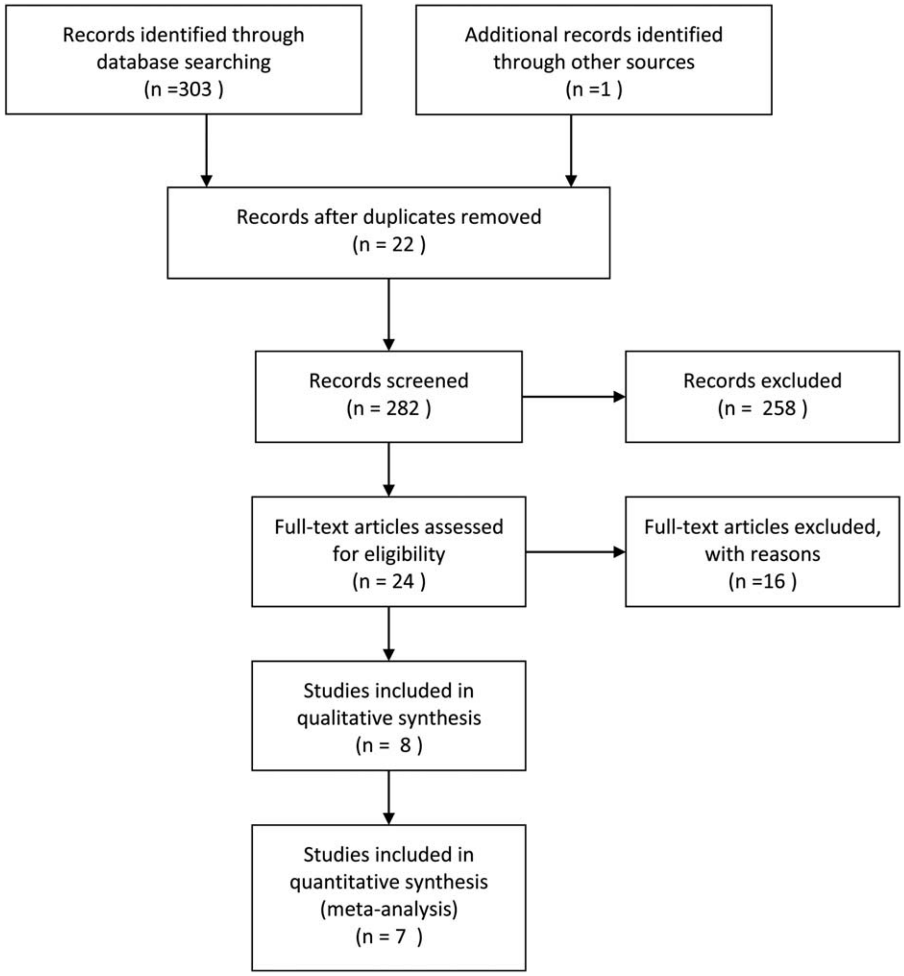

Figure 1. Flow diagram for selection of the included trials reviewed.

3.6. Sensitivity analysis and publication bias

A sensitivity analysis was performed by deleting a study at a time to assess the influence of an individual study on synthetic statistics. In terms of HT, when Liu trial[13] was removed, I^2 altered from 82% to 68%. In addition, when Xu trial[12] was removed, I^2 altered from 82% to 77%. When both trials[12,13] were removed, the overall results altered obviously, I^2 altered from 82% to 43%, which indicated that those 2 studies should be responsible for the heterogeneity of our eligible statistics. The reason could be explained as follows: the study type of Xu trial[12] was a randomized controlled trial, it is different from other eligible studies. Moreover, when Chen trail[11] was removed with respect to OT, I^2 altered from79% to 60%, this heterogeneity could be explained by the laser type. Chen trail performed ETURBT using green-light laser, and other trails included performed ETURBT using holmium laser or 2-μm continuous-

Table 1

Characteristics of trials included in the meta-analysis.

Study ID	Study type	Surgical method	N (T/C)	Male, % (T/C)	Age, y (T/C)	Follow-up, mo (T/C)	Outcomes OT	HT	CT	RFS	RR	RC
Zhu 2008	Prospective	Ho:YAG	101/111	78.2/82.9	N	34/34	Y	Y	Y	Y	Y	Y
Song 2010	Prospective	Ho:YAG	64/51	81.3/78.4	72.5/74.5	24/24	N	Y	Y	N	Y	Y
Zhong[1] 2010	Retrospective	Ho:YAG	25/42	N	65.76/66.26	24/24	Y	Y	Y	N	Y	N
Zhong[2] 2010	Retrospective	Tm:YAG	30/42	N	68.3/66.26	24/24	Y	Y	Y	N	Y	N
Liu 2013	Prospective	Tm:YAG	64/56	71.9/71.4	67.1/66.3	36/36	Y	Y	Y	N	Y	Y
Chen 2015	RCT	Tm:YAG	71/71	76.1/71.8	63/62	18/18	Y	Y	Y	Y	N	N
Chen 2016	Prospective	LBO laser	83/75	72.3/68.0	63.43/65.31	36/36	Y	Y	Y	Y	Y	Y

24-mon RR = 24-month recurrence rate, CT = catheterization time, Ho:YAG = holmium laser, HT = hospitalization time, LBO = lithium triborate, N (T/C) = number of patients (test group/control group), N = no mention in the paper, OT = operation time, RC = reported complication, RFS = recurrence-free survival, Tm:YAG = 2- μm continuous-wave laser, Y = have mentioned in the paper.

Table 2

Tumor characteristics.

Study ID		Tumor maximum diameter, cm; tumor size, mm*			Tumor multiplicity and tumor number*			Tumor location			T-stage			Grade			Risk group (EAU		Mitomycin used†	Epirubicin used†
		ETURBT	CTURBT		ETURBT	CTURBT		ETURBT	CTURBT		ETURBT	CTURBT		ETURBT	CTURBT		ETURBT	CTURBT		
Zhu 2008	<3cm	95 (94.1)*	104 (93.7)*	Single	67 (66.3)	73 (65.8)		N		Ta	67 (66.3)	70 (63.1)	1	36 (35.6)	38 (34.2)	Low	29 (28.7)	25 (22.5)	Y	N
	>3cm	6 (5.9)*	7 (6.3)*	Multiple	34 (33.7)	38 (34.2)				T1	34 (33.7)	41 (36.9)	2	54 (53.5)	63 (56.8)	Intermediate	61 (60.4)	73 (65.8)		
										Concomitant CIS			3	9 (8.9)	10 (9.0)	High	11 (10.9)	13 (11.7)		
										Yes	5 (5.0)	7 (6.3)	Unknown	2 (2.0)	0 (0.0)					
										No	96 (95)	104 (93.7)								
Song 2010		18.5*	17.4*		2.0*	1.9*	Lateral	25 (39.1)	20 (39.2)	Ta	36 (56.3)	30 (58.8)	PUNLMP	5 (7.8)	4 (7.8)	Low	20 (31.3)	14 (27.5)	Y	N
							Other	39 (60.9)	31 (60.8)	T1	23 (35.9)	17 (33.4)	1	22 (34.4)	21 (41.2)	Intermediate	27 (42.2)	26 (51.0)		
										CIS	5 (7.8)	4 (7.8)	2	35 (54.7)	25 (49.0)	High	17 (26.5)	11 (21.5)		
													3	7 (10.9)	5 (9.8)					
Zhong[1] 2010		2.23 ± 0.76	1.54 ± 0.66		1.53 ± 0.57	1.45 ± 0.50		N		Ta	23 (76.66)	30 (71.43)	PUNLMP	4 (13.33)	7 (16.67)	Low	6 (20)	15 (35.71)	N	Y
										T1	5 (16.67)	8 (19.05)	Low	21 (70)	26 (61.9)	Intermediate	24 (80)	27 (64.29)		
										CIS	2 (6.67)	4 (9.52)	High	5 (16.67)	9 (21.43)	High	0	0		
Zhong[2] 2010		1.38 ± 0.58	1.54 ± 0.66		1.40 ± 0.50	1.45 ± 0.50		N		Ta	19 (76)	30 (71.43)	PUNLMP	3 (12)	7 (16.67)	Low	10 (40)	15 (35.71)	N	Y
										T1	5 (20)	8 (19.05)	Low	18 (72)	26 (61.9)	Intermediate	15 (60)	27 (64.29)		
										CIS	1 (4)	4 (9.52)	High	4 (16)	9 (21.43)	High	0	0		
Liu 2013		13.1 ± 2.3*	12.8 ± 3.1*		2.8 ± 1.2*	2.7 ± I.5*	Lateral	24 (37.5)	21 (37.5)	Ta	37 (57.8)	34 (60.7)	PUNLMP	11 (I7.2)	10 (I7.9)		N		N	Y
							Other	40 (62.5)	35 (62.5)	Tl	27 (42.2)	22 (39.3)	Low	46 (71.9)	41 (73.2)					
													High	7 (10.9)	5 (8.9)					
Chen 2015		2.6 ± 1.4	2.3 ± 1.2		1.8 ± 1.5	1.7 ± 1.7	Right lateral	28 (39.4)	29 (40.8)	Ta	43 (60.6)	55 (77.5)	PUNLMP	5 (7.0)	9 (12.7)		N		N	Y
							Left lateral	45 (63.4)	34 (47.9)	T1	25 (35.2)	15 (20)	Low grade	43 (60.6)	45 (63.4)					
										CIS	3 (4.2)	1 (1.4)	High grade	23 (32.4)	17 (23.9)					
Chen 2016		1.85 ± 1.07	1.71 ± 0.98		1.76 ± 0.81	1.85 ± 0.87	Lateral	83 (100)	69 (92)	Ta	70 (84.3)	64 (85.33)	PUNLMP	12 (14.5)	8 (10.7)	Low	34 (41.0)	24 (32)	Y	N
										T1	13 (15.7)	11 (14.7)	Low	61 (73.5)	55 (73.3)	Intermediate	37 (44.6)	38 (50.7)		
										Concomitant CIS			High	10 (12)	12 (16)	High	12 (14.5)	13 (17.3)		
										Yes	5 (6.0)	3 (4.0)								
										No	78 (94.0)	72 (96.0)								

Data presented as n (%) or mean ± SD. CIS = carcinoma in situ, CTURBT = conventional transurethral resection of bladder tumor, EAU = European association of urology, ETURBT = en bloc transurethral resection of bladder tumor, SD = standard deviation, PUNLMP = papillary urothelial neoplasm of low malignant potential.

* Tumor size and tumor number.

† Postoperative chemotherapy regimen was identical for both groups.

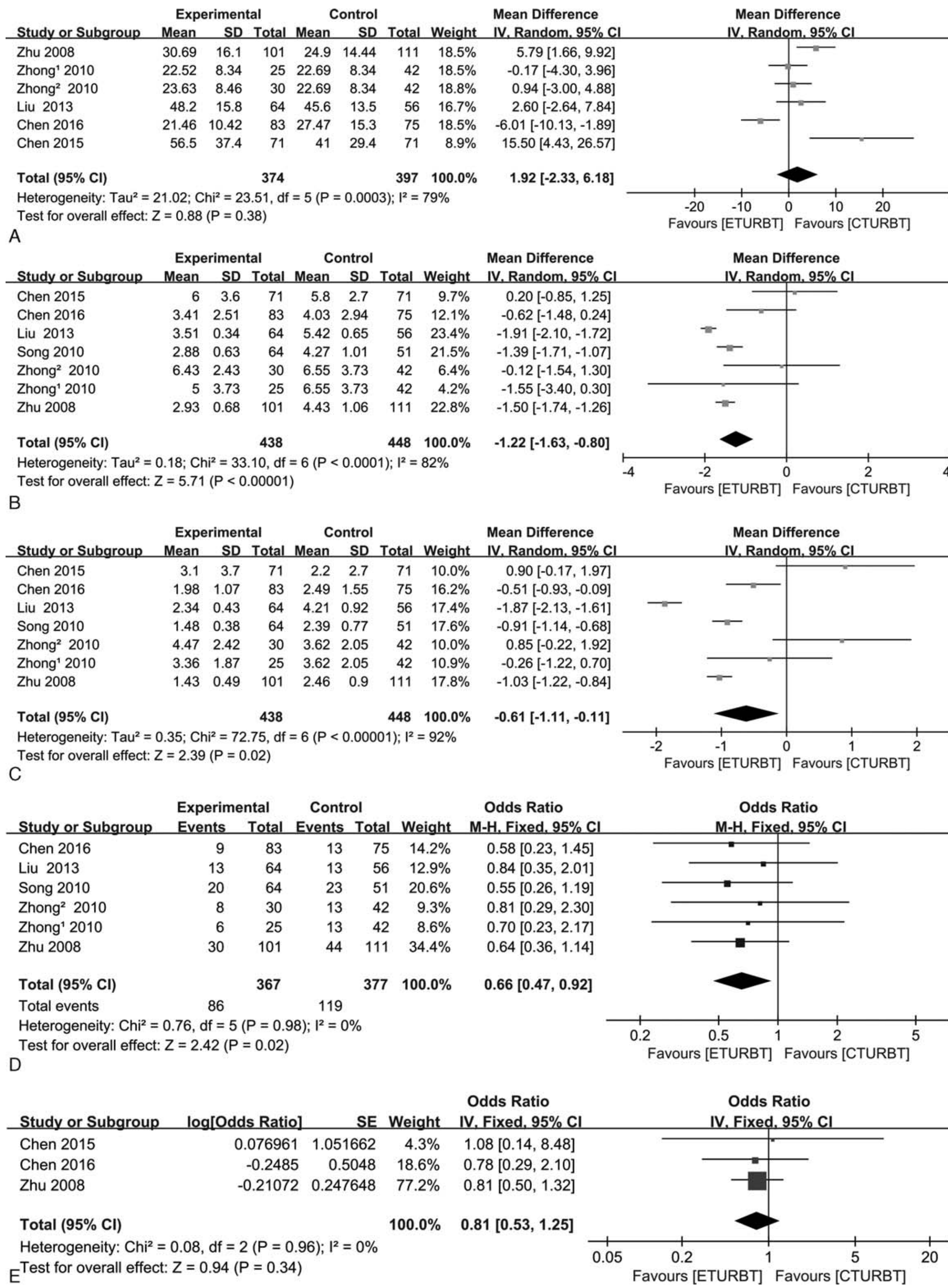

Figure 2. Forest plot comparing operation time (A), hospitalization time (B), catheterization time (C), 24-month recurrence rate (D), and recurrence-free survival (E).

wave laser. In addition, publication bias was evaluated by Begg funnel plot and Egger test, and no obvious biases were identified.

4. Discussion

To the best of our knowledge, this study is the first meta-analysis with a focus on comparing the efficacy and feasibility between ETURBT and CTURBT. It remains controversial whether the actual potential of ETURBT resides more in the therapeutic or diagnostic sector.[21,22] On one hand, CTURBT is dependent on in situ tumor fragmentation for tumor removal and specimen retrieval, and basic oncological surgical tenet was violated by CTURBT. This practice will promote tumor cell dispersal, and the pathological integrity of the specimen will be jeopardized.[21]

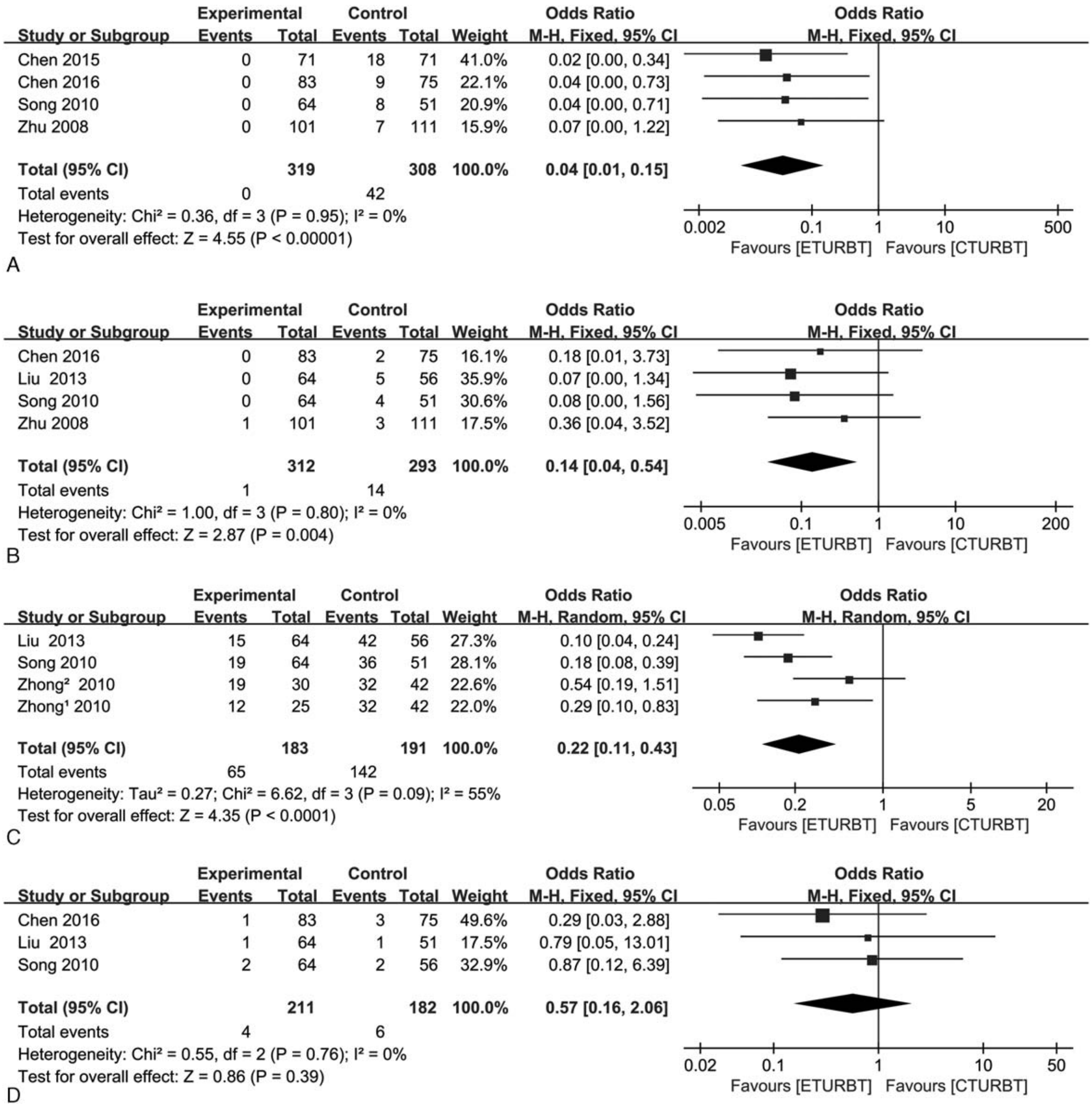

Figure 3. Forest plot comparing complications in terms of obturator nerve reflex (A), bladder perforation (B), bladder irritation (C), and urethral stricture (D).

On the other hand, well controlled resection of the whole tumor was yield, and the detrusor muscle present in the specimen was significantly better with ETURBT due to better visualization.[10] Therefore, this meta-analysis was performed to systematically evaluate these 2 techniques, providing evidence for the optimal treatment of NMIBC.

After combining results from 6 studies consisting of 7 trials, no significant trend of decreased OT in patients treated with ETURBT than CTURBT was observed. There were statistically significant differences in HT and CT between ETURBT and CTURBT. Moreover, it appeared that patients who underwent ETURBT experienced significant reductions in 24-month RR. But in terms of RFS, there was no statistically significant difference between the 2 arms. The complications including bladder perforation, obturator nerve reflex, and bladder irritation were less in ETURBT. No statistically significant difference in urethral stricture rate was noted. The CT and HT in ETURBT were less than that in CTURBT. However, the heterogeneity in pooled HT and CT should not be ignored ($I^2=82\%$, $P<0.001$ and $I^2=92\%$, $P<0.001$). There are several reasons for those differences: first of all, the high heterogeneity indicated that these differences might be unrelated to the technique itself, there are plenty of confounding factors that should be taken into account[11]; second, in personal comprehension, patient demographics and tumor characteristics are different, further researches should be done to ascertain the affect factors; third, previous studies[11–13] demonstrated that ETURBT may have some advantages in terms of perioperative complication rates. Our meta-analysis indicated that ETURBT may cause less bladder perforation, obturator nerve reflex, and shorter durations of postoperative bladder irritation than CTURBT. Moreover, 2 kinds of study type were pooled (retrospective study and prospective study), some bias may exist in this procedure, which would increase the heterogeneity of outcome and diminish the validity of our study. Finally, patients underwent surgery in different hospitals, different hospitals possessed different medical levels.

Staging quality was determined by the condition of detrusor muscle presented in specimens and demonstrated complete

Table 3

Postoperative adjuvant intravesical chemotherapy regimen.

Study ID	Started time after surgery	Drug dose	Postoperative monthly maintenance year	Regimen for both groups
Zhu 2008	1 wk after surgery	Mitomycin C, 30 mg for 6 wk, once every 2 wk for 6 wk	2	Identical
Song 2010	1 wk after surgery	Mitomycin C, 40 mg for 6 wk, once every 2 wk for 6 wk	2	Identical
Zhong[1] 2010	1 wk after surgery	Epirubicin, 50 mg for 6 wk, once every 2 wk for 12 wk	2	Identical
Zhong[2] 2010	1 wk after surgery	Epirubicin, 50 mg for 6 wk, once every 2 wk for 12 wk	2	Identical
Liu 2013	1 wk after surgery	Epirubicin, 40 mg for 8 wk	1	Identical
Chen 2015	Immediately after the operation	Epirubicin, 50 mg for 8 wk	1	Identical
Chen 2016	24 h after surgery	Mitomycin C, 30 mg for 8 wk	2	Identical

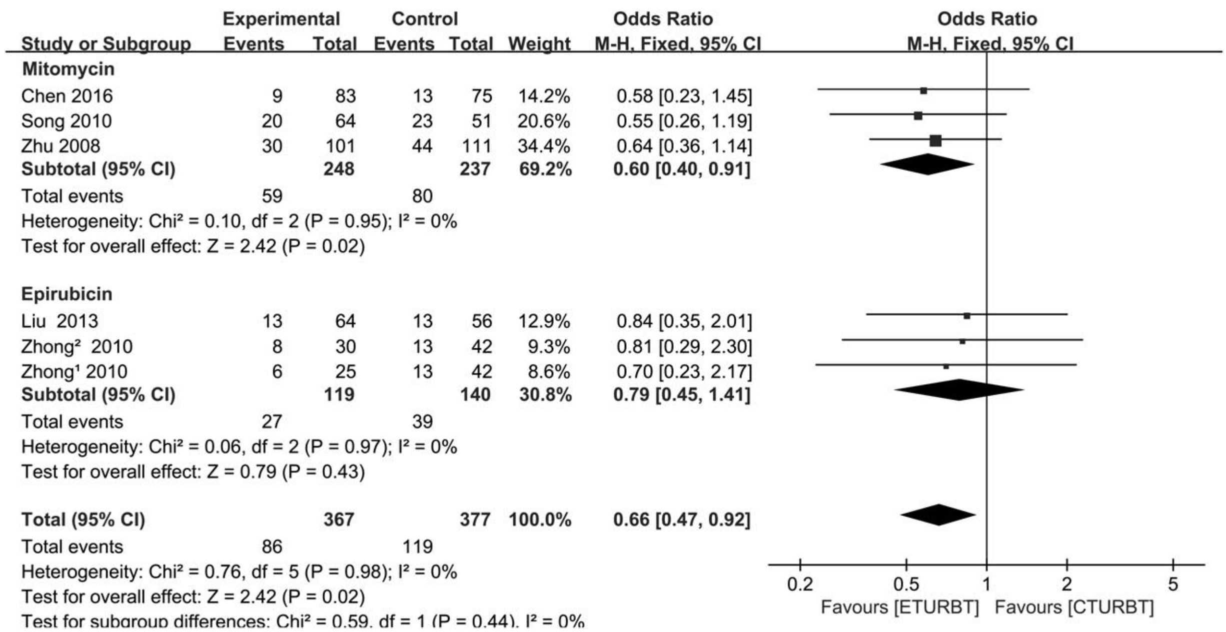

Figure 4. Subgroup analysis of the 2 groups according to the mitomycin and eprirubicin used for postoperative adjuvant intravesical chemotherapy.

resection.[11] Complete resection of the pathologic specimen plays an important role in bladder tumor transurethral resection, which determines postoperative pathologic diagnosis and prognosis.[23] Unfortunately, the trials enrolled in our study had not provided sufficient information about the data of detrusor muscle-positive specimens. To the best of our knowledge, detrusor muscle-positive specimens in 78% and 100% were reported in 2 small case series,[24,25] and the presence of the detrusor muscle layer in 97.3% of 221 samples was demonstrated by Kramer et al.[26] All of enrolled trials possessed the view that ETURBT can obtain adequate complete tumor specimens, containing the mucosa, lamina propria, and muscle layer for determining pathological diagnosis and treatment procedure.[12]

The postoperative adjuvant intravesical chemotherapy was performed for each patient in our meta-analysis. The characteristics of regimen of every trial were demonstrated in Table 3. The application of postoperative adjuvant intravesical chemotherapy was quite inconsistent in each trial. Three trials[11,15,16] received mitomycin and 4 trials[12–14] received epirubicin. However, the duration of administration and the drugs administered varied. We performed a subgroup analysis to evaluate the definitive relationship between 24-month RRs and postoperative adjuvant intravesical chemotherapy (Fig. 4). In mitomycin group, 3 trials[11,15,16] were enrolled. The results showed a statistical significant difference between 2 arms when mitomycin was postoperatively used ($P=0.02$). In eprirubicin group, 3 trials[13,14] were included, and there was a statistical significant difference between the 2 arms when eprirubicin was postoperatively used ($P=0.43$). The subgroup analysis demonstrated that postoperatively used mitomycin might be an important factor which affected the 24-month RRs between ETURBT and CTURBT.

There are several limitations of our study. First of all, included trails are consisted of 2 retrospective studies and 4 prospective nonrandomized studies and 1 randomized controlled trial. This certainly attenuated the value of our meta-analysis. Further studies need to be done in the near future. Second, in terms of the small sample size and limited number of studies enrolled, the results may lack statistical power.

5. Conclusion

ETURBT is superior to CTURBT in terms of shorter HT and CT, less complication rate, and lower recurrence-free rate. Moreover, it can provide a better tumor specimen for pathological evaluation. ETURBT is potentially useful alternative to CTURBT. However, this result needs to be validated in further prospective, randomized, controlled studies.

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