Comparison of the Safety and efficacy of enucleation of nonmuscle-invasive bladder cancer versus transurethral resection of nonmuscle-invasive bladder cancer: a systematic review and meta-analysis

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Abstract

Purpose: Transurethral resection of bladder tumor (TURBT) via a wire loop has been regarded as a standard procedure dealing with nonmuscle-invasive bladder cancer (NMIBC) for a long time, and en-bloc resection of bladder tumors (ERBT) is a promising alternative to conventional transurethral resection of bladder tumor. A few studies assessing the two techniques were reported. The objective of our study is to review the published literature and compare en-bloc resection for non-muscle-invasive bladder cancer (NMIBC) with conventional transurethral resection of bladder tumor (TURBT) in terms of safety and efficacy.

Methods: We performed a systematic review and meta-analysis based on randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) and some retrospective studies which were searched and screened. A systematic search up to the 1st of March 2019 was conducted in the following databases: PubMed, Web of Science, the Cochrane Central Register of Controlled Trials and Embase. Data such as resection techniques, morbidity, specimens' quality, and recurrence were collected from the manuscripts.

Results: Sixteen studies were included in this systematic review finally. No statistical difference is detected between the two techniques regarding operative time, the 2-year recurrence-free survival and the occurrence of ureterostenosis. Analysis of some complications showed that ERBT was better than TURBT for NMIBC, including obturator nerve reflex, cystic stimulation rate, bladder perforation, operation time, duration of catheterization, postoperation duration of postoperation bladder irritation and length of hospital stay. In addition, detrusor miss rate is lower in ERBT group, the 1-year and 3-year recurrence-free survival improved in the ERBT group than in the TURBT group.

Conclusions: This systematic review and meta-analysis suggests that ERBT technique is a feasible, safe procedure that may provide an alternative treatment for NMIBC.

Introduction

Bladder cancer is the ninth most common cancer and the fourteenth lethal cancer worldwide^[1]. It is defined as an international public health problem for high recurrence rate, high economic costs and high mortality^[2]. Approximately 75% of patients diagnosed bladder cancer present with non-muscle-invasive bladder cancer (NMIBC), including mucosa (Ta), submucosa (T1) and carcinoma in situ^[3]. A standard procedure of non-muscle-invasive bladder cancer is transurethral resection of bladder tumor (TURBT), and it's necessary, however, to improve the performance of TURBT because of the residual tumor rates (up to 33%) and recurrence rates (up to 75%) after TURBT^[4]. With the technological advances achieved in endourology, technique of en-bloc resection of bladder tumors (ERBT) is popularized and mastered by clinicians gradually since its first report by Ukai and colleagues in 2000^[5]. Two decades witnessed the publication of several literatures pertaining to this very technique by using various instruments. However, it still remains a matter of debate about the safety and efficacy of ERBT, mainly in that most studies comparing ERBT to TURBT were, instead of RCT, nonrandomized controlled trials (NRCTs) and retrospective studies. In addition, inadequate sample sizes and data obtained from a single center were not capable of providing a convincing conclusion. Consequently, a systematic review and meta-analysis were applied to validate differences between the intraoperative and postoperative situation of both procedures.

Materials And Methods

Literature Search Strategy

Literature was searched by two reviewers (Ting Huang and Qing Yang) independently up to 21st March 2019. We searched Web of Science, the Cochrane Central Register of Controlled Trials and Embase without publication date restrictions. The article language was restricted to English. The following search terms and words were used: “bladder tumor”, “bladder cancer”, “bladder carcinoma”, “transurethral resection”, “TURBT”, “resection of bladder tumor”, “resection of bladder tumor”, “en bloc resection” and “enucleation”.

Inclusion and Exclusion Criteria

Studies were included only if the following criteria were fulfilled: (1) studies that compared the safety and efficacy of ERBT with traditional TURBT in adult patients diagnosed as non-muscle-invasive bladder cancer; (2) the study was an RCT or a controlled clinical trial, including nRCT and retrospective studies; (3) the primary outcomes of retrospective studies were reported include complications, duration of catheterization, hospital stay, recurrence rate, detrusor mass rate, and at least three of the primary outcomes were included.

The exclusion criteria were as follows: (1) studies that did not compare ERBT with traditional TURBT; (2) The study was not an RCT or CCT; (3) studies that cannot find full text or did not provide the sufficient date.

Data extraction and outcome of interest

After being reviewed by two searchers (Ting Huang and Qing Yang), data wanted from these studies was extracted and filled into a specifically designed form including studies and population characteristics, surgery techniques, complications, duration of catheterization, hospital stay, recurrence rate, methodological quality and other relevant information. We also managed to contact the authors to obtain unpublished data. When there was a disagreement between the two researchers, a third researcher (Haixiao Wu) will participate in a discussion about the divergence until a consensus was achieved.

Assessment of Quality and Risk of Bias

Two authors (Ting Huang and Qing Yang) assessed the quality of the included literatures according to the type of research. As to RCTs, the Cochrane Collaboration’s risk of bias tool[6] was used to evaluate literatures according to the following items: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other biases. Each item was assigned a risk value (i.e., low risk, high risk, or uncertain). As to nRCTs and retrospective studies, the Newcastle-Ottawa Quality Assessment Scale[7] was used to evaluate literatures, which is consist of three parts: patient selection, comparability of the study groups, and assessment of outcomes. We get a final score of each study then evaluated the quality of the studies in accordance with the final score: 7–9 is considered as “good”, 4–6 is considered as “fair”, 0–4 is considered as “poor”. Similarly, any divergence was resolved by discussion until consensus was achieved.

Statistical Analysis

Statistical analysis was conducted using Stata 14.0. The odds ratio (OR) was used for dichotomous variables, and mean difference (MD) was used for continuous data, both with 95% confidence intervals (CI). Methodological heterogeneity was assessed during selection, and statistical heterogeneity was measured using the χ^2 test and I^2 scores. If χ^2 heterogeneity was reported as $P > 0.1$ and $I^2 < 50\%$, heterogeneity was considered low. A fixed-effects model was used to assess the data of included studies with minimal or no heterogeneity while a random-effects model was applied. A P-value for significance was set at <0.05 . In addition, RevMan5.3 was used for assessing the quality of RCTs.

Results

Search Results

854 publications were screened after a systematic search. 404 publications were removed as duplicates, then 364 publications were removed after screening the titles and abstracts. 50 full-text were screened out, including 34 were review articles. 16 literatures were finally screened out after removing 3 publications lacking of sufficient data. We described the study procedure's details in Figure 1.

Study Characteristics

A total of 16 trials with 2262 participants were included, of which 1147 and 1115 underwent ERBT and TURBT respectively. The enrolled individuals and tumor characteristics are presented in Table 1^[8-23]. The result of our research are based on the prospective studies and retrospective studies are only for reference as few data was available in RCTs, so subgroup analysis stratified by research categories is completed and our conclusions are made based on the prospective studies. Risk of bias are assessed by the Cochrane Collaboration's risk of bias tool^[6] in RCTs (Figure 2). The Newcastle-Ottawa Quality Assessment Scale^[7] was used to evaluate the quality of nRCTs and retrospective studies, most researches scored 7 except two researches scored 6

The data of outcome of interest

We enumerated main outcomes of complications, perioperative and postoperative data extracted from included articles in Table 2. The result of our research are based on the prospective studies and retrospective studies that are only for reference as prospective data was limited. No statistical difference was found on operation duration between ERBT and TURBT for NMIBC (WMD = -0.173 , 95% CI [$-0.533, 0.186$], $P = 0.345$) (Figure 3). Significant differences were noted for the catheterization duration (WMD = -2.773 , 95% CI [$-3.169, -2.374$], $P < 0.001$) (Figure 3), hospitalization time (WMD = -2.142 , 95% CI [$-3.940, -0.344$], $P = 0.02$) (Figure 3), duration of postoperation bladder irritation (WMD = -3.627 , 95% CI [$-4.120, -3.134$], $P < 0.001$) (Figure 3), obturator nerve reflex (OR = 0.072 , 95% CI [$0.028, 0.186$], $P < 0.001$) (Figure 4), bladder irritation rate (OR = 0.382 , 95% CI [$0.167, 0.874$], $P = 0.023$) (Figure 4), bladder perforation (OR = 0.165 , 95% CI [$0.038, 0.720$], $P = 0.016$) (Figure 4), while no statistical difference was noted for ureterostenosis (OR = 0.698 , 95% CI [$0.230, 2.124$], $P = 0.527$) (Figure 4). In addition, detrusor present rate is higher in ERBT group (OR = 1.269 , 95% CI [$1.062, 1.518$], $P = 0.009$) (Figure 5). The 1-year (OR = 0.565 , 95% CI [$0.336, 0.952$], $P = 0.032$) and 3-year recurrence rate (OR = 0.754 , 95% CI [$0.610, 0.933$], $P = 0.009$) improved in the ERBT group compared to that in

the TURBT group but no statistical difference was detected for 2-year recurrence-free survival (OR = 0.577, 95% CI [0.307,1.085], P = 0.088) (Figure 6). Four items(operation time,hospitalization time, detrusor present, obturator nerve reflex) exhibited heterogeneity,so we repeated the sensitivity analysis for these studies and obtained similar results in there items(operation time,hospitalization time, detrusor present) which using a random-effects model. Meanwhile, bias was found in sensitivity analysis for obturator nerve reflex,we repeated meta analysis after picking out a study where bias had a great impact on the results,then we get a homogeneous result. After reading the excluded study carefully,we found some mixed surgical techniques were used in ERBT group,and it probably impact the result of the study in obturator nerve reflex.

Discussion

Bladder carcinoma is the most common malignancy of the urinary tract. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for men and 2.5 per 100,000 for women ^[24]. Although most patients present with non-muscle invasive bladder cancer (NMIBC) (70%), formerly known as superficial bladder cancer which is confined to either the mucosa (stage Ta, carcinoma in situ) or submucosa (stage T1), the high rate of recurrence and long-term monitoring cost much both physically and financially^[25]. All mainstream guidelines including guidelines published by American Urological Association(AUA), European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN) recommend TURBT as the gold standard for the initial diagnosis and treatment of NMIBC^[26], and repeat TURBT 2 to 6 weeks after the initial procedure is recommended in patients with high grade T1 tumors, incomplete initial resection or when the specimen contained no muscle tissue^[27]. Gontero^[28] have shown in a recent study with more than 2000 patients that the most important parameter associated with recurrence-free survival was the detection of detrusor muscle (DM) within the tissue. The authors stated that second resection may be avoided in the presence of DM in high-risk NMIBC. As a matter of fact, a recent retrospective study demonstrated that 70% of included patients had an incomplete initial resection^[29]. Complete resection including a sample of the underlying muscularis propria is recommended by the guidelines of the European Association of Urology (EAU) and American Urological Association (AUA) ^[30,31]. In order to achieve this goal, appropriate resection techniques were developed and applied in recent decades, including bipolar TURB, photodynamic diagnosis, Narrow band imaging (NBI), Confocal laser endomicroscopy (CLE) and so on. ERBT technique is popularized and mastered by clinicians gradually since it was first reported by Ukai in 2000^[5].

The feasibility and Safety of en bloc resection has been demonstrated by several researchers. Herrmann^[32] confirm the hypothesized potential of ERBT as a concept to overcome limitations of cTURBT with regard to reproducibility of surgical result and limitations of pathological staging in cTURBT specimen. Rohit Upadhyay^[33] reported that en-bloc TURBT was safe and gave well-controlled resection of the whole tumor due to better visualization. Yield of detrusor muscle present in the specimen is significantly better with en-bloc TURBT. However, there are some limitations of ERBT like the size and location of the lesion. Bach T deemed roughly 30% of patients are not eligible because of tumor size, formation, and localization^[34]. Few surgeons favor ERBT in cases when tumors are located at the anterior and posterior bladder wall, at the bladder cervix, and when tumors exceed the size of 3 cm^[35]. EAU outlined this resection techniques depending on the size of the lesion^[27]. Many researchers consider that small tumors can be resected by en bloc and larger tumors

should be resected separately in fractions^[36]. Naselli A^[37] concluded that irrespective of the equipment, it was possible to resect the tumor without fragmentation lesions of 4–5 cm whereas the biggest lesion ever treated successfully was 7 cm^[38]. Surgeons may master the characteristics of lesions by different kinds of imaging checkups or cystoscopy and assess whether it's suitable for enucleation and make an operative planning before the surgery. In the 7 prospective studies included, no statistically significant differences were found in tumor size or tumor multiplicity between ERBT group and TURBT group except for tumor size limitation in research of Sureka SK^[9].

Our review of the published data of sixteen comparative studies (seven prospective studies and nine retrospective studies) suggested that ERBT was better than conventional TURBT group for NMIBC in following aspects: catheterization time, hospitalization time and the duration of postoperation bladder irritation are shorter in ERBT group than TURBT group. In addition, the incidence rate of obturator nerve reflex, bladder irritation, bladder perforation is significantly lower in ERBT group. No statistical difference was noted for ureterostenosis rate and the 2-year recurrence-free survival. It is worth mentioning that the detrusor present rate is significantly higher in ERBT group which means specimens of higher quality can get by this technique. And the 1-year and 3-year recurrence-free survival improved in the ERBT group than in the TURBT group. In conclusion, ERBT may decrease the incidence rate of common complication and increase the quality of specimens and recurrence-free survival. The outcomes may related with the procedures of ERBT, surgeons commonly made a circular incision around the tumor at first, this procedure can cut off blood supply to local mucosa and provide a clearer view for the surgery, so that a specific histrionic layer can be recognized which is the major procedure of ERBT. Finding the accurate layer can avoid bladder perforation effectively and ensuring the presence of detrusors. Blunt separation and dot cutting to the basis of lesions decreased the risk of obturator nerve reflex which is closely related to bladder perforation. Based on the advantages of hemostasis and the mastery to surgical wounds, catheterization time, hospitalization time and the duration of postoperation bladder irritation are shortened in ERBT group. Long-term and near-term cost are both mitigated.

The nature of surgical research limited the blinding of the participants and personnel in the RCTs, resulting in an increased risk of bias. Moreover, most of our included articles were single center studies, which may have limited the generalization and significance of our results. Therefore, further high-quality and multicenter RCTs are needed to draw stronger conclusions.

Conclusions

The latest studies confirm potential of ERBT as a concept to overcome limitations of cTURBT. Although data on longer follow-up are available now, no final conclusion on recurrence can be drawn, our study integrated the date and get a systematic conclusion that ERBT technique is a feasible, safe procedures that may provide an alternative treatment for NMIBC. With the technological progress and innovation, the limitations of the size and location to ERBT may be overcome and the technique translates in to daily clinical practice.

Declarations

Conflict of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Abbreviations

Transurethral resection of bladder tumor (TURBT)

nonmuscle-invasive bladder cancer (NMIBC)

en-bloc resection of bladder tumors (ERBT)

randomized controlled trials (RCTs)

non-randomized controlled trials(nRCTs)

clinical controlled trials(CCT)

American Urological Association(AUA)

European Association of Urology (EAU)

National Comprehensive Cancer Network (NCCN)

detrusor muscle (DM)

narrow band imaging (NBI)

confocal laser endomicroscopy (CLE)

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Tables

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

Table 2 The outcomes of complications and perioperative data

outcome of interest	No. of studies	OR/WMD(95%CI)		P	heterogeneity		
					df	I ²	P
Operation time	4	-0.173	[-0.533,0.186]	0.345	3	72.40%	0.012
Catheterization time	2	-2.773	[-3.169,-2.374]	<0.001	1	0.00%	0.397
Hospitalization time	3	-2.142	[-3.940,-0.344]	0.02	3	98.40%	<0.001
Bladder irritation time	2	-3.627	[-4.120,-3.134]	<0.001	1	0.00%	0.826
Obturator nerve reflex	6	0.072	[0.028,0.186]	<0.001	5	4.50%	0.388
Bladder perforation	4	0.165	[0.038,0.720]	0.016	3	0.00%	0.939
ureterostenosis	3	0.698	[0.230,2.124]	0.527	2	0.00%	0.642
Bladder irritation	2	0.382	[0.167,0.874]	0.023	1	0.00%	0.621
Detrusor present	4	1.269	[1.062,1.518]	0.009	3	80.60%	0.001
1-year-recurrence	5	0.565	[0.336,0.952]	0.032	4	0.00%	0.625
2-year-recurrence	2	0.577	[0.307,1.085]	0.088	1	0.00%	0.724
3-year-recurrence	5	0.754	[0.610,0.933]	0.009	4	0.00%	0.797

Figures

Figure 1

Diagram of studies identified, included and excluded.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
H Liu 2013
Xin-Ru Zhang 2015
Xu Chen 2015

Figure 2

Quality assessment. Chart summarizes our judgments about each risk of bias item for each included RCT study.

Figure 3

Operation time:ERBT VS TURBT

Figure 4

Catheterization time:ERBT VS TURBT

Figure 5

Hospitalization time:ERBT VS TURBT

Figure 6

Duration of postoperation bladder irritation:ERBT VS TURBT

Figure 7

Obturator nerve reflex:ERBT VS TURBT

Figure 8

Bladder irritation:ERBT VS TURBT

Figure 9

Bladder perforation:ERBT VS TURBT

Figure 10

Ureterostenosis:ERBT VS TURBT

Figure 11

Detrusor present rate:ERBT VS TURBT

Figure 12

Figure 12.1-year recurrence rate:ERBT VS TURBT

Figure 13

Figure 13.3-year recurrence rate:ERBT VS TURBT

Figure 14

Figure 14.2-year recurrence rate:ERBT VS TURBT