Review Articles

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En Bloc Resection for Bladder Tumors: An Updated Systematic Review and Meta-Analysis of Its Differential Effect on Safety, Recurrence and Histopathology

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Abbreviations and Acronyms

CIS = carcinoma in situ
cTURBT = conventional transurethral resection of bladder tumor
DM = detrusor muscle
ERBT = *en bloc* resection of bladder tumor
LVI = lymphovascular invasion
MM = muscularis mucosae
NMIBC = nonmuscle-invasive bladder cancer
NRCT = nonrandomized control trial
PSM = propensity score-matched
RCT = randomized control trial
reTUR = repeat transurethral resection
RFS = recurrence-free survival

Purpose: *En bloc* resection for bladder tumors has been developed to overcome shortcomings of conventional transurethral resection of bladder tumors with regard to safety, pathological evaluation and oncologic outcomes. However, the potential benefits and utility compared to conventional transurethral resection of bladder tumors have not been conclusively demonstrated. We aimed to update the current evidence with focus on the pathological benefits of *en bloc* resection for nonmuscle-invasive bladder cancer.

Materials and Methods: The PubMed®, Web of Science™ and Scopus® databases were searched in August 2021 according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. Studies were deemed eligible if they compared safety, and pathological and clinical outcomes in patients who underwent *en bloc* resection with conventional transurethral resection of bladder tumors.

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Results: Overall, 29 studies comprising 4,484 patients were eligible for this meta-analysis. Among 13 randomized controlled trials, the pooled 12- and 24-month recurrence risk ratios were not statistically different between the 2 surgical techniques (0.96, 95% CI 0.74−1.23 and 0.83, 95% CI 0.55−1.23, respectively). The pooled risk ratio for bladder perforation was 0.13 (95% CI 0.05−0.34) in favor of *en bloc* resection. In randomized controlled trials, the differential rates of detrusor muscle presence (pooled RR 1.31, 95% CI 1.19−1.43) and of detectable muscularis mucosae (pooled RR 2.69, 95% CI 1.81-3.97) were more likely in patients receiving *en bloc* resection. Patients who underwent *en bloc* resection had a lower rate of residual tumor at repeat transurethral resection than those treated with conventional transurethral resection of bladder tumors in 1 randomized controlled trial and 3 observational studies (pooled RR 0.47, 95% CI 0.31−0.71).

Conclusions: *En bloc* resection for bladder tumors seems to be safer, and to yield superior histopathological information and performance compared to conventional transurethral resection of bladder tumors. Despite the failure to improve the recurrence rate, the more accurate histopathological analysis is likely to improve clinical decision making and care delivery in nonmuscle-invasive bladder cancer.

Key Words: urinary bladder neoplasms, pathology, recurrence

NONMUSCLE-INVASIVE bladder cancer (NMIBC) represents approximately 75% of all bladder cancers at initial diagnosis in developed countries.[1] The clinical behavior of NMIBC is highly variable with accurate histopathological evaluation being essential for patient-centric optimal management for each NMIBC patient.[2,3]

Conventional transurethral resection of bladder tumors (cTURBTs) is the standard treatment for bladder cancer. However, this procedure inherently involves fragmentation, vast cauterization and disorientation of tumor specimens, which tends to reduce quality of histopathological reporting and diagnostic usefulness.[1,4] *En bloc* resection of bladder tumors (ERBTs) was first introduced by Kawada et al in 1997 to overcome the drawbacks associated with cTURBT.[5] ERBT applies a novel technique to cTURBT, resecting not only the entire tumor and the surrounding mucosa but also underlying stroma and the superficial muscularis propria in a single specimen.[6] Recently, ERBT has been gaining acceptance as there is increasing evidence that it improves the quality of the resected specimen.[7,8]

Several prospective randomized controlled trials (RCTs) of ERBT vs cTURBT assessed perioperative complications and oncologic outcomes.[9−16] Reports of these trials suggested that ERBT results in lower recurrence rates, however without any significant difference. In 6 different meta-analyses of ERBT vs cTURBT published between 2020 and 2021, including previous nonrandomized control trials (NRCTs) and observational studies, the oncologic benefit of ERBT versus cTURBT remained controversial depending on the included studies.[17−23] The limitation of these studies is the inclusion/analysis of noncontrolled studies which suffered from significant selection bias. Indeed, to allow reliable, reproducible and valid conclusions for oncologic outcomes, only RCTs should be included for meta-analysis when possible. Furthermore, although these meta-analyses demonstrated the superior safety of ERBT, the pathological utility, which seems to be a potential benefit of ERBT, has not been well assessed.[17−23]

Regarding the pathological utility, some previous studies and 1 meta-analysis have suggested a higher rate of detrusor muscle (DM) presence compared to cTURBT.[10−12,21] However, a meta-analysis conducted by Zhang et al did not show a significant difference in rates of DM presence.[23] Since then, increasing evidence has emerged that ERBT provides specimens that allow for higher-quality examination. For example, higher detection of muscularis mucosa (MM)[10,24−26] allows for better T1 sub-staging[12,27,28] and assessment of surgical margin.[11,27,29] There has not been a recent updated meta-analysis of the differential pathological performance of ERBT compared to cTURBT.

Therefore, we performed a systematic review and meta-analysis to assess the differential effect of ERBT compared to cTURBT with regard to safety, recurrence and, most importantly, histopathological diagnostic accuracy, in patients with bladder tumors. We relied on RCTs and analyzed RCTs and the others separately to assess for the effect biases associated with noncontrolled studies.

METHODS

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42021262387).

Search Strategy

This systematic review and meta-analysis was conducted based on the guidelines of the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement (supplementary fig. 1, https://www.jurology.com).[30] In August 2021, a literature search on the PubMed®, Web of Science™ and Scopus® databases was performed to identify reports investigating clinical (eg operation time, bladder perforation, catheterization

period, 12- and 24-month recurrence rate, progression rate) and histopathological (eg DM presence rate, MM detective rate, concomitant carcinoma in situ [CIS] rate, surgical margin diagnostic rate, any residual tumor at repeat transurethral resection [reTUR]) outcomes in patients with bladder tumors who underwent either ERBT or cTURBT. The keywords used in our search strategy were as follows: (bladder) OR (urothelial) AND (tumor) OR (cancer) OR (carcinoma) AND (en bloc) OR (ERBT) OR (TURBO) OR (laser) OR (needle electrode) OR (endoscopic submucosal dissection) OR (hybrid knife) AND (transurethral) OR (TURBT). Initial screening was performed independently by 2 investigators based on the titles and abstracts to identify eligible reports. Potentially relevant reports were subjected to a full-text review. Additionally, manual searches of reference lists of relevant articles were performed to identify additional studies. Disagreements were resolved by consensus with the co-investigators.

Inclusion and Exclusion Criteria

Studies were included if they investigated patients with bladder tumors (Patients) who underwent ERBT (Interventions) compared to those who underwent cTURBT (Comparisons) to assess clinical (eg operation time, bladder perforation rate, catheterization period, 12- and 24-month recurrence rate, progression rate) and histopathological (eg DM presence rate, MM detectable rate, concomitant CIS rate, surgical margin diagnostic rate, any residual tumor at reTUR) outcomes (Outcome) in RCTs as well as NRCTs and observational studies. Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports and nonEnglish articles were excluded. Data from conference proceedings were included or updated in the results to reduce the risk of publication bias.[31] Studies were excluded if they did not involve patients treated with cTURBT in the control arm. In cases of duplicate publications, the higher quality or the most recent publication was selected.

Data Extraction

Data were extracted independently by 2 authors. First author's name, publication year, recruitment country, study design, number of patients, age, sex, tumor diameter, tumor multiplicity, pathological T stage, grade, operation time, obturator nerve reflex rate, bladder perforation rate, catheterization period, 12- and 24-month recurrence rate, progression rate, adjuvant instillation therapy, DM presence rate, MM detectable rate, concomitant CIS detectable rate, surgical margin diagnostic rate and any residual tumor at reTUR were retrieved. Disagreements were resolved via consensus with the co-investigators.

Risk of Bias Assessment

Assessment of study quality and risk of bias was carried out using the ROBINS-I (Risk Of Bias In Non-Randomized Studies of Interventions) tool and the risk-of-bias (RoB version 2) evaluation following the Cochrane Handbook for Systematic Reviews of Interventions.[32] In ROBINS-I, each bias domain and overall risk of bias was judged as "Low," "Moderate," "Serious" or "Critical" risk of bias. The presence of confounders was determined by consensus and review of the literature. The ROBINS-I and risk-of-bias assessment of each study was performed independently by 2 authors (supplementary fig. 2 and supplementary table, https://www.jurology.com).

Statistical Analyses

Forest plots were applied to assess the risk ratio (RR) to summarize the RR of bladder perforation, 12- and 24-month recurrence rate, DM presence rate, MM detectable rate, CIS detectable rate, surgical margin diagnostic rate and residual tumor at reTUR in patients treated with ERBT and cTURBT. For outcomes of continuous variables (ie operation time and catheterization period), the weighted mean difference was used to measure the difference. We included only RCTs to minimize the selection biases for assessing the oncologic and perioperative outcomes. For pathological outcomes, RCTs as well as observational studies were included for analysis owing to being less susceptible to patient demographics; instead, subgroup analyses were performed by study design (RCTs or propensity score-matched [PSM] studies, or retrospective observational studies). Heterogeneity among the outcomes of included studies in this meta-analysis was assessed by using Cochrane's Q test and the I^2 statistic. When significant heterogeneity (p value of <0.05 in the Cochrane Q test and a ratio $>50\%$ in I^2 statistics) was observed, a random-effects model was applied.[33,34] Fixed-effects models for the calculation of pooled HRs for non-heterogeneous results were applied.[35] All analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the statistical significance level was set at $p < 0.05$.

RESULTS

Study Selection and Characteristics

Our initial search identified 1,355 records, and after removing duplicates 810 records remained (fig. 1). A total of 720 articles were excluded after screening the titles and abstracts, and a full-text review was performed for 90 articles. According to our inclusion criteria, we finally identified 29 studies comprising 4,484 patients for meta-analysis.[9–16,24,25,29,36–50,51–53] Of 29 included studies, 13 RCTs comprising 1,792 patients were eligible for analysis of oncologic and perioperative outcomes,[9–16,36–40] and 5 RCTs and 16 NRCTs/observational studies comprising 3,369 patients were eligible for analysis of pathological and reTUR outcomes.[10–13,24,25,29,40–50,51–53] The demographics of each included study are represented in tables 1 and 2.

Risk of Bias Assessment

The summary of the risk of bias and authors' judgments of each domain for each included RCT are shown in supplementary figure 2 (https://www.jurology.com). All included RCTs had some concerns about bias regarding the randomization process and measurement of outcome. Therefore,

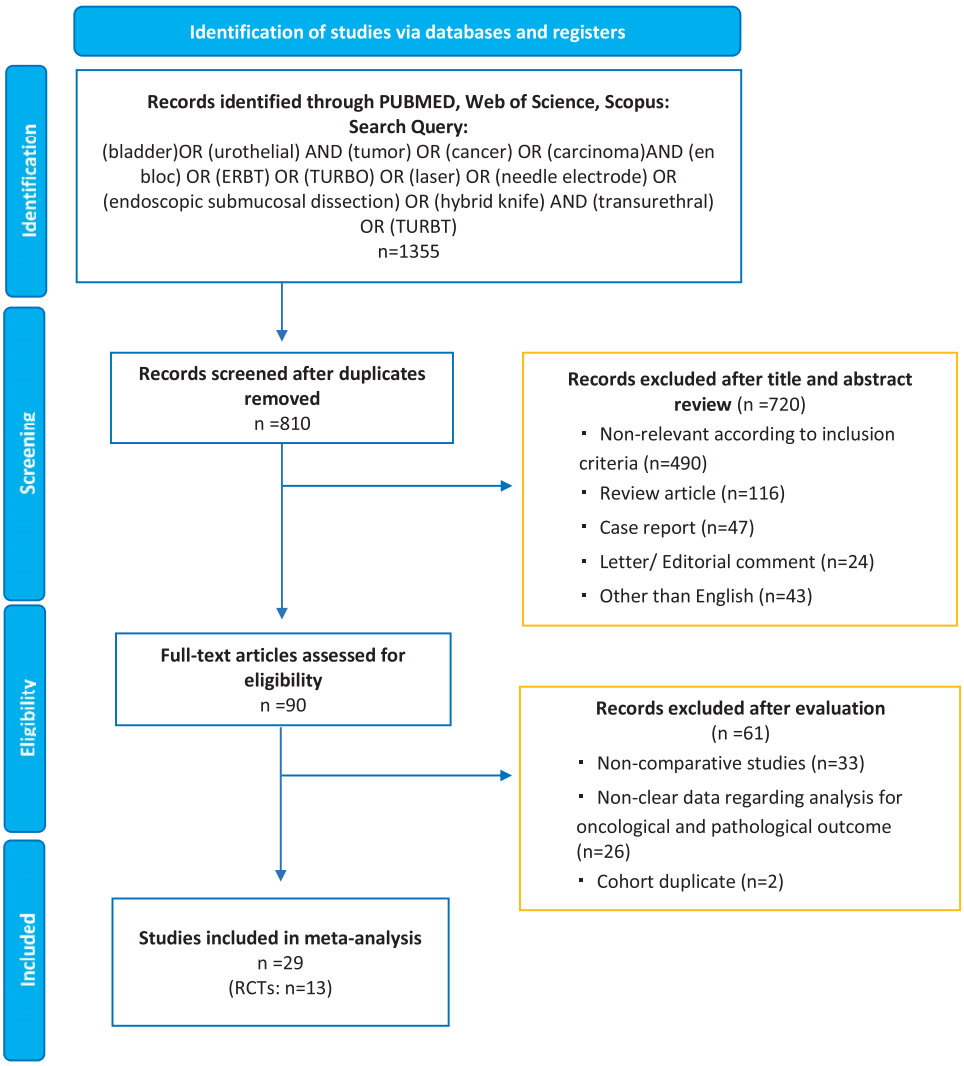


Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow chart detailing the article selection process.

included RCTs had some concerns or a high risk of bias as the overall risk of bias judgment.

Clinical Outcomes Based on RCTs Only

Perioperative and oncologic outcomes of the included 13 RCTs are shown in table 3.

Operation time. Nine studies including 1,274 patients provided data for evaluation of operation time of ERBT compared to cTURBT. The forest plot (fig. 2, *A*) revealed that ERBT had a longer operative time than cTURBT (mean difference 5.38 minutes, 95% CI 0.33 to 10.4, z=2.09). The Cochrane's Q test ($Chi^2=171$; $p<0.001$) and I^2 test ($I^2=95\%$) revealed significant heterogeneity.

Risk of bladder perforation and catheterization period. Eight studies including 1,297 patients provided data on the rate of bladder perforation of ERBT compared to cTURBT. The forest plot (fig. 2, *B*) revealed that ERBT had a lower risk of bladder perforation than cTURBT (RR: 0.13, 95% CI 0.05 to 0.34, z=4.15). The Cochrane's Q test ($Chi^2=3.29$; $p=0.86$) and I^2 test ($I^2=0\%$) revealed no significant heterogeneity.

Seven studies including 889 patients provided data on the length of catheterization of ERBT compared to cTURBT. The forest plot (fig. 2, *C*) revealed that ERBT had a shorter catheterization period than cTURBT (mean difference 1.07 days, 95% CI −1.63 to −0.51, z=2.09). The Cochrane's Q test ($Chi^2=109$; $p<0.001$) and I^2 test ($I^2=94\%$) revealed significant heterogeneity.

Twelve- and 24-month recurrence. For evaluation of the 12- and 24-month recurrence rates, 6 studies comprising 744 patients and 4 studies comprising 582 patients provided the data. The forest plot (fig. 2, *D* and *E*) revealed no statistically significant difference in 12- and 24-month recurrence rates between ERBT and cTURBT (RR: 0.96, 95% CI 0.74 to 1.23; z=0.35) and 0.83 (95% CI 0.55 to

Table 1. *Characteristics of included RCTs*

				No. Pts			No. Sex		Age		Tumor Diameter		Multiplicity		T Stage	
Study	Yr	Country	ERBT Method	Total	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT
Liu[14]	2013	China	2-μm laser	120	64	56	Male: 46 Female: 18	Male: 40 Female: 16	67.1±8.3	66.3±9.8	1.31±0.23	1.28±0.31	2.8±1.2	2.7±1.5	Ta: 37 T1:27	Ta: 34 T1: 22
Chen[9]	2015	China	2-μm laser	142	71	71	Male: 54 Female: 17	Male: 51 Female: 20	63	62	2.6±1.4	2.3±1.2	1.8±1.5	1.7±1.7	Ta: 43 T1:25 Tis: 3	Ta: 55 T1: 15 Tis: 1
Zhang[40]	2015	China	Thulium laser	292	149	143	Male: 70 Female: 79	Male: 79 Female: 64	≤60: 42 <60: 107	≤60: 35 60<: 107	>3 cm: 98 ≤3 cm: 51	>3 cm: 95 ≤3 cm: 48	Single: 52% Multiple: 48%	Single: 55% Multiple: 45%	Ta:106 T1: 43	Ta: 107 T1: 36
Cheng[37]	2016	China	HybridKnife®	75	38	37	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Huang[39]	2016	China	Holmium laser	140	70	70	Male: 45 Female: 25	Male: 48 Female: 22	59.97±5.75	57.87±4.99	1.58±0.51	1.53±0.20	N.A.	N.A.	Ta: 37 T1: 28 Tis: 5	Ta: 35 T1: 27 Tis: 8
Balan[36]	2018	Romania	Bipolar electrode	90	45	45	N.A.	N.A.	64.7	66.1	1.82	1.69	Single: 38% Multiple: 62%	Single: 42% Multiple: 58%	Ta: 24 T1: 21	Ta: 23 T1: 22
He[13]	2018	China	Holmium laser	95	49	46	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Hu[37]	2018	China	HybridKnife	93	46	47	Male: 71 Female: 22			57.1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Gakis[11]	2020	Germany	HybridKnife (with photodynamic diagnosis)	115	56	59	Male: 45 Female: 11	Male: 47 Female: 12	68.3	72.5	>3cm: 2 ≤3cm: 46	>3 cm: 10 ≤3 cm: 41	N.A.	N.A.	Ta: 50 T1: 6	Ta: 42 T1: 17
Lu[15]	2020	China	Holmium laser	218	109	109	Male: 76 Female: 33	Male: 80 Female: 29	59.1±8.1	58.0±8.0	>3 cm: 15 ≤3 cm: 94	>3 cm: 17 ≤3 cm: 92	N.A.	N.A.	Ta: 61 T1: 48	Ta: 59 T1: 50
Hashem[12]	2020	Egypt	Holmium laser	100	50	50	Male: 37 Female: 13	Male: 39 Female: 11	60.4±11.9	61.1±11.3	3.2±1.1	2.9±1.4	Single: 66% Multiple: 34%	Single: 56% Multiple: 44%	Ta: 2 T1: 42	Ta: 3 T1: 46
Fan[10]	2021	China	Green-light laser	233	116	117	Male: 96 Female: 20	Male: 87 Female: 30	60	57	1.5 (1.2—1.5)	1.5 (1.0—2.0)	Single: 75% Multiple: 25%	Single: 79% Multiple: 21%	Ta: 91 T1: 25	Ta: 104 T1: 13
Razzaghi[16]	2021	Iran	Holmium laser	79	40	39	Male: 38 Female: 2	Male: 35 Female: 4	65.8±10.8	68.2±9.8	19.8±10.7	22.2±8.1	Single: 63% Multiple: 37%	Single: 59% Multiple: 41%	Ta: 25 T1: 15	Ta: 23 T1: 16

Age, diameter and multiplicity are represented as mean±SD or median (IQR) or percent unless noted otherwise. *N.A.*, Not applicable.

Table 2. *Characteristics of included NRCTs and observational studies*

Study	Yr	Country	Prospective/ Retrospective	ERBT Method	No. Pts			No. Sex		Age		Tumor Diameter		Multiplicity		T Stage	
					Total	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT
Migliari[46]	2015	Italy	Retrospective	Thulium laser	119	58	61	Male: 41 Female: 17	Male: 45 Female: 16	71	72.5	2.5	2.3	N.A.	N.A.	Ta: 30 T1: 37 T2: 5	Ta: 38 T1: 33 T2: 4
Zhang[52]	2017	China	Retrospective	Classic resection loop	90	40	50	Male: 35 Female: 5	Male: 38 Female: 12	60.7±13.1	60.8±14.0	≥3 cm: 8 <3 cm: 32	≥3 cm: 12 <3 cm: 38	Single: 73% Multiple: 27%	Single: 76% Multiple: 24%	Ta: 15 T1: 25	Ta: 27 T1: 23
Sorokin[48]	2018	Russia	Retrospective	Thulium laser	129	71	58	Male: 52 Female: 19	Male: 48 Female: 10	59.4±1.37	61.8±1.84	2.28±0.15	1.81±0.15	1.72±0.18	1.81±0.27	T1: 64 T2: 7	T1: 53 T2: 5
Hu[43]	2019	China	Retrospective	HybridKnife	109	51	58	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	T1: 21	T1: 13
Kransy[29]	2019	Belarus	Retrospective	Classic resection loop	273	136	137	Male: 96 Female: 40	Male: 96 Female: 41	60.5	63	≥3 cm: 51 <3 cm: 85	≥3 cm: 21 <3 cm: 116	Single: 71% Multiple: 29%	Single: 83% Multiple: 17%	Ta: 13 T1: 123	Ta: 14 T1: 123
Li K[44]	2019	China	Retrospective	Thulium laser	256	136	120	Male: 110 Female: 26	Male: 98 Female: 22	<65: 80 ≥65: 56	<65: 72 ≥65: 48	2.39±1.09	2.15±0.92	Single: 84% Multiple: 16%	Single: 85% Multiple: 15%	N.A.	N.A.
Liang[24]	2019	China	Retrospective	Green-light laser	158	88	70	Male: 78 Female: 10	Male: 51 Female: 19	<75: 76 ≥75: 12	<75: 66 ≥75: 4	≥2 cm: 22 <2 cm: 66	≥2 cm: 21 <2 cm: 49	Single: 72% Multiple: 28%	Single: 76% Multiple: 24%	Ta: 29 T1: 59	Ta: 33 T1: 37
Bangash[41]	2020	Pakistan	Retrospective	Collins knife	82	41	41	Male: 34 Female: 7	Male: 36 Female: 5	58.5±15.0	58.6±12.3	2.5 (2–3)	2.5 (1.8–4)	1.0 (1–2)	1.0 (1–2.5)	Ta: 20 T1: 21	Ta: 19 T1: 22
Vladanov[50]	2020	Moldova	Retrospective	Collins knife	152	67	85	Male: 57 Female: 10	Male: 66 Female: 19	58.43±8.5	61.5±12.4	≥3cm: 18 <3 cm: 49	≥3cm: 16 <3 cm: 69	Single: 79% Multiple: 21%	Single: 81% Multiple: 19%	Ta: 35 T1: 32	Ta: 49 T1: 36
Enikeev[42]	2020	Russia	Prospective	Thulium laser	129	71	58	Male: 52 Female: 19	Male: 48 Female: 10	62	64.5	2	1.5	1.0 (1–3)	1.0 (1–2)	Ta: 39 T1: 32	Ta: 30 T1: 28
Yang[22]	2020	China	Prospective	Classic resection loop	183	96	87	Male: 70 Female: 26	Male: 62 Female: 25	54.6±12.1	55.4±11.7	1.79±0.47	1.72±0.57	1.25±0.73	1.21±0.69	Ta: 61 T1: 25 T2: 10	Ta: 57 T1: 26 T2: 4
Liu[45]	2021	China	Retrospective	Thulium laser	286	134	152	Male: 101 Female: 33	Male: 111 Female: 41	61.5±8.0	60.3±8.5	1.9±1.1	2.2±1.2	2.7±2.6	2.3±2.2	Ta: 72 T1: 49 Tis: 13	Ta: 87 T1: 48 Tis: 17
Teoh[49]	2021	China	Retrospective	Classic resection loop	135	99	36	Male: 67 Female: 32	Male: 29 Female: 7	69.1±11.2	77.3±11.5	1.93±1.04	3.58±1.64	Single: 61% Multiple: 39%	Single: 31% Multiple: 69%	T0: 17 Ta: 65 T1: 17	T0: 0 Ta: 20 T1: 16
Yanagisawa[27]	2021	Japan	Retrospective	Collins knife	123	32	91	Male: 19 Female: 13	Male: 73 Female: 18	73.5	71	19.5±6.5	21.5±9.1	Single: 56% Multiple: 44%	Single: 32% Multiple: 68%	All T1	
Struck[25]	2021	Germany	Retrospective	Thulium laser: 17 HybridKnife: 6 Electrocauterization: 11	34	23	11	Male: 31 Female: 3		<70: 19 ≥70: 15		≥3 cm: 4 <3 cm: 30		Single:85% Multiple: 15%		Benign: 2 Ta: 26 T1: 6	

(continued)

Table 2. (*continued*)

Study	Yr	Country	Prospective/ Retrospective	ERBT Method	No. Pts			No. Sex		Age		Tumor Diameter		Multiplicity		T Stage	
					Total	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT
Poletajew[47]	2021	Poland	Prospective	Collins knife or a classic resection loop	427 (276)*	153 (138)	274 (138)	Male: 117 Female: 36	Male: 201 Female: 73	68±11.39	69.5±11.47	>3 cm: 24 ≤3 cm: 129	>3 cm: 66 ≤3 cm: 208	Single: 63% Multiple: 37%	Single: 58% Multiple: 42%	Ta: 94 T1: 38 T2: 6	Ta: 126 T1: 58 T2: 32

Age, diameter and multiplicity are represented as mean±SD or median (IQR) or percent unless noted otherwise. *N.A.*, Not applicable.
*Propensity score matching.

1.23; z = 0.94), respectively. Confidence intervals did not include clinically meaningful differences. The Cochrane's Q test and I^2 test of 12- and 24-month recurrence revealed no significant heterogeneity (12 months: $Chi^2 = 8.06$; $p = 0.15$, $I^2 = 38\%$; 24 months: $Chi^2 = 0.37$; $p = 0.95$, $I^2 = 0\%$).

Progression rate. Four studies including 767 patients provided data for evaluation of progression rates of ERBT compared with cTURBT. However, these studies differ in the timing to evaluate progression rates; thus, meta-analysis was not performed. In 12-month progression rates, Gakis et al reported 8.3% (4/48) for ERBT and 4.1% (2/49) for cTURBT.[11] In 24-month progression rates, Lu et al reported 9.2% (10/109) for ERBT and 10% (11/109) for cTURBT.[15] In 36-month progression rates, Zhang et al reported 5.4% (8/149) for ERBT and 7.0% (10/143) for cTURBT.[40] On the other hand, Chen et al reported no progression in both treatment arms during the 18-month followup.[9] Importantly, the rate of pT1 patients differed depending on each study (table 1); however, progression rates seem to be comparable between ERBT and cTURBT at any timing.

Pathological Outcomes

The probability of DM presence. Four RCTs and 14 observational studies including 2,782 patients provided data on the rate of DM presence of ERBT compared to cTURBT. The forest plot of included RCTs revealed that ERBT was significantly associated with a higher rate of DM presence than cTURBT (RR: 1.31, 95% CI 1.19 to 1.43, z = 5.70; fig. 3, *A*). The Cochrane's Q test ($Chi^2 = 5.56$; $p = 0.14$) and I^2 test ($I^2 = 46\%$) revealed no significant heterogeneity.

In the analysis of observational studies, ERBT was also associated with a higher rate of DM presence than cTURBT (RR: 1.35, 95% CI 1.21 to 1.50, z = 5.57; fig. 3, *B*). The Cochrane's Q test ($Chi^2 = 103$; $p < 0.001$) and I^2 test ($I^2 = 87\%$) revealed significant heterogeneity.

The probability of MM detection. Two RCTs and 4 observational studies including 670 patients provided data on the rate of detectable MM, including T1 sub-staging, of ERBT compared to cTURBT. The forest plot of included RCTs revealed that ERBT was significantly associated with a higher rate of detectable MM than cTURBT (RR: 2.69, 95% CI 1.81 to 3.97, z = 4.94; fig. 3, *C*). The Cochrane's Q test ($Chi^2 = 1.55$; $p = 0.21$) and I^2 test ($I^2 = 35\%$) revealed no significant heterogeneity.

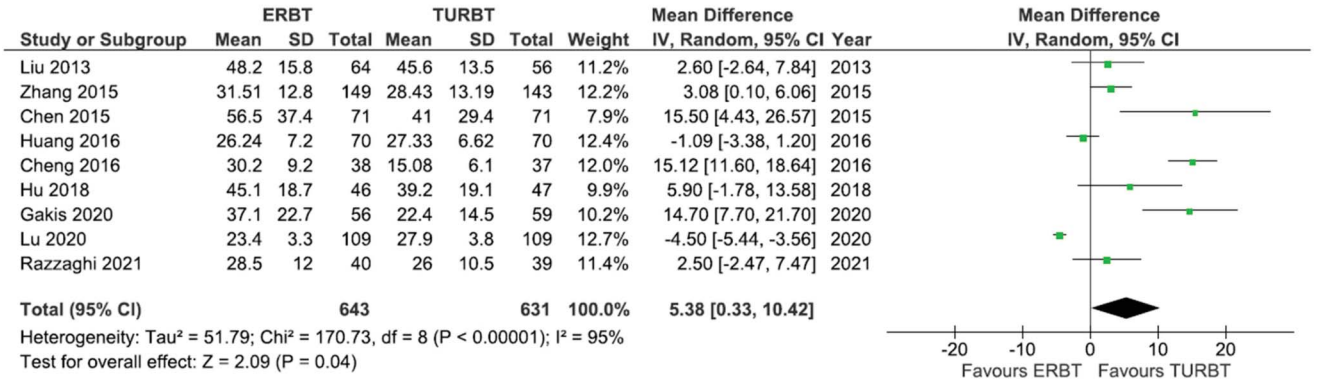
In the analysis of observational studies, ERBT was also associated with a higher rate of detectable MM than cTURBT (RR: 2.02, 95% CI 1.09 to 3.75, z = 2.22; fig. 3, *D*). The Cochrane's Q test ($Chi^2 = 8.60$; $p = 0.04$) and I^2 test ($I^2 = 65\%$) revealed significant heterogeneity.

Table 3. *Perioperative and oncologic outcomes of RCTs*

Study	Yr	Country	No. Pts			Tumor Diameter (cm)		Operation Time (mins)		No. Bladder Perforation Cases		Catheterization Period (days)		Recurrence		Progression		Followup (mos)	Adjuvant Instillation Therapy	
			Total	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT	ERBT	TURBT		ERBT	TURBT
Liu[14]	2013	China	120	64	56	1.31±0.23	1.28±0.31	48.2±15.8	45.6±13.5	0	5	2.3±0.4	4.2±0.9	7 (12 mos) 13 (24 mos) 20 (36 mos)	6 (12 mos) 13 (24 mos) 19 (36 mos)	N.A.		36	Epirubicin 40 mg weekly×8 and monthly×12 as maintenance	
Chen[9]	2015	China	142	71	71	2.6±1.4	2.3±1.2	41±29.4	56.5±37.4	0	0	3.1±3.7	2.2±2.7	4/60 (18 mos)	7/62 (18 mos)	0 (18 mos)	0 (18 mos)	18	Epirubicin 40 mg weekly×8 and monthly×12 as maintenance	
Zhang[40]	2015	China	292	149	143	>3 cm: 98 ≤3 cm: 51	>3 cm: 95 ≤3 cm: 48	28.4±13.2	31.5±12.8	0	6	N.A.		46 (12 mos) 68 (36 mos)	45 (12 mos) 61 (36 mos)	8 (36 mos)	10 (36 mos)	36	Epirubicin 40 mg weekly×8	
Cheng[37]	2016	China	75	38	37	Pts with <20 mm were comparable		15.8±6.1	30.2±9.2	N.A.		2.3±0.9	4.8±1.3	2 (12 mos)	8 (12 mos)	N.A.		12	N.A.	
Huang[39]	2016	China	140	70	70	1.58±0.51	1.53±0.20	27.3±6.6	26.2±7.2	0	5	2.4±0.5	3.3±0.5	8/62 (24 mos)	9/60 (24 mos)	N.A.		24	Epirubicin 40 mg weekly×8 and monthly×12 as maintenance	
Balan[36]	2018	Romania	90	45	45	1.82	1.69	13.4 (mean)	19.7 (mean)	N.A.		1.9 (mean)	2.8 (mean)	7/41 (12 mos)	11/40 (12 mos)	N.A.		12	Following European Organization for Research and Treatment of Cancer risk classification, epirubicin or BCG was applied	
He[13]	2018	China	95	49	46	N.A.		52.5±9.5	45.8±10.9	0	12	4.6±2.6	4.8±2.7	9 (12 mos)	13 (12 mos)	N.A.		12–36	Epirubicin 40 mg weekly×8 and monthly×12 as maintenance	
Hu[37]	2018	China	93	46	47	N.A.		39.2±19.1	45.1±18.7	N.A.		N.A.		N.A.		N.A.		N.A.	N.A.	
Gakis[11]	2020	Germany	115	56	59	>3 cm: 2 ≤3 cm: 46	>3 cm: 10 ≤3 cm: 41	22.4±14.5	37.1±22.7	1	1	2.0±0.8	2.0±1.4	19/48 (12 mos)	11/49 (12 mos)	4/48 (12 mos)	2/49 (12 mos)	12	Mitomycin C and/or BCG: 13	Mitomycin C and/or BCG: 20
Lu[15]	2020	China	218	109	109	>3 cm: 15 ≤3 cm: 94	>3 cm: 17 ≤3 cm: 92	27.9±3.8	23.4±3.3	0	8	3.6±1.2	4.7±1.7	13 (24 mos)	15 (24 mos)	10 (24 mos)	11 (24 mos)	24	Epirubicin 50 mg weekly×8 and monthly×12 as maintenance	
Hashem[12]	2020	Egypt	100	50	50	3.2±1.1	2.9±1.4	10 (5–35) median (range)	13 (5–60) median (range)	0	2	2 (median)	2 (2–8) median (range)	Median RFS: 31.8 mos (95% CI: 28.7–34.9)	Median RFS: 28.3 mos (95% CI: 24.9–31.6)	N.A.		20±9.9 (mean±SD)	IPIC: 47/47 Maintenance; Epirubicin: 4 BCG: 39	IPIC: 43/47 Maintenance; Epirubicin: 1 BCG: 45
Fan[10]	2021	China	233	116	117	1.5 (1.2–1.5)	1.5 (1.0–2.0)	7.3 (4.1–11.4)	5.9 (4.1–11.4)	0	1	2 (2.0–3.0)	2 (2.0–2.8)	2/86 (overall)	3/99 (overall)	N.A.		48 (36–60) median, IQR	Pirarubicin 30 mg weekly×8 and monthly×12 as maintenance	
Razzaghi[16]	2021	Iran	79	40	39	19.8±10.7	22.2±8.1	26±10.5	28.5±12	0	3	1.1±0.6	2.5±1.1	7 (12 mos)	6 (12 mos)	N.A.		18	Following European Association of Urology recommendation	

Operation time and catheterization period are represented as mean±SD or median (IQR) or percent unless noted otherwise. *N.A.*, Not applicable. *BCG*, bacillus Calmette-Guérin. *IPIC*, immediate postoperative instillation of chemotherapy.

(A) Operation time



(B) Bladder perforation

(C) Catheterization period

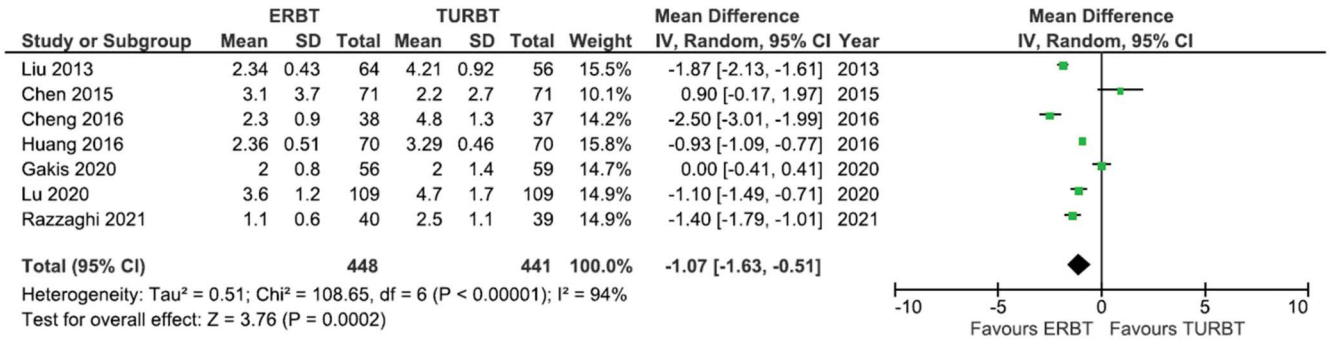


Figure 2. Forest plot; association of clinical and oncologic outcomes with ERBT and cTURBT only in RCTs. *A,* operation time. *B,* bladder perforation. *C,* catheterization period. *D,* 12-month recurrence. *E,* 24-month recurrence. *IV,* inverse variance. *M-H,* Mantel-Haenszel.

The probability of concomitant CIS detection. Three RCTs and 2 observational studies including 906 patients provided data on the rate of concomitant CIS as detected by ERBT compared to cTURBT. The forest plot revealed no statistically significant difference in the rate of concomitant CIS between ERBT and cTURBT (RR: 0.92, 95% CI 0.66 to 1.29, z=0.49; fig. 3, *E*). The Cochrane's Q test (Chi^2=3.61; p=0.46) and I^2 test (I^2=0%) revealed no significant heterogeneity. In the subgroup analysis assessing only RCTs, there was also no statistically significant difference in the rate of concomitant CIS between ERBT and cTURBT (RR: 1.03, 95% CI 0.64 to 1.65, z=0.11). The Cochrane's Q test (Chi^2=2.87; p=0.24) and I^2 test (I^2=30%) revealed no significant heterogeneity.

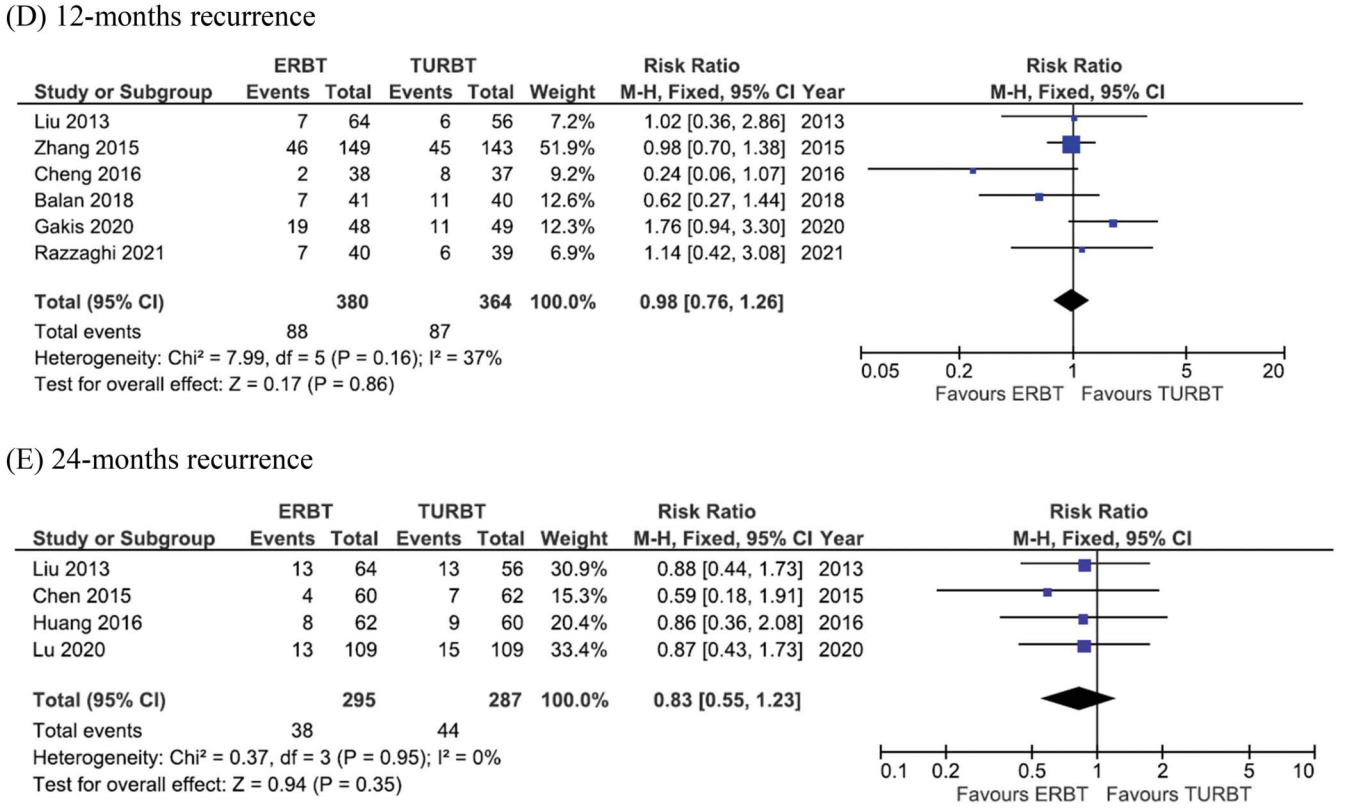


Figure 2. Continued

The probability of surgical margin diagnosis. One RCT and 2 observational studies provided data on the rate of surgical margin diagnosis of ERBT.[11,29,51] Pooled rates of surgical margin diagnosis in ERBT specimen were 85% (191/224). On the other hand, in some cases the cTURBT specimen allowed evaluation of the surgical margin, specifically vertical margins. Pooled rates of surgical margin diagnosis in cTURBT specimens were 8.7% (13/150).[11,51] An observational study of 140 NMIBC patients who underwent ERBT, which evaluated the horizontal and vertical margins, reported that the rate of horizontal margins and vertical margins were 63% and 99%, respectively.[51]

Probability of Any Residual Tumor at reTUR

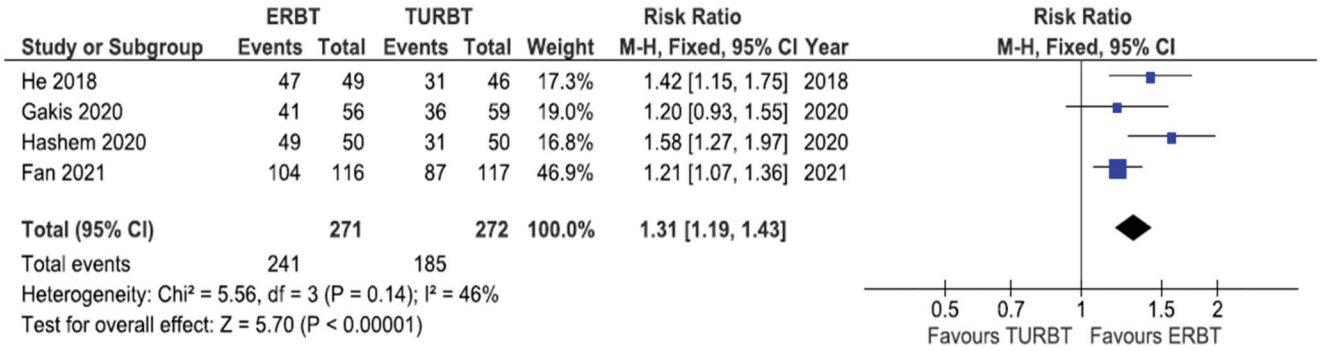
Four studies including 401 patients provided data for evaluating any residual tumor at reTUR of ERBT compared to cTURBT. The forest plot revealed that ERBT had a lower residual tumor rate at reTUR than cTURBT (RR: 0.47, 95% CI 0.31 to 0.71, z=3.56; fig. 3, *F*). The Cochrane's Q test ($Chi^2=5.07$; p=0.17) and I^2 test ($I^2=41\%$) revealed no significant heterogeneity. In the subgroup analysis assessing RCT and PSM studies, ERBT also had a lower residual tumor rate at reTUR than cTURBT (RR: 0.46, 95% CI 0.28 to 0.77, z=2.99). The Cochrane's Q test ($Chi^2=2.09$; p=0.15) and I^2 test ($I^2=52\%$) revealed no significant heterogeneity.

DISCUSSION

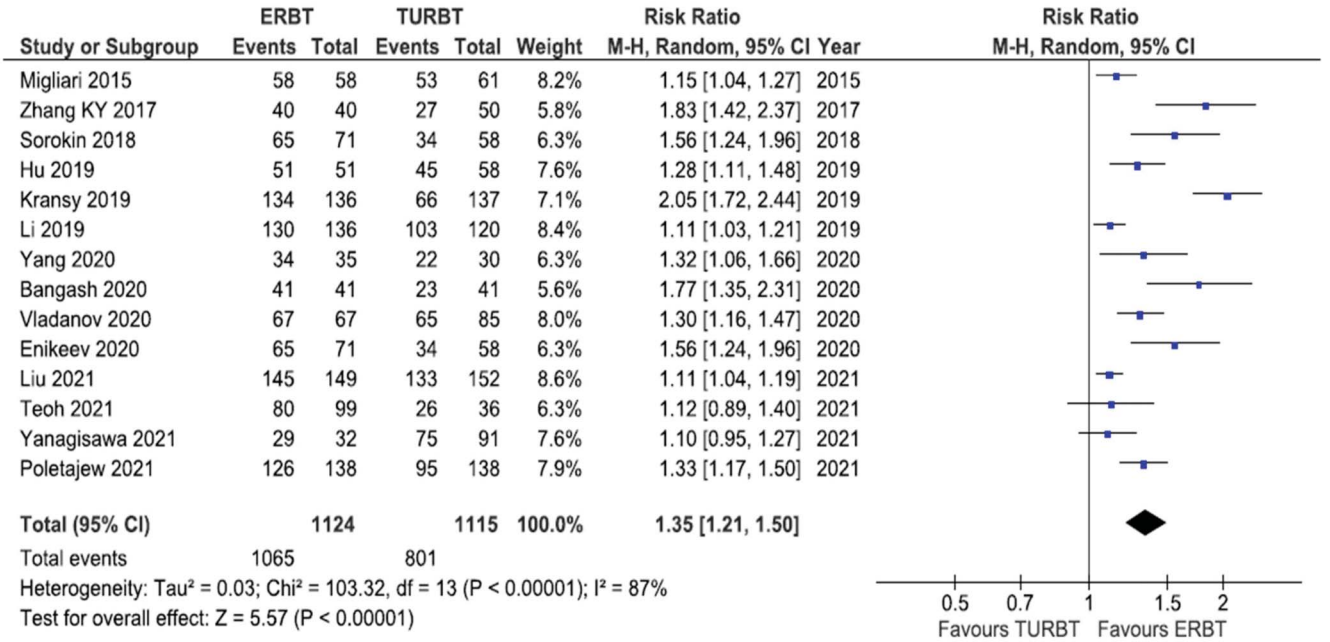
ERBT has been gaining acceptance as there is increasing evidence that it improves the safety and quality of resected specimens of bladder tumors. However, although recent meta-analyses assessed the oncologic benefit of ERBT versus cTURBT, it remains controversial due to selection bias caused by inclusion/analysis of noncontrolled studies.[17–19,21–23] In addition, the pathological utility, which seems to be a potential benefit of ERBT, has not been well assessed or discussed.[17–23] Moreover, as there have been increasing publications regarding this topic, 5 RCTs and 9 observational studies have been published since 2020.[10–12,15,16,25,41,42,45,47,49–52] Thus, we conducted this updated systematic review and meta-analysis of the potential utility of ERBT compared to cTURBT regarding oncologic outcomes only in RCTs and with a focus on its pathological utility.

In this systematic review and meta-analysis, we failed to find any difference in the 12- and 24-month recurrence rates between ERBT and cTURBT based on 13 RCTs. However, ERBT had a better safety profile than cTURBT as it resulted in a lower risk of bladder perforation and a shorter catheterization period. As above, the results of recent meta-analyses of ERBT vs cTURBT were controversial with half of them showing a better recurrence rate for ERBT and the other half not.[17–19,21–23] These

(A) DM presence in RCTs



(B) DM presence in observational

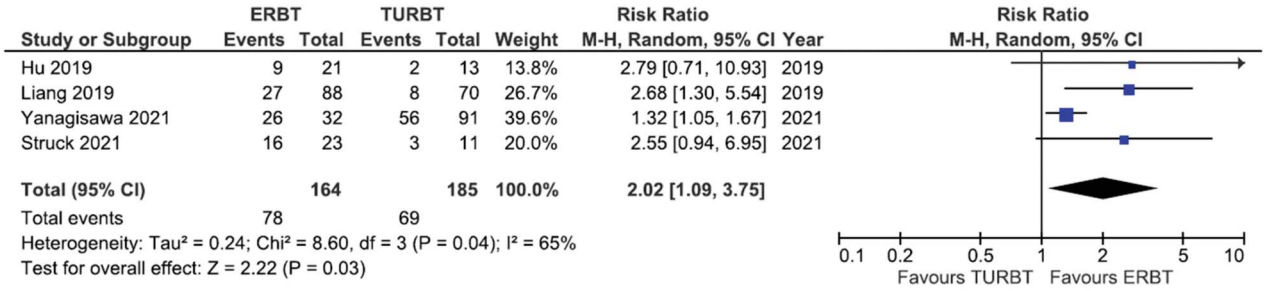


(C) MM detection in RCTs

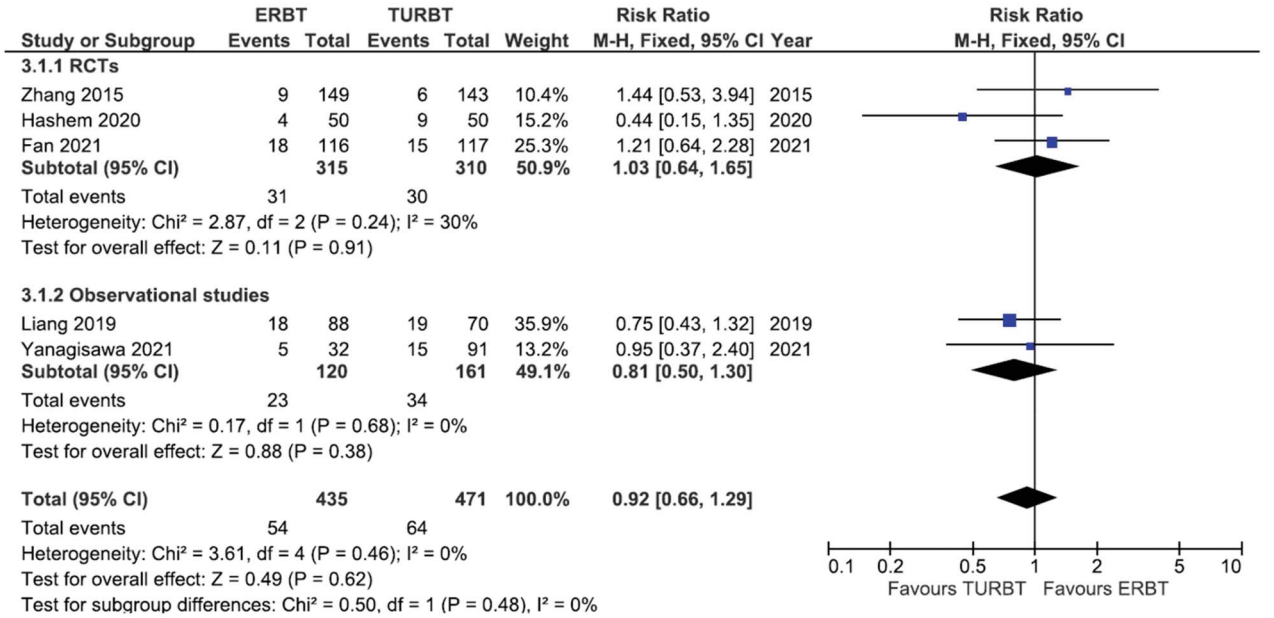
Figure 3. Forest plot; association of pathological and reTUR outcomes with ERBT and cTURBT stratified by quality of studies. *A,* DM presence in RCTs. *B,* DM presence in observational studies. *C,* MM detection in RCTs. *D,* MM detection in observational studies. *E,* concomitant CIS detection. *F,* residual tumor at reTUR. *M-H,* Mantel-Haenszel.

data need to be interpreted with care, owing to limitations regarding the retrospective and non-randomized nature of the majority of primary data.[17–19,21–23] On the other hand, the feasibility and safety of ERBT has reached widespread consensus.[17–19,21–23] Several prospective RCTs

(D) MM detection in observational studies



(E) Concomitant CIS detection



(F) Residual tumor at reTUR

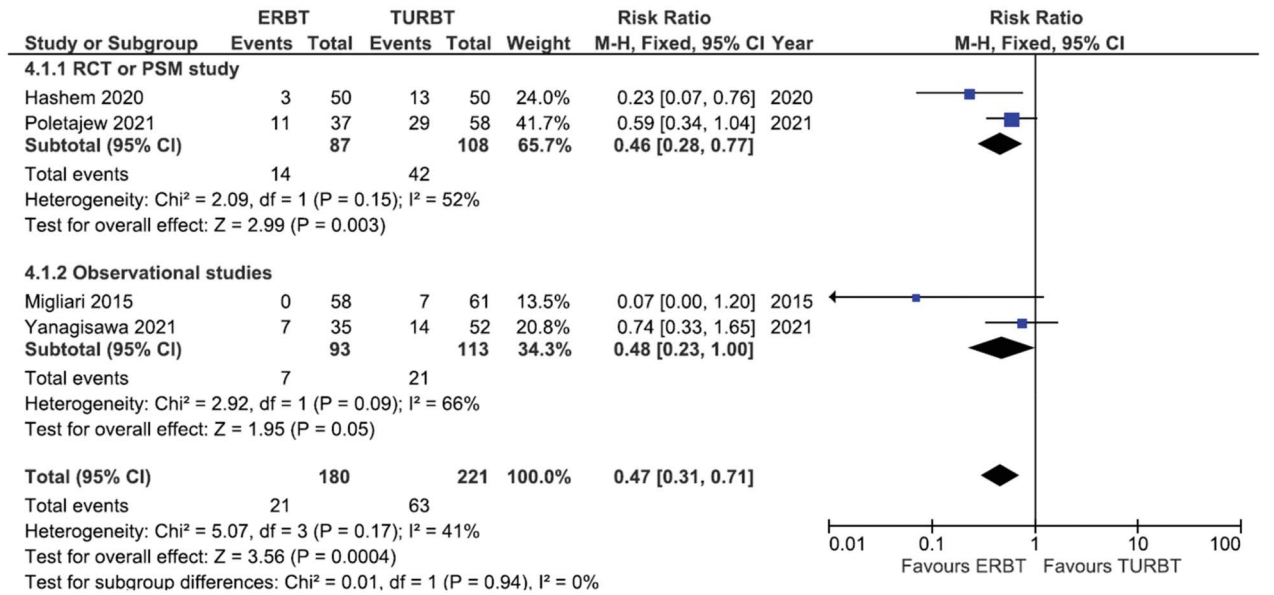


Figure 3. Continued.

reported on the absence of obturator nerve reflex during ERBT particularly using laser and the consequently low risk of bladder perforation.[9,10,12,14–16,39,54] This, together with the supposed precision dissection of ERBT, is likely the explanation for the shorter catheterization and shorter hospitalization periods compared to cTURBT.[14–16,36,39]

Conventional TURBT is the standard for diagnosis and initial therapy of bladder cancer; it has, however, several serious drawbacks that break with the principles of cancer surgery and are associated with worse pathological evaluation.[4] Conventional resection reduces the quality of specimens due to the fragmentation of the specimen and the thermal artifacts causing a lack of spatial orientation and preventing accurate evaluation of pathological stage and histological grade.[55] ERBT was developed to overcome these limitations and is expected to improve the pathological diagnostic accuracy.[5,6] Liu et al, for example, reported that pathological stage could not be defined in 15% of cTURBT patients compared to only 3% of ERBT patients.[45]

In this systematic review and meta-analysis we found that ERBT was associated with a higher DM presence rate, higher MM detectable rate and higher surgical margin diagnostic rate compared to cTURBT. The presence or absence of DM in tumor specimens is a key indicator for the quality and completeness of transurethral tumor resection.[56] DM presence is necessary to ensure adequate staging; it ensures a lower rate of under staging, recurrence and progression.[42,57,58] To ensure adequate sample acquisition, energy sources such as bipolar, holmium and thulium laser for hemostatic control have been tested successfully. Good hemostasis is one of the criteria necessary to ensure good vision in order to achieve precise dissection with lamina propria and superficial muscle layers.[59,60]

We further found that ERBT seems to improve the MM detectable rate in the specimen. This leads to more accurate T1 sub-staging diagnosis which in turn leads to more reliable prediction for recurrence and progression.[12,51] Previous studies have shown that the T1a/b/c sub-staging could predict cancer recurrence and progression.[61] However, such sub-staging has not been widely used in clinical practice because MM is difficult to identify in fragmented and/or cauterized specimens and has a discontinuous nature. Furthermore, disorientation and tangential section plane render the morphological distinction between muscularis propria and MM difficult.[62]

Based on principles of cancer surgery in the gastrointestinal fields, pathological evaluation such as horizontal and vertical margins of specimens is material factor whether complete resection has been achieved.[63,64] Pathological evaluation of horizontal and vertical margins of specimens is a material factor in whether complete resection has been achieved. However, numerous studies did not report the rate of positive surgical margins.[11,12,46] Surgical margin diagnostic rate was 63% to 95% in our included studies.[11,29,51] In our previous study, the vertical margin could be diagnosed almost 100% of cases, but horizontal margin diagnosis was difficult mainly owing to exfoliation and/or cauterization damage of the end of the mucosa.[27] Moreover, the clinical significance of surgical margin positivity has not been well discussed. Gakis et al showed that patients who underwent ERBT with surgical margin negative were associated with less intravesical recurrence, leading to favorable 12-month recurrence-free survival (RFS).[11] On the other hand, we previously showed that horizontal margin status was not associated with 2-year RFS.[27] Furthermore, surgical margin diagnosis has potential issues with specimen processing. Whether the circumferential mucosal edge should be pinned or whether peripheral and vertical margins should be inked for better orientation and better histological assessment is still discussed.[20] Further accurate definitions of surgical margin diagnosis and specimen processing are needed, specifically in the age of ERBT.

In addition to the pathological diagnostic benefits, we found that ERBT results in a lower residual tumor rate at reTUR compared to cTURBT. This suggests that ERBT leads to more complete resection of the initial tumor. Soria et al researched 4 large medical centers on 300 pT1 high-grade patients, which showed that *en bloc* resection is a reliable predictor of no residual tumor at reTUR.[58] Zhou et al conducted a retrospective observational study on 251 NMIBC patients, demonstrating no significant difference in recurrence and progression between the reTUR group and the observation group in NMIBC patients who underwent ERBT.[65] In addition, according to our previous study both horizontal and vertical margin negative pT1 patients revealed no residual tumor at reTUR.[27] ReTUR is strongly recommended for pT1 bladder cancer owing to possibility of residual tumor detection or tumor under staging, despite that there is no RCT to assess the impact of reTUR on oncologic outcome.[1] We hypothesize that accurate pathological diagnosis with ERBT enables avoidance of unnecessary reTUR in well-selected patients treated with ERBT.[65]

We found no statistical difference in the diagnostic rate of concomitant CIS detectable between ERBT and cTURBT. Only 1 RCT evaluated lymphovascular invasion (LVI) rate, which showed 10% in the ERBT and 22% in the cTURBT groups.[12] Theoretically, the

diagnostic convenience of LVI is in favor in ERBT specimens; however, given the low rate of LVI in NMIBC, this is unlikely to be accurately assessable due to the necessity of large cohorts.

This study has several limitations that need to be taken into account. First, reporting bias could have led to the nonpublication of negative results. Then, the ERBT procedure itself suffers from technical limitations. ERBT is applied for bladder tumors with a small, not multifocal and limited location. Thus, this study design did not reflect all of NMIBC patients. In addition, there has been gaining acceptance of enhanced cystoscopy such as photodynamic diagnosis; however, although some studies applied this technique, the potential utility of enhanced cystoscopy combined with ERBT is not assessed. Although only RCTs were included for analysis of clinical outcomes, heterogeneity was detected in the analysis of operation time and catheterization periods. These results might be affected by the surgeon's experience, institutional principle and volume. Furthermore, we analyzed pathological outcomes in RCTs and observational studies separately to minimize the heterogeneity. However, heterogeneity was detected in the analysis of the rate of DM presence and detectable MM in observational studies. Sensitivity analyses suggested that some included studies with low quality of cTURBT, less than 70% in DM presence, were the possible source of heterogeneity (data not shown). Regarding the results of MM detection rate, 1 study, which evaluated sub-staging among only pT1 patients by a single genitourinary pathologist, showed a high rate of detectable MM in cTURBT specimens and thus caused heterogeneity. Although the random effect model was used to address heterogeneity among the evaluated studies, these results should be interpreted with care. In addition, as previously mentioned, some included RCTs suffered from a high risk of bias. Moreover, most RCTs were conducted in China; thus, the generalizability of analyzed results might be limited. Finally, regarding oncologic outcomes, most RCTs set the recurrence rate at a fixed timing (eg 12 or 24 months) as a primary endpoint, not reporting HR on RFS. Therefore, further well-designed RCTs are awaited to conclude robust, reliable oncologic outcomes.

CONCLUSIONS

This systematic review and meta-analysis suggested that ERBT is safer than cTURBT. However, there was no statistical difference in the recurrence rate of cTURBT and ERBT. On the other hand, ERBT was associated with a higher rate of DM presence and MM detection, leading to more accurate pathological diagnosis for NMIBC and improving risk stratification. Furthermore, we found that ERBT resulted in a lower residual tumor rate at reTUR than cTURBT, suggesting a lower likelihood of reTUR benefit in well-selected ERBT patients. Further investigation is mandatory to explore the pathological evaluation of ERBT specimens to better dissect the benefits underlying this technique and help guide clinical decision making.

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