

Title: An International Collaborative Consensus Statement on En Bloc Resection of Bladder Tumour Incorporating Two Systematic Reviews, a Two-round Delphi Survey and a Consensus Meeting.

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Abstract

Background

There has been increasing interest in en bloc resection of bladder tumour (ERBT) as an oncologically non-inferior alternative to transurethral resection of bladder tumour (TURBT) with fewer complications and better histology specimens. However, there is a lack of robust randomised controlled trial (RCT) data for making recommendations.

Objective

We aimed to develop a consensus statement to standardise various aspects of ERBT for clinical practice and to guide future research.

Design, Setting and Participants

We developed the consensus statement on ERBT using a modified Delphi method. First, two systematic reviews were performed to investigate the clinical effectiveness of ERBT versus TURBT (effectiveness review), and to identify areas of uncertainty in ERBT (uncertainties review). Next, 200 health care professionals (urologists, oncologists and pathologists) with experience in ERBT were invited to complete a two-round Delphi survey. Finally, a 16-member consensus panel meeting was held to review, discuss and re-vote on the statements as appropriate.

Outcome Measurements and Statistical Analysis

Meta-analyses were performed for RCT data in the effectiveness review. Consensus statements were developed from the uncertainties review. Consensus was defined as: (1) $\geq 70\%$ scoring a statement 7-9 AND $\leq 15\%$ scoring the statement 1-3 (consensus agree); OR (2) $\geq 70\%$ scoring a statement 1-3 AND $\leq 15\%$ scoring the statement 7-9 (consensus disagree).

Results and Limitations

A total of 10 RCTs were identified upon systematic review. ERBT had a shorter irrigation time (mean difference -7.24 hours, 95% CI -9.29 - -5.20, $I^2=85\%$, $p<0.001$) and lower rate of bladder perforation (Risk ratio [RR] 0.30, 95% CI 0.11-0.83, $I^2=1\%$, $p=0.02$) than TURBT, both with moderate certainty of evidence. There were no significant differences in recurrences at 0-12 months, 13-24 months or 25-36 months (all very low certainty of evidence). A total of 103 statements were developed and 99

of them reached consensus. In summary: ERBT should always be considered for treating non-muscle-invasive bladder cancer; ERBT should be considered feasible even for bladder tumours larger than 3cm; Number and location of bladder tumours are not major limitations in performing ERBT; The planned circumferential margin should be at least 5mm from any visible bladder tumour; After ERBT, additional biopsy of the tumour edge or tumour base should not be performed routinely; For the ERBT specimen, T1 substage, circumferential and deep resection margins must be assessed; It is safe to give single-dose of immediate intravesical chemotherapy, to perform second look transurethral resection, and to give intravesical BCG therapy after ERBT; In studies of ERBT, both per patient and per tumour analysis should be performed for different outcomes as appropriate. Important outcomes for future ERBT studies were also identified. A limitation is that as consensus statements are brief, concise and binary in nature, areas of uncertainty which are complex in nature may not be addressed adequately.

Conclusions

We have provided the most comprehensive review of the evidence base to date with meta-analysis where appropriate and GRADE applied, and mobilized the international urology community to develop a consensus statement on ERBT using transparent and robust methods. The consensus statement will provide interim guidance for health care professionals who practice ERBT and inform researchers on ERBT-related studies in the future.

Patient summary

ERBT is a surgical technique aiming to resect the bladder tumour in one piece. We included an international panel of experts to agree on the best practice of ERBT, and this will provide guidance to clinicians and researchers in the future.

1. Introduction

En bloc resection of bladder tumour (ERBT) was first described by Kitamura *et al.* in 1980 [1]. ERBT has three potential benefits in treating non-muscle-invasive bladder cancer (NMIBC) when compared to conventional transurethral resection of bladder tumour (TURBT). First, bladder tumour is resected in one piece and the tumour specimen remains intact for a proper histological assessment. Whether a complete resection has been achieved can be ascertained by histological means rather than the surgeon's judgment alone. Second, the resection process is more precise and controlled, thus the complication profile, in particular the risk of bladder perforation may be reduced. Third, ERBT can avoid tumour fragmentation as in the case of conventional piecemeal resection. It can potentially minimize the amount of floating tumour cells and reduce the risk of tumour re-implantation.

ERBT upholds the basic principles in cancer surgery and it has gained increasing interests globally in the past decade. However, high-quality data is limited to make robust recommendations. There is a lack of standardization leading to heterogeneity in the clinical and technical aspects of ERBT. It is important to develop a consensus statement on ERBT that can serve as a standard reference for health care professionals in the future. It will have important implications in our clinical practice as well as future studies of ERBT.

2. Material and methods

We developed the consensus statement on ERBT using a modified Delphi method. The development process included two systematic reviews, a two-round Delphi survey and a face-to-face consensus meeting (Fig.1).

2.1. Systematic reviews

Two systematic reviews were performed according to the PRISMA guidelines [2] and the study protocol was registered on PROSPERO [3]. The ‘effectiveness’ review assessed the benefits and harms of ERBT compared to conventional TURBT and provided certainty of evidence ratings using the GRADE methodology [4,5]. The ‘uncertainties’ review identified clinical and technical uncertainties in the area of ERBT. The findings of the systematic reviews provided the basis for the statements developed for voting in the Delphi survey and consensus meeting.

2.1.1. Search strategy

A comprehensive literature search to encompass the effectiveness and uncertainties reviews was performed using combination of keywords (MeSH terms and free text words) related to ‘bladder tumor’, and ‘en bloc resection’/ ‘ERBT’. MEDLINE, EMBASE, and Cochrane library (CENTRAL and CDSR) were searched. The search strategy was presented in Appendix 1. Additional references were sought from the reference lists of the included studies.

2.1.2. Types of studies included

All randomized and non-randomized comparative studies, reported in journals or conference proceedings, were included in the effectiveness review. Single-arm case series or case reports were excluded from the effectiveness review but were retained for the uncertainties review. There was no cut-off date for the literature search. Only articles with English texts were included. Conference proceedings, letters to editors, commentaries and international guidelines were included in the uncertainties review.

2.1.3. Assessment of risk of bias

For the effectiveness review, the risk of bias in RCTs was assessed by using the recommended tool in the Cochrane Handbook for Systematic Reviews of Intervention [6]. Risk of bias in non-randomised comparative studies was assessed with the same

tool, with an extra item to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to assessing risk of bias in non-randomised studies, and it is the approach adopted in systematic reviews commissioned by the EAU guidelines office to inform their guidelines [7].

2.1.4. Data synthesis and statistical analysis

For the effectiveness review, meta-analysis was performed if there were two or more RCTs reporting on the same outcome. [Data from RCT conference proceedings were included to reduce the risk of publication bias](#) [6]. Reports of the same studies were linked together, where the report containing the most complete data and longest follow-up were used. Relative risk (RR) and its 95% confidence interval (CI) were used to summarise statistic dichotomous data. Mean differences were used to summarise continuous data. Some clinical and methodological heterogeneity across the studies was suspected and therefore a random effects model was used. Narrative synthesis, using the methods outlined in the Centre for Reviews and Dissemination handbook, were used to synthesize the results from non-randomised studies [8]. [Results from non-randomised studies were not included in the quantitative analysis, as there may be significant selection bias especially in the context of ERBT.](#) Application of GRADE certainty of evidence was done in accordance with the GRADE handbook [9].

For the uncertainties review, areas of uncertainties in ERBT were extracted verbatim from any of the studies or sources meeting inclusion criteria. The extracted data were categorised with reference to the usual management pathway, and grouped under domains such as case selection, surgical procedure, post-operative management and follow-up schedule. To reduce the data further, statements relating to the same concept were subsumed within one statement, resulting in a conceptual map of uncertainties identified in the ERBT literature. These statements were then used to create positively worded statements which can be agreed or disagreed with, for inclusion in the Delphi survey. The statements were discussed within the steering group (JYCT, SM, HM, TH, MB) and finalised before proceeding to the Delphi survey.

2.2. Two-round Delphi survey

Delphi survey methods were used to promote anonymity and to control for the influence of dominant voices or perceived authoritative voices, yet still provided controlled feedback to participants [10].

2.2.1. Conduct of the two-round Delphi survey

The two-round Delphi survey was conducted using DelphiManager [11]. A total of 200 urologists, oncologists and pathologists involved in the field of ERBT were purposively sampled for expertise and geographical location, to ensure we covered adequate breadth of international experience. The steering group provided the names of known experts in the field. This was supplemented by inviting the authors of studies included in the systematic reviews. Finally, in order to gather opinion from a more general perspective, a Twitter advert was promoted using the hashtags #ERBT and #UroSoMe [12]. Interested individuals were verified to have personal experience in ERBT before they were invited to participate in the online Delphi survey via an email providing a link to the study. The link took them to a webpage providing information about the aims and objectives of the study, with a further link to a registration page. Informed consent was implied if the participant registered to take part.

As ERBT is heavily surgery-oriented, a single heterogeneous panel model was used, as we did not think it is necessary to look for differences across stakeholder groups (i.e. urologists, pathologists and oncologists) [10,13]. Participants were asked to state their strength of agreement on a scale of 1 (Strongly disagree) to 9 (Strongly agree). There was also an 'unable to score' option. Participants were instructed to choose 'unable to score', rather than '5' (neither agree nor disagree) if they felt they did not have enough knowledge or expertise on a particular statement, because these two concepts are qualitatively different. We made this explicit because this phenomenon has been noted as a limitation in other consensus projects [14,15]. During the first round, participants could suggest additional items to be incorporated into the second round of survey (subjected to review by the steering group). Only those who had completed the first-round survey could participate in the second-round survey. In the second round, they were reminded of their own round one score and were shown a distribution of the group scores across the 1-9 scale for each statement. They were

allowed to use this information to consider retaining their previous scores or changing their scores relative to the field. All voting results were anonymous to minimize bias and influence to agree with dominant or authoritative voices.

2.2.2. Definition of consensus and analysis plan

Consensus is defined as: (1) $\geq 70\%$ scoring a statement 7-9 AND $\leq 15\%$ scoring the statement 1-3 (consensus agree); OR (2) $\geq 70\%$ scoring a statement 1-3 AND $\leq 15\%$ scoring the statement 7-9 (consensus disagree). This definition has been used in other urology consensus meetings [14-16] and achieves a balance between being over-inclusive and over-exclusive whilst still allowing a consideration of variance (i.e. spread or divergent opinions) [17].

2.3. Consensus meeting

A consensus meeting was held to review the statements that reached consensus in the Delphi survey, and to discuss in-depth and re-vote on those statements upon which there was no consensus. The consensus panel consisted of 16 members, including 12 urologists, one oncologist, one pathologist, one methodologist (non-voting member) and one patient representative. The meeting was chaired by the methodologist with experience in chairing consensus meetings and no conflicts of interest regarding ERBT. First, the results of the effectiveness review were presented and discussed. Next, the two-round Delphi survey results were discussed. Panel members were provided with a hard-copy overview of the Delphi voting results for both rounds, along with a reminder of their own votes in both rounds. Statements where there was clear consensus were reviewed to ensure the results were sensible. Then statements in which >5 participants had chosen 'unable to score' were reviewed to explore reasons for this. Finally, statements not reaching consensus from the Delphi survey were discussed in depth before anonymous voting using their own smart devices and the Poll Everywhere software [18]. The same consensus definitions were used.

3. Results

3.1 Systematic review and meta-analysis

The PRISMA flow diagram was shown in Fig. 2. The initial search yielded 669 records. After removing duplicates, 430 articles were screened based on title and abstract. For the effectiveness review, 44 articles were reviewed in full-text. At the end of the process, 32 studies (with 39 reports) were included in qualitative synthesis. Among them, 10 were RCTs (with 13 reports) [19-31] and they were included in quantitative analysis. For the uncertainties review, 151 articles were reviewed in full-text and included for generation of consensus statements. The studies included in the uncertainties review were listed in Appendix 1.

Table 1 summarized the study characteristics of the RCTs. Only data from RCTs were extracted for subsequent meta-analysis. Risk of bias assessment of the RCTs was presented in Fig. 3. Study characteristics and risk of bias assessment of the non-randomised studies were presented in Appendix 1. The GRADE summary of findings profiles was included in Appendix 1.

3.1.1. Effectiveness review - Outcome measures from RCTs

ERBT had a longer operative time than TURBT (mean difference 9.07 minutes, 95% CI 3.36-14.79, $I^2=86%$, $p=0.002$; very low certainty evidence). ERBT had a shorter irrigation time than TURBT (mean difference -7.24 hours, 95% CI -9.29 - -5.20, $I^2=85%$, $p<0.001$; moderate certainty evidence), but there were no significant differences in the catheterisation time (mean difference -0.90 days, 95% CI -2.21-0.41, $I^2=97%$, $p=0.18$; low certainty evidence) and hospital stay (mean difference -1.32 days, 95% CI -2.71-0.06, $I^2=97%$, $p=0.06$; low certainty evidence). Although there was no significant difference in the occurrence of obturator nerve reflex (RR 0.19, 95% CI 0.03-1.22, $I^2=79%$, $p=0.08$; very low certainty evidence), ERBT had a lower rate of clinical bladder perforation than TURBT (RR 0.30, 95% CI 0.11-0.83, $I^2=1%$, $p=0.02$; moderate certainty evidence). Presence of detrusor muscle in specimen was similar between ERBT and TURBT (RR 1.11, 95% CI 0.40-3.11, $I^2=77%$, $p=0.84$; very low certainty evidence). There were no significant differences in 0-12 months (RR 0.82, 95% CI 0.56-1.19, $I^2=12%$, $p=0.29$), 13-24 months (RR 0.79, 95% CI 0.44-1.42, $I^2=0%$, $p=0.43$) and 25-36 months (RR 0.89, 95% CI 0.65-1.22, $I^2=47%$, $p=0.47$) recurrence rates (all very low certainty evidence). Data was too

limited for the subgroup comparisons between different modalities of ERBT and TURBT. The key findings of the meta-analysis were summarized in Fig. 4, and other results were summarized in Appendix 1.

3.1.2. Effectiveness review - Outcome measures from non-randomized studies

Most studies showed that ERBT had a shorter irrigation time and lower rate of bladder perforation than TURBT, and this is in line with the RCT data. However, the results on the operative time were controversial. Most studies showed that ERBT had a shorter catheterization time, shorter hospital stay, lower rate of obturator nerve reflex and higher rate of detrusor muscle than TURBT. Most studies also showed lower 0-12 months, 13-24 months and 25-36 months recurrence rates in favour of ERBT. All outcomes were judged to be at low or very low certainty of evidence. The results were summarized in Appendix 1.

3.2. Uncertainties review - Generation of consensus statements

Based on the results of the systematic review, 102 statements were generated for the first-round survey. After the first-round survey, one additional statement was added, resulting in 103 statements in total for the second-round survey.

The statements were grouped under 8 domains as follows.

1. Definitions and objectives of ERBT
2. Case selection
3. Surgical procedure
4. Different modalities of ERBT
5. Reporting of intra-operative findings
6. Specimen preparation and reporting of histological findings
7. Post-operative management and follow-up schedule
8. Data reporting and outcome measures

3.3. Two-round Delphi survey

In the first-round survey, there were 139 respondents out of 200 invitations (69.5%). Among the first-round survey respondents, 123 completed the second-round survey (88.5%). There was a wide coverage of respondents globally, with the majority practising in Europe and Asia. The majority had more than 10 years of clinical

practice. 90.2% were urologists, 6.5% were pathologists and 3.3% were oncologists. This is reflective of the situation that NMIBC is managed mostly by urological surgeons. Table 2 summarizes the characteristics of the Delphi participants completing both rounds of survey. After the two-round Delphi survey, consensus was reached in 88 out of 103 statements (85.4%).

3.4. Consensus panel meeting

Table 3 listed the characteristics of the panel members. After the discussion and re-voting processes, the consensus panel was able to reach consensus in 11 out of 15 statements. Overall, 99 out of 103 statements (96.1%) reached consensus after the whole development process.

3.5. Principal findings of the consensus statement

Table 4 summarized the results of all statements and consensus status after two rounds of survey. Table 5 summarized the statements that were discussed and re-voted, and their consensus status after the voting session. The final results of the consensus statements on ERBT were summarized in Table 6.

3.5.1. Definition and objectives of ERBT

Removal of bladder tumour in one piece [32] is the most appropriate definition for ERBT. The main goals of ERBT are to ensure complete local resection of bladder tumour, to ensure proper local staging of the disease, and to reduce the risk of tumour re-implantation. Upon ERBT, we must aim to include the detrusor muscle layer in the specimen. ERBT should always be considered for treating NMIBC [19,22-26,28-30]. However, in cases of muscle-invasive bladder cancer (MIBC) and carcinoma-in-situ (CIS) of the bladder, ERBT should not be considered [22,25,26,29].

3.5.2. Case selection

3.5.2.1. Size of bladder tumour

Size of bladder tumour is a major limitation in performing ERBT. Most studies used bladder tumour size of 3cm as a cut-off in performing ERBT [19,25,26,33,34]. Upon Delphi survey, it was agreed that ERBT is feasible for bladder tumour size of less than 3cm. For bladder tumour size of more than 3cm, no consensus was reached upon Delphi survey. The panel members agreed that, in such situation, it might be difficult

to extract the specimen in one piece. However, the resection procedure itself is still technically possible [22,29,35-38], and the potential benefits of ensuring proper staging and complete resection of NMIBC can still be preserved. Therefore, the panel members concluded that ERBT should be regarded as a feasible surgical approach even for bladder tumours larger than 3cm.

3.5.2.2. Number of bladder tumours

Number of bladder tumours is not a major limitation in performing ERBT. Most studies used 4 bladder tumours as a cut-off in performing ERBT [39-43]. Upon Delphi survey, it was agreed that ERBT is feasible for patients with less than 4 bladder tumours. For patients with more than 4 bladder tumours, no consensus was reached upon Delphi survey. The panel members agreed that, in such situation, it might take more time and effort to perform ERBT. However, ERBT is still feasible in most of the patients within a reasonable operative time [29,33]. Therefore, the panel members concluded that ERBT should be regarded as a feasible surgical approach even for patients with more than 4 bladder tumours.

3.5.2.3. Tumour location

Tumour location is not a major limitation in performing ERBT. Upon Delphi survey, it was agreed that ERBT is feasible for bladder tumours located at the posterior wall, anterior wall, right lateral wall, left lateral wall, trigone, bladder neck and near the ureteric orifice areas. Although there was no consensus reached for bladder tumours located at the bladder dome upon Delphi survey, there was a 100% consensus in the panel meeting that ERBT is feasible in such tumour location. The panel members concluded that, although bladder dome tumours might be more technically difficult to resect, by allowing more time for resection and with relevant experiences [38,44], ERBT is still a feasible approach in such situations.

3.5.3. Surgical procedure

As bladder cancer changes can be subtle, a thorough cystoscopic examination must be performed before any ERBT [22,34,36,45]. However, the evidence on the use of enhanced imaging (narrow-band imaging, Image 1S or photodynamic diagnosis) is limited especially in the context of ERBT and no consensus was reached in this aspect. The bladder should be distended enough, but not over-distended [29,37], to

facilitate ERBT while avoiding bladder perforation during the procedure. The planned circumferential margin should be marked first to facilitate subsequent ERBT [35,37,44,45], and it should be at least 5mm from any visible bladder tumour [34,36,37]. The depth of incision should be at the detrusor muscle layer [19,22,34,36,37,44,45]. As ERBT specimens can provide comprehensive information regarding the depth of tumour invasion and resection margins [33,35,46-48], additional biopsy of the tumour base and tumour edge should not be routinely performed after ERBT. If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered. If the bladder tumour is too large, after ERBT, dividing the specimen into 2-3 pieces for retrieval [45,49] can be considered. Should there be any technical difficulty being encountered upon ERBT, conversion to conventional TURBT should be considered. Special extraction methods can be considered in retrieving large ERBT specimens [35,49,50].

3.5.4. Different modalities of ERBT

It is technically feasible to use monopolar energy [37,48,49], bipolar energy [19-21,46-48,51], holmium laser [33,48,52], thulium laser [22,29,30,48] and HybridKnife (hydrodissection) [24-27,35] to perform ERBT. Monopolar and bipolar ERBT allow conversion to piecemeal resection readily when technical difficulty arises. Holmium and thulium laser ERBT eliminate the risk of obturator nerve reflex during the procedure [22,29,33,44]. There is however a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation [35,53].

3.5.5. Reporting of intra-operative findings

The EAU guidelines stated that the operative record of conventional TURBT must describe tumour location, appearance, size and multi-focality, all steps of the procedure, as well as extent and completeness of resection [54], and these also apply to ERBT. In addition, the modality used for ERBT, success of ERBT, the need of conversion to conventional TURBT, method of tumour extraction, and any additional biopsy of the tumour base and tumour edge must be documented. Any problems encountered during the ERBT procedure, including the occurrence of obturator reflex, bladder perforation and any difficulty in tumour extraction must be documented.

3.5.6. Specimen preparation and reporting of histological findings

Every ERBT specimen must be prepared and sent for histological assessment separately. The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS and detrusor muscle [54], and these also apply to ERBT specimens. In addition, the maximal dimension of the bladder tumour [36], T1 substage [55-57], circumferential and deep resection margins [33,35,46-48] must be assessed.

3.5.7. Post-operative management and follow-up schedule

It is safe to give single-dose of immediate intravesical chemotherapy [19,22,29,33,36,37,44,45], to perform second-look TURBT [39,44], and to give intravesical BCG therapy after ERBT [19,33,49]. The indications should follow the EAU guidelines recommendation as in the case of conventional TURBT [54]. The flexible cystoscopy surveillance protocol after ERBT should also follow the EAU guidelines recommendation as in the case of conventional TURBT [54]. In addition, upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in-field and out-of-field recurrence [19,34,37].

3.5.8. Data reporting and outcome measures

In studies of ERBT, both per patient and per tumour analyses should be performed for different outcomes as appropriate [46,47]. Peri-operative outcomes, including operative time, obturator nerve reflex, successful en bloc resection rate, need of bladder irrigation, duration of urethral catheterization and hospital stay should be documented. Severity of complications should be measured using the Clavien-Dindo grading system [58]. Complications including bladder perforation, need of blood transfusion, ureteric stricture, urethral stricture, urinary tract infection and transurethral resection syndrome should be documented. For the histological assessment, presence of detrusor muscle, circumferential and deep resection margins are important outcomes to measure. Whether adjunct treatments, including post-operative intravesical instillation of chemotherapy, second-look TURBT and intravesical BCG therapy, have been given or performed should be reported. For those with second-look TURBT performed, any residual or upstaging of disease

should be reported. For the oncological outcomes, 3-month recurrence rate, 1-year recurrence and progression rates, and 5-year recurrence and progression rates are important outcomes to measure.

4. Discussion

In our effectiveness review, which is the most comprehensive and methodologically robust systematic review of the ERBT evidence base to date, we identified 10 RCTs comparing ERBT and TURBT, however, only 4 of them [19,22,29,31] were published as full-text articles. [High-quality data is limited for making robust recommendations in ERBT, and this explains why it is important to develop a consensus statement to provide the highest level of evidence that we can achieve so far, which can serve as a standard reference for health care professionals in the future.](#)

This consensus statement is the first attempt trying to standardize the management of bladder cancer patients with special focus on ERBT. We mobilized the international community and used transparent and robust methods to review the evidence, identify current uncertainties, and survey expert opinion in an unbiased way, in order to provide recommendations for interim practice guidance and a basis to inform the research agenda. Health care professionals from different specialties (i.e. urologists, oncologists and pathologists) were involved to ensure we had a comprehensive collection of opinion across different fields.

4.1. Relevance and impact of study findings on clinical practice and research

There are several important messages that may impact on our clinical practice. Although tumour size has long been recognized as a major limitation, we must emphasize that ERBT is a treatment intended for patients with NMIBC. In patients with bladder tumours larger than 3cm, there is a reasonable chance of MIBC and ERBT should not be considered a definitive treatment when there is a suspicion of MIBC. Moreover, it is recognized that the major benefit of ERBT is the ability to ensure a complete local resection, and this holds true even when the specimen cannot be retrieved in one piece. Therefore, we should still consider ERBT in patients with large bladder tumours where NMIBC is considered a possibility. We also offered practical solutions on how we can extend the indication of ERBT to patients with large bladder tumours. Modified ERBT, e.g. en bloc resection followed by division of specimen into 2-3 pieces for retrieval is considered acceptable [45,49]. The use of special tumour extraction methods may also facilitate tumour extraction [50], but we need to be aware that the devices being used implied additional costs and were not formally approved for such indication, and whether they would lead to increased risk of complications such as urethral stricture is unknown. There is an urgent need for

innovative methods of tumour extraction so as to achieve a true ERBT even for large bladder tumours.

ERBT is a surgical approach that aims to uphold the basic oncological principles in bladder cancer resection. Although there are different modalities of ERBT, they are all technically feasible and there is no data showing superiority of one over the other. In ERBT, surgical technique is primary and tools are secondary. Of note, bipolar ERBT appears to be the most acceptable modality based on the percentage of agreement. This might be explained by its widespread availability, ease and precision of resection as well as the allowance of instant conversion to conventional TURBT. Although there is a risk of residual disease and understaging when using HybridKnife (hydrodissection) for ERBT, this is only theoretical based on its nature of submucosal elevation and whether this is genuinely true is unknown.

As ERBT specimens allow assessment of the depth of invasion as well as the resection margins, routine additional biopsy of tumour base and tumour edge after ERBT is considered unnecessary. If there is any doubt on the completeness of resection, additional resection of tumour base and tumour edge can be considered, and they should be sent for histological assessment separately. Although pinning of circumferential mucosal margin and inking of resection margins in ERBT specimens are commonly performed (and possibly a good practice), it is not considered mandatory for a proper histological assessment. ERBT specimens also allow more precise assessment of the T1 substage. WHO classification of T1a, T1b and T1c disease is considered acceptable [57], but more research work will be needed to see whether they carry any important prognostic implications in NMIBC after ERBT.

We noticed a significant variation in the reporting of outcome measures across the non-randomised studies and RCTs. Data on important outcomes such as the presence of detrusor muscle were not readily reported in RCTs. There is also a wide variation in the study quality as reflected by our risk of bias assessment. Standardisation on data reporting and outcome measures is important to move ERBT forward. Future studies on ERBT should consider incorporating the important outcome measures as identified by our consensus statement.

4.2. Strengths and limitations

This consensus statement was developed using a robust and reproducible method [10,14-16]. Our systematic reviews were conducted according to the PRISMA guidelines [2]. When compared to previous meta-analyses in the literature [59-62], our search strategy was most comprehensive, and we only included RCTs in our meta-analysis with a proper risk of bias assessment. The GRADE method was used for assessing certainty of evidence [9] and this is useful for decision making at many levels, including for clinical practice guidelines development. Our uncertainties review also provided a solid basis for the survey items being developed. Invitations were sent to a large panel of health care professionals purposively sampled from across the world. The consensus building process was based on a two-round Delphi survey, followed by a consensus panel meeting, where anonymous voting techniques were used. All of these improved the internal and external validity of the study results. The definition of consensus was also based on previously described methodology.

There are several limitations in this study. First, we do recognize the lack of high-quality studies in ERBT. We were also not able to stratify the results according to patient and disease factors. Therefore, some results of the effectiveness review (e.g. recurrence rates) have to be interpreted with caution. Second, statements generated were brief, concise and binary in nature. Areas of uncertainty which are complex in nature may not be addressed adequately. Some terminology (e.g. degree of bladder distension) was also difficult to define. Third, most of the participants involved were urologists, and they might lack the knowledge regarding certain aspects of ERBT such as reporting of histological findings. [The](#) statements generated had an extensive coverage of every surgical aspect of ERBT. Even urologists may not have sufficient personal experience to vote in every statement (e.g. different modalities of ERBT). [Fourth, we recognized there was a strong representation from Europe and Asia in the Delphi survey. This may represent a selection bias from purposive sampling and the results may not be applicable in regions outside Europe and Asia. On the other hand, it may reflect a genuine situation that ERBT is much more commonly practised in Europe and Asia.](#)

4.3. Future directions of ERBT

Whether ERBT should replace conventional TURBT as the standard of care will require more results from high-quality RCTs. In our systematic review, we noticed that a number of RCTs have been presented but not fully published. Proper reporting according to the CONSORT statement is strongly encouraged [63]. There are also a number of on-going RCTs with clinically important primary outcomes. The EB-StaR study is a multi-centre study comparing the 1-year recurrence rate between bipolar ERBT and bipolar conventional TURBT for patients with bladder tumour size of less than 3cm [64]. There are two RCTs comparing between laser ERBT and conventional TURBT with the primary outcome of residual tumour upon second TURBT [65,66]. There is another RCT investigating the presence of detrusor muscle in the specimen, which may serve as a surrogate marker for the quality of resection [67].

One of the major criticisms of ERBT is the inability to retrieve large bladder tumours in one piece. Acknowledging the benefit of ensuring a complete resection, we should accept modified approaches of ERBT (e.g. ERBT followed by retrieval of bladder tumour in several pieces [45,49], piecemeal resection of the exophytic part of bladder tumour followed by en bloc resection of the tumour base [68], etc.). Moreover, ERBT is focused on patients with NMIBC (presumably smaller in size in most cases), so a true ERBT is still feasible for the majority of the patients. An exploratory study investigating the role of modified ERBT for patients with bladder tumour size of more than 3cm is currently under way [69].

Although ERBT is a promising surgical technique for NMIBC, the learning curve of ERBT and whether it can be easily generalized is an important issue to address. More effort will be needed for proper education and training globally. With the foundation of the consensus statement, a prospective international registry study on ERBT is planned. This will provide us more insights on the generalisability and practicality of implementing ERBT in our clinical practice. Long-term real world data will also be useful in determining the true value of ERBT. We believe oncological principles exist for good reasons, and our group will continue to work together and contribute to the development of ERBT in a collaborative manner.

5. Conclusions

A consensus statement for ERBT has been developed, and it has a comprehensive coverage regarding every aspect of ERBT. The findings will guide and inform health care professionals about the routine clinical practice of ERBT, and has important implications regarding future studies of ERBT. The consensus statement will serve as a standard of reference until higher level of evidence from prospective RCTs is available.

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References

Fig 1. Overview of the development of the consensus statement.

Fig 2. PRISMA flow diagram.

Fig 3. Risk of bias assessment of the randomised controlled trials

Fig 4. Key findings of the meta-analysis results from randomised controlled trials.

Table 1. Study characteristics of included randomised controlled trials.

Table 2. Characteristics of the Delphi participants who completed both rounds of survey.

Table 3. Panel members of the consensus meeting.

Table 4. Summary of statements and consensus status after two rounds of Delphi survey.

Table 5. Summary of the statements that were discussed and re-voted, and their consensus status after the voting session.

Table 6. Final consensus statements on en bloc resection of bladder tumour.

Appendix 1. Supplementary data.

Fig. 1 - Overview of the development of the consensus statement.

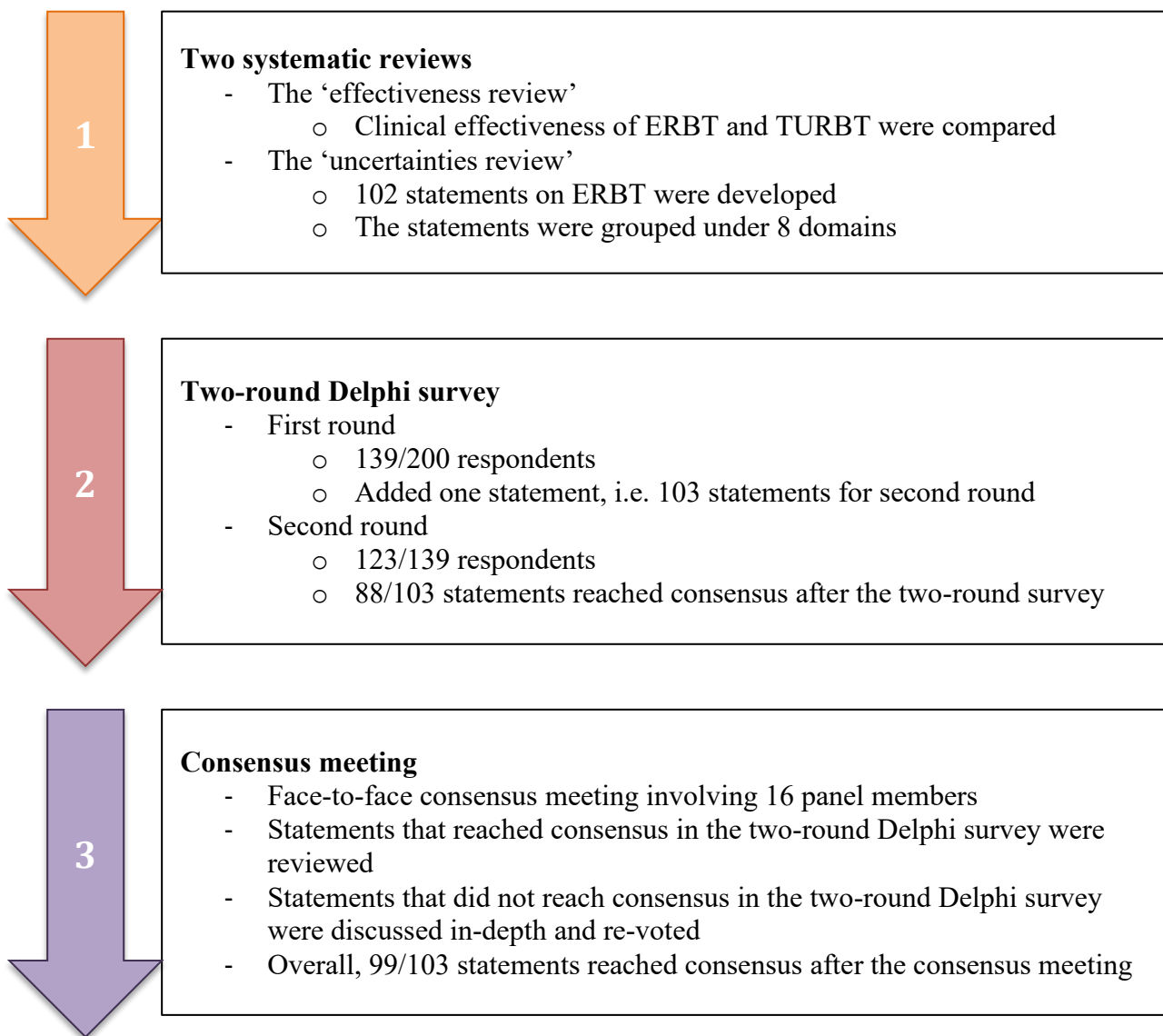


Fig. 2 - PRISMA flow diagram.

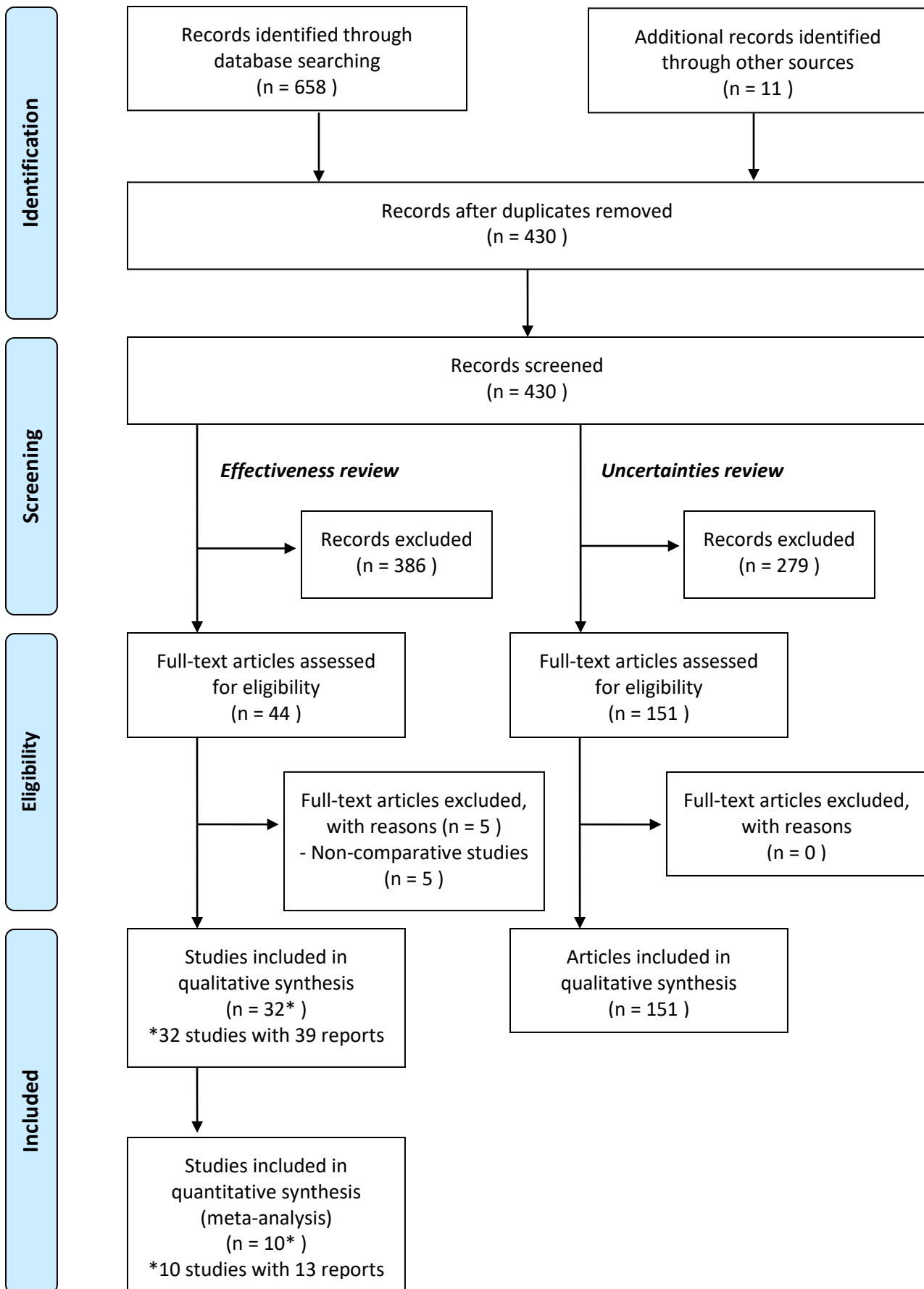


Fig. 3 - Risk of bias assessment of the randomised controlled trials.

A)

	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
Bălan 2018	⊖	⊖	⊕	?	⊕	⊕	?
Chen 2015	⊕	?	⊕	?	⊕	⊖	?
Cheng 2016	?	?	⊕	?	?	⊕	?
Gakis 2017	?	?	⊕	⊕	⊕	⊖	?
Geavlete 2018	⊖	⊖	⊕	?	⊕	⊕	?
Geavlete 2019	⊖	⊖	⊕	?	⊕	⊕	?
Hu 2017	?	?	⊕	?	⊕	⊕	?
Hu 2018	?	?	⊕	?	⊕	⊕	?
Kufner 2014	?	?	⊕	?	⊕	⊕	?
Li 2014	⊕	?	⊕	?	?	⊖	?
Liu 2013	⊕	?	⊕	?	?	⊕	⊕
Ruffo 2017	?	?	⊕	?	⊕	⊕	?
Zhang 2015	⊕	?	⊕	?	⊕	⊕	⊖

B)

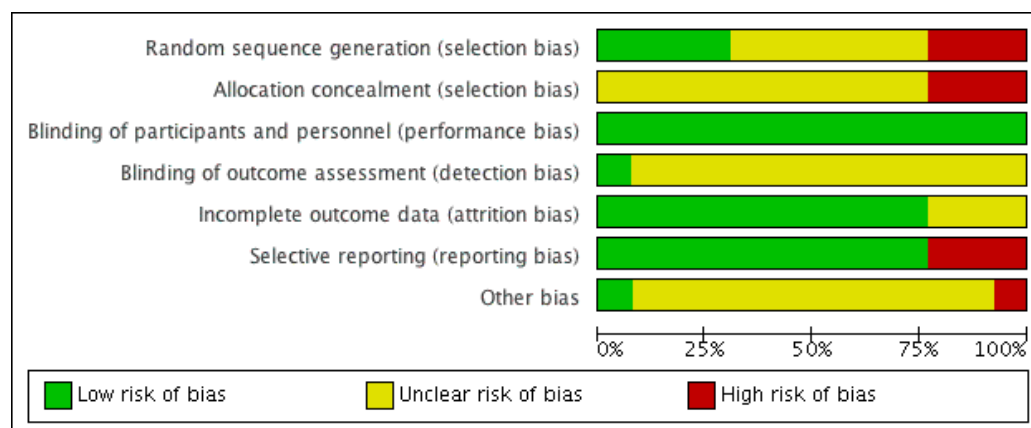
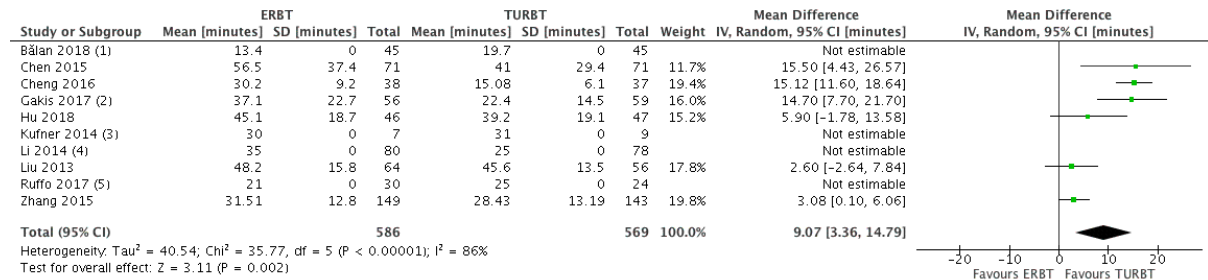


Fig. 4 - Key findings of the meta-analysis results from randomised controlled trials.

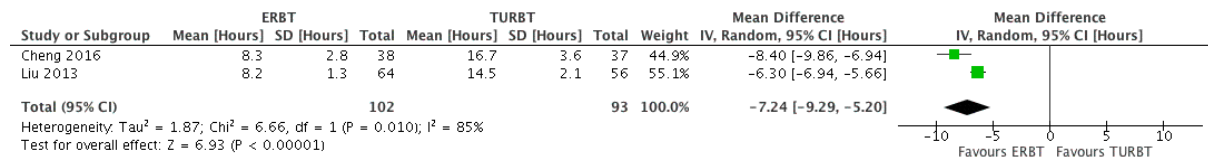
A) Operative time (minutes)



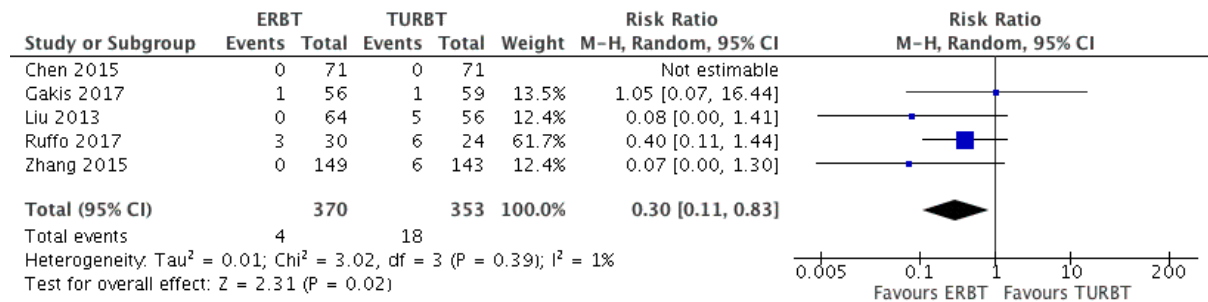
Footnotes

- (1) Standard deviation was not provided
- (2) Data on 'resection time' was used.
- (3) Standard deviation was not provided
- (4) Standard deviation was not provided
- (5) Standard deviation was not provided

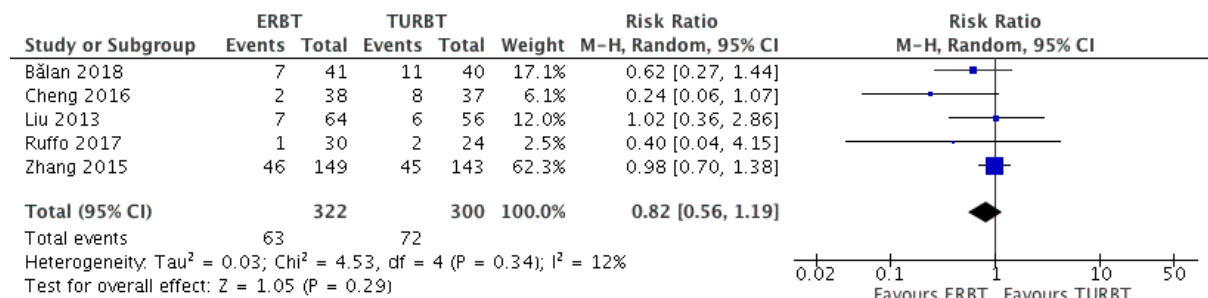
B) Irrigation time (hours)



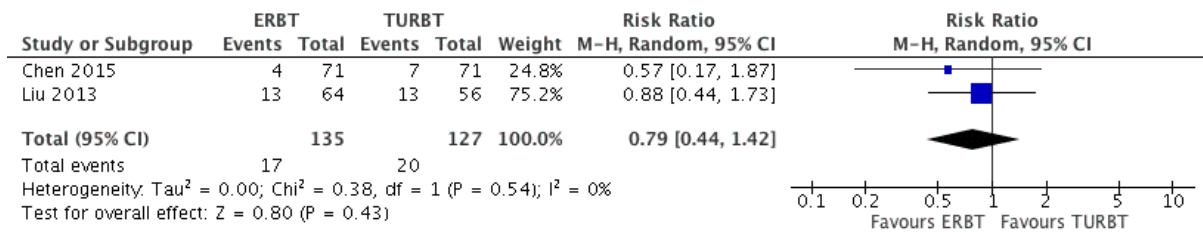
C) Bladder perforation



D) Recurrence at 0-12 months



E) Recurrence at 13-24 months



F) Recurrence at 25-36 months

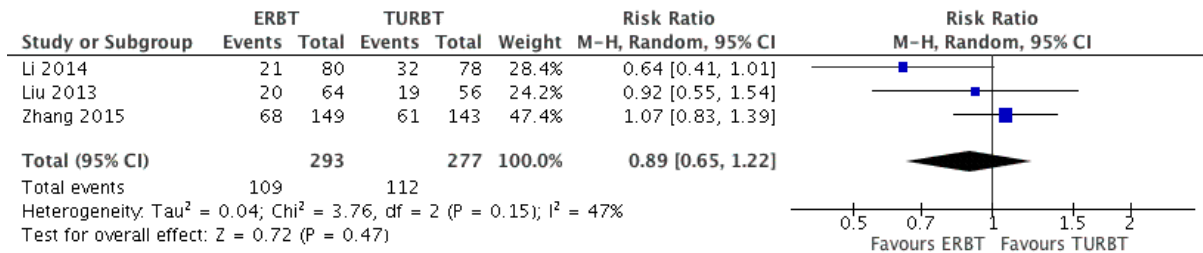


Table 1. Study characteristics of included randomised controlled trials.

Study	Country	Eligibility criteria	Comparison	Total (n)	ERBT arm (n)	Control arm (n)
Balan et al. (2018), Geavlete et al. (2018) and Geavlete et al. (2019) ^a	Romania	NMIBC 1-3 cm in diameter No solid sessile tumours Not located at bladder neck or involving the ureteral orifice	Bipolar ERBT vs Monopolar TURBT	90	45	45
Chen et al. (2015)	China	Primary NMIBC No suspicion of MIBC No serious heart, lung or brain conditions	Thulium laser ERBT vs TURBT ^b	142	71	71
Cheng et al. (2016)	China	NMIBC	HybridKnife ERBT vs TURBT ^b	75	38	37
Gakis et al. (2017)	Germany	NMIBC Tumour size >5mm	HybridKnife ERBT vs TURBT ^b	115	56	59
Hu et al. (2017) and Hu et al. (2018) ^a	China	Primary NMIBC Not CIS Not >3cm and not <1cm in diameter Not more than 5 tumours	HybridKnife ERBT vs TURBT ^b	93	46	47
Kufner et al. (2014)	Germany	Superficial papillary bladder tumour	HybridKnife ERBT vs TURBT ^b	16	7	9
Li et al. (2014)	China	NMIBC	ERBT ^b vs TURBT ^b	158	80	78
Liu et al. (2013)	China	Newly diagnosed NMIBC Not urothelial papillomas Not MIBC or CIS No upper urinary tract tumours No extravesical extension, lymphatic metastasis or invasion of adjacent organs	Thulium laser ERBT vs Monopolar TURBT	120	64	56

Ruffo et al. (2017)	Italy	Newly diagnosed NMIBC	Thulium laser ERBT vs Monopolar TURBT	54	30	24
Zhang et al. (2015)	China	Primary NMIBC Not inverted papilloma No extravesical extension, lymph node metastasis or adjacent organ invasion No upper urinary tract tumours Excluded patients who could not tolerate general anaesthesia No severe cardiovascular or pulmonary disease, or disturbance of blood coagulation contradicting operation	Thulium laser ERBT vs Bipolar TURBT	292	149	143

CIS: Carcinoma in-situ; ERBT: En bloc resection of bladder tumour; MIBC: Muscle-invasive bladder cancer; NMIBC: Non-muscle-invasive bladder cancer; TURBT: Transurethral resection of bladder tumour.

^a Same study with numerous reports; report with the most complete data and longest follow-up was presented

^b Unknown energy source

	Round 1 N (%)	Round 2 N (%)
Region		
Africa	4 (2.9%)	2 (1.6%)
Asia	70 (50.4%)	62 (50.4%)
Australia/New Zealand	2 (1.4%)	2 (1.6%)
Europe	53 (38.1%)	48 (39.0%)
North America	3 (2.2%)	2 (1.6%)
South America	7 (5.0%)	7 (5.7%)
Years of practice		
1-5	15 (10.8%)	14 (11.4%)
6-10	37 (26.6%)	33 (26.8%)
11-15	41 (29.5%)	36 (29.3%)
16-20	26 (18.7%)	23 (18.7%)
21-25	12 (8.6%)	9 (7.3%)
26-30	5 (3.6%)	5 (4.1%)
>30	3 (2.2%)	3 (2.4%)
Specialty		
Oncologist	6 (4.3%)	4 (3.3%)
Pathologist	8 (5.8%)	8 (6.5%)
Urologist	125 (89.9%)	111 (90.2%)
Total	139 (100%)	123 (100%)

Table 2. Characteristics of the Delphi participants who completed both rounds of survey.

Name	Role	Representing body / institution
Steven MacLennan	Chair (Methodologist)	University of Aberdeen, United Kingdom
Darren Poon	Oncologist	The Chinese University of Hong Kong, Hong Kong, China
Fernand Lai	Pathologist	The Chinese University of Hong Kong, Hong Kong, China
Chow Wing-Kie	Patient	New Territories East Cluster Bladder Cancer Support Group, Hong Kong, China
Alberto Breda	Urologist	Fundacion Puigvert, Universitat Autònoma de Barcelona, Spain
Bernard Malavaud	Urologist	Institut Universitaire du Cancer, France
Edmund Chiong	Urologist	National University Hospital, National University Health System, Singapore
Hugh Mostafid	Urologist	Royal Surrey County Hospital, United Kingdom
Jeremy Teoh	Urologist	The Chinese University of Hong Kong, Hong Kong, China
Jun Miki	Urologist	Jikei University School of Medicine, Japan
Lee Hsiang-Ying	Urologist	Kaohsiung Municipal Ta-Tung Hospital, Taiwan
Lee Lui-Shiong	Urologist	Sengkang General Hospital, Singapore General Hospital, Singapore
Marek Babjuk	Urologist	Hospital Motol, Charles University, Czech Republic; Medical University of Vienna, Austria.
Mario Kramer	Urologist	University Clinic of Schleswig-Holstein, Campus Luebeck, Germany
Thomas Herrmann	Urologist	Spital Thurgau AG, Switzerland; Hanover Medical School (MHH), Germany
Wei Yong	Urologist	First Affiliated Hospital of Fujian Medical University, Fuzhou, China

Table 3. Panel members of the consensus meeting.

Table 4. Summary of statements and consensus status after two rounds of Delphi survey.

Domains and statements	Round 1 ^a						Round 2 ^a						
	% Disagree (1-3)	% Equivocal (4-6)	% Agree (7-9)	Total N	Unable to score N	Consensus status	% Disagree (1-3)	% Equivocal (4-6)	% Agree (7-9)	Total N	Unable to score N	Consensus status	
<i>Definitions and objectives of ERBT</i>													
1	Removal of bladder tumour in one piece is the most appropriate definition for ERBT	3.6%	9.4%	87.0%	139	1	Agree	0.8%	6.5%	92.7%	123	0	Agree
2	The depth of ERBT must include the detrusor muscle layer in the specimen	5.8%	9.4%	84.8%	139	1	Agree	4.1%	7.3%	88.6%	123	0	Agree
3	One of the main goals of ERBT is to ensure complete local resection of bladder tumour	0.7%	3.6%	95.7%	139	1	Agree	0.8%	0.8%	98.4%	123	0	Agree
4	One of the main goals of ERBT is to ensure proper local staging of the disease	0.7%	0%	99.3%	139	2	Agree	1.6%	0%	98.4%	123	1	Agree
5	One of the main goals of ERBT is to reduce the risk of tumour re-implantation	8.8%	14.6%	76.6%	139	2	Agree	4.1%	15.7%	80.2%	123	2	Agree
6	ERBT should always be considered for treatment of non-muscle-invasive bladder cancer	8.8%	24.8%	66.4%	139	2	Not reached	4.9%	17.2%	77.9%	123	1	Agree
7	ERBT should be considered for treatment of muscle-invasive bladder cancer	53.7%	26.5%	19.9%	139	3	Not reached	63.9%	19.7%	16.4%	123	1	Not reached
8	ERBT should be considered to treat carcinoma in-situ of the bladder to optimize subsequent treatment	48.1%	31.1%	20.7%	139	4	Not reached	56.3%	26.1%	17.6%	123	4	Not reached
<i>Case selection</i>													
9	Size of bladder tumour is a major limitation in performing ERBT	8.8%	6.6%	84.6%	139	3	Agree	9.2%	3.3%	87.5%	122	2	Agree
10	ERBT is feasible for patients with bladder tumour size of less than 3cm	2.2%	4.4%	93.3%	139	4	Agree	1.7%	1.7%	96.6%	122	3	Agree
11	ERBT is feasible for patients with bladder tumour size of more than 3cm	21.1%	41.4%	37.6%	139	6	Not reached	15.3%	37.3%	47.5%	122	4	Not reached
12	Number of bladder tumours is a major limitation in performing ERBT	36.5%	29.9%	33.6%	139	2	Not reached	38.3%	17.5%	44.2%	122	2	Not reached
13	If tumour size is not an issue, ERBT is feasible for patients with	7.4%	13.3%	79.3%	139	4	Agree	5.0%	5.0%	89.9%	122	3	Agree

	less than 4 bladder tumours												
14	If tumour size is not an issue, ERBT is feasible for patients with more than 4 bladder tumours	18.8%	34.6%	46.6%	139	6	Not reached	15.1%	21.8%	63.0%	122	3	Not reached
15	Tumour location is a major limitation in performing ERBT	20.9%	23.1%	56.0%	139	5	Not reached	16.1% ^b	12.7%	71.2%	122	4	Not reached
16	ERBT is feasible for bladder tumour located at the posterior wall	3.0%	5.9%	91.1%	139	4	Agree	1.7%	0.8%	97.5%	122	4	Agree
17	ERBT is feasible for bladder tumour located at the anterior wall	14.9%	26.9%	58.2%	139	5	Not reached	12.8%	14.5%	72.6%	122	5	Agree
18	ERBT is feasible for bladder tumour located at the right lateral wall	0.7%	5.9%	93.3%	139	4	Agree	0%	3.4%	96.6%	122	4	Agree
19	ERBT is feasible for bladder tumour located at the left lateral wall	1.5%	5.9%	92.6%	139	4	Agree	0%	3.4%	96.6%	122	4	Agree
20	ERBT is feasible for bladder tumour located at the trigone	2.2%	8.1%	89.6%	139	4	Agree	0.8%	2.5%	96.6%	122	4	Agree
21	ERBT is feasible for bladder tumour located at the bladder dome	17.8%	30.4%	51.9%	139	4	Not reached	16.9%	22.0%	61.0%	122	4	Not reached
22	ERBT is feasible for bladder tumour located at the bladder neck	13.4%	15.7%	70.9%	139	5	Agree	10.3%	7.7%	82.1%	122	5	Agree
23	ERBT is feasible for bladder tumour located near the ureteric orifice	11.2%	17.2%	71.6%	139	5	Agree	7.6%	9.3%	83.1%	122	4	Agree
	<i>Surgical procedure</i>												
24	A thorough cystoscopic examination must be performed before any ERBT	3.0%	3.8%	93.2%	137	4	Agree	0.8%	0%	99.2%	122	3	Agree
25	Narrow-band imaging, Image 1S or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	19.5%	30.9%	49.6%	137	14	Not reached	14.4%	26.1%	59.5%	122	11	Not reached
26	The bladder should be distended enough to facilitate ERBT	12.7%	22.4%	64.9%	137	3	Not reached	9.2%	11.8%	79.0%	122	3	Agree
27	The bladder should not be over-distended to avoid bladder perforation upon ERBT	4.6%	10.7%	84.7%	137	6	Agree	4.3%	5.1%	90.6%	122	5	Agree
28	The planned circumferential margin should be marked first to facilitate subsequent ERBT	4.5%	14.4%	81.1%	137	5	Agree	1.7%	6.8%	91.5%	122	4	Agree
29	Upon ERBT, the planned circumferential margin should be at least 5mm from any visible bladder tumour	7.6%	18.2%	74.2%	137	5	Agree	3.4%	11.0%	85.6%	122	4	Agree

30	Upon ERBT, the incision should be made deep into the detrusor muscle layer	12.9%	12.1%	75.0%	137	5	Agree	11.1%	6.8%	82.1%	122	5	Agree
31	After ERBT, additional biopsy of the tumour base should be performed routinely	39.8%	24.1%	36.1%	137	4	Not reached	45.8%	17.8%	36.4%	122	4	Not reached
32	After ERBT, additional biopsy of the tumour edge should be performed routinely	47.3%	27.5%	25.2%	137	6	Not reached	62.4%	21.4%	16.2%	122	5	Not reached
33	If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered	3.0%	8.3%	88.6%	137	5	Agree	1.7%	3.4%	94.9%	122	4	Agree
34	If the size of bladder tumour is too big, after ERBT, dividing the specimen into 2-3 pieces for retrieval can be considered	12.2%	22.1%	65.6%	137	6	Not reached	8.5%	12.8%	78.6%	122	5	Agree
35	Should there be any technical difficulty being encountered upon ERBT, conversion to conventional TURBT should be considered	1.5%	3.0%	95.5%	137	3	Agree	0.8%	0.8%	98.3%	122	3	Agree
36	Special extraction methods (Endobag, laparoscopic instrument through nephroscope, etc.) can be considered in retrieving large ERBT specimens	12.2%	11.4%	76.4%	137	14	Agree	8.1%	7.2%	84.7%	122	11	Agree
<i>Different modalities of ERBT</i>													
37	It is technically feasible to use monopolar energy for ERBT	7.5%	20.8%	71.7%	135	15	Agree	5.5%	11.0%	83.5%	122	13	Agree
38	It is technically feasible to use bipolar energy for ERBT	0.8%	3.2%	96.0%	135	10	Agree	0%	0.9%	99.1%	122	9	Agree
39	It is technically feasible to use holmium laser for ERBT	1.8%	19.6%	78.6%	135	23	Agree	2.0%	12.9%	85.1%	122	21	Agree
40	It is technically feasible to use thulium laser for ERBT	2.1%	20.0%	77.9%	135	40	Agree	1.1%	11.1%	87.8%	122	32	Agree
41	It is technically feasible to use HybridKnife (hydrodissection) for ERBT	3.4%	26.1%	70.5%	135	47	Agree	0%	18.1%	81.9%	122	39	Agree
42	ERBT using monopolar energy allows conversion to piecemeal resection readily when technical difficulty arises	6.7%	12.6%	80.7%	135	16	Agree	4.5%	6.4%	89.1%	122	12	Agree
43	ERBT using bipolar energy allows conversion to piecemeal resection readily when technical difficulty	0.8%	9.0%	90.2%	135	13	Agree	0%	5.3%	94.7%	122	9	Agree

	arises												
44	Holmium laser eliminates the risk of obturator nerve reflex during ERBT	1.0%	20.4%	78.6%	135	32	Agree	0%	8.1%	91.9%	122	23	Agree
45	Thulium laser eliminates the risk of obturator nerve reflex during ERBT	1.1%	24.7%	74.2%	135	42	Agree	0%	8.9%	91.1%	122	32	Agree
46	HybridKnife (hydrodissection) is the safest modality in performing ERBT	18.1%	50.6%	31.3%	135	52	Not reached	18.2%	57.1%	24.7%	122	45	Not reached
47	There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	11.3%	47.5%	41.3%	135	55	Not reached	7.7%	52.6%	39.7%	122	44	Not reached
	<i>Reporting of intra-operative findings for patients undergoing ERBT</i>												
48	The modality used for ERBT must be documented	0%	3.0%	97.0%	135	1	Agree	0%	0.8%	99.2%	122	1	Agree
49	Whether ERBT has been successfully performed, or any need of conversion to conventional TURBT, must be documented	0%	1.5%	98.5%	135	1	Agree	0%	0.8%	99.2%	122	1	Agree
50	Whether additional biopsy of the tumour base has been performed must be documented	0%	3.7%	96.3%	135	1	Agree	0%	0.8%	99.2%	122	1	Agree
51	Whether additional biopsy of the tumour edge has been performed must be documented	2.2%	4.5%	93.3%	135	1	Agree	0.8%	0.8%	98.3%	122	1	Agree
52	The EAU guidelines stated that the operative record of TURBT must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection	0%	0%	100.0%	135	1	Agree	0%	0%	100.0%	122	1	Agree
53	Any occurrence of obturator nerve reflex and the laterality of obturator nerve reflex being encountered during ERBT must be documented	2.3%	18.8%	78.9%	135	2	Agree	0%	9.9%	90.1%	122	1	Agree
54	Any occurrence of extraperitoneal or intraperitoneal bladder perforation during ERBT must be documented	0.7%	1.5%	97.8%	135	1	Agree	0.8%	0%	99.2%	122	1	Agree
55	The method of tumour extraction must be documented	1.5%	4.5%	94.0%	135	1	Agree	0%	0%	100.0%	122	1	Agree

56	Any difficulty in tumour extraction must be documented	1.5%	6.7%	91.8%	135	1	Agree	0%	4.1%	95.9%	122	1	Agree
57	Whether the ERBT specimen has been divided for extraction must be documented	0.7%	5.2%	94.0%	135	1	Agree	0%	0.8%	99.2%	122	1	Agree
<i>Specimen preparation and reporting of histological findings</i>													
58	Every ERBT specimen must be prepared and sent for histological assessment separately	1.5%	6.0%	92.5%	135	2	Agree	0.8%	3.3%	95.8%	121	1	Agree
59	For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	7.9%	31.0%	61.1%	135	9	Not reached	5.2%	30.4%	64.3%	121	6	Not reached
60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	14.3%	32.5%	53.2%	135	9	Not reached	8.0%	31.0%	61.1%	121	8	Not reached
61	For the ERBT specimen, it should be serially sectioned at 2mm intervals	3.1%	38.1%	58.8%	135	38	Not reached	0%	29.2%	70.8%	121	32	Agree
62	The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of carcinoma-in-situ and detrusor muscle	0%	3.0%	97.0%	135	1	Agree	0%	2.5%	97.5%	121	1	Agree
63	Upon histological assessment of the ERBT specimen, the maximal dimension of bladder tumour must be documented	5.8%	22.3%	71.9%	135	14	Agree	2.7%	12.7%	84.5%	121	11	Agree
64	Upon histological assessment of the ERBT specimen, T1 substage must be assessed	1.5%	10.4%	88.1%	135	1	Agree	0.8%	8.3%	90.8%	121	1	Agree
65	Upon histological assessment of the ERBT specimen, circumferential resection margin must be assessed	3.0%	6.7%	90.3%	135	1	Agree	4.2%	2.5%	93.3%	121	1	Agree
66	Upon histological assessment of the ERBT specimen, deep resection margin must be assessed	0.7%	3.0%	96.3%	135	1	Agree	0%	1.7%	98.3%	121	1	Agree
<i>Post-operative management and follow-up schedule</i>													
67	It is safe to give single dose of	4.7%	14.2%	81.1%	135	8	Agree	1.7%	6.1%	92.2%	121	6	Agree

68	intravesical chemotherapy immediately after ERBT The indications of single-dose of intravesical chemotherapy immediately after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	2.3%	9.9%	87.8%	135	4	Agree	1.7%	4.3%	94.0%	121	4	Agree
69	It is safe to perform second look TURBT after the first ERBT	3.9%	11.6%	84.5%	135	6	Agree	2.5%	6.8%	90.7%	121	3	Agree
70	The indications of second look TURBT after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	10.0%	14.6%	75.4%	135	5	Agree	7.0%	10.4%	82.6%	121	6	Agree
71	It is safe to give intravesical BCG therapy after ERBT	3.9%	7.0%	89.1%	135	6	Agree	1.7%	5.1%	93.2%	121	4	Agree
72	The indications of intravesical BCG therapy after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	1.5%	3.8%	94.7%	135	4	Agree	0%	3.4%	96.6%	121	3	Agree
73	The flexible cystoscopy surveillance protocol after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	0%	4.5%	95.5%	135	2	Agree	0%	3.4%	96.6%	121	2	Agree
74 ^c	Upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in-field and out-of-field recurrence	-	-	-	-	-	-	0.9%	2.6%	96.5%	121	7	Agree
<i>Data reporting and outcome measures</i>													
75	In studies of ERBT, both per patient and per tumour analyses should be performed for different outcomes	3.8%	10.6%	85.6%	135	3	Agree	1.7%	5.0%	93.3%	121	1	Agree
76	In studies of ERBT, the operative time is an important outcome to measure	10.7%	26.0%	63.4%	135	4	Not reached	8.5%	19.5%	72.0%	121	3	Agree
77	In studies of ERBT, the presence of obturator nerve reflex an important outcome to measure	4.7%	25.0%	70.3%	135	7	Agree	1.8%	16.7%	81.6%	121	7	Agree
78	In studies of ERBT, the need for bladder irrigation is an important	12.2%	25.2%	62.6%	135	4	Not reached	6.0%	17.9%	76.1%	121	4	Agree

79	outcome to measure In studies of ERBT, the duration of urethral catheterization is an important outcome to measure	11.5%	20.8%	67.7%	135	5	Not reached	8.5%	12.0%	79.5%	121	4	Agree
80	In studies of ERBT, hospital stay is an important outcome to measure	10.5%	21.1%	68.4%	135	2	Not reached	7.6%	10.9%	81.5%	121	2	Agree
81	In studies of ERBT, the complication rate is an important outcome to measure	0%	1.5%	98.5%	135	1	Agree	0%	0.8%	99.2%	121	1	Agree
82	In studies of ERBT, the Clavien-Dindo grading system is the preferred system to measure the severity of complication	2.3%	9.4%	88.3%	135	7	Agree	1.7%	5.2%	93.0%	121	6	Agree
83	In studies of ERBT, the need for blood transfusion is an important outcome to measure	9.8%	16.7%	73.5%	135	3	Agree	5.9%	12.6%	81.5%	121	2	Agree
84	In studies of ERBT, the occurrence of urethral stricture is an important outcome to measure	11.2%	22.4%	66.4%	135	1	Not reached	6.7%	15.8%	77.5%	121	1	Agree
85	In studies of ERBT, the occurrence of bladder perforation is an important outcome to measure	0%	2.3%	97.7%	135	2	Agree	0%	1.7%	98.3%	121	1	Agree
86	In studies of ERBT, the occurrence of urinary tract infection is an important outcome to measure	12.7%	27.6%	59.7%	135	1	Not reached	6.7%	20.8%	72.5%	121	1	Agree
87	In studies of ERBT, the occurrence of transurethral resection syndrome is an important outcome to measure	14.9%	23.1%	61.9%	135	1	Not reached	12.5%	15.0%	72.5%	121	1	Agree
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	18.7%	29.1%	52.2%	135	1	Not reached	10.0%	28.3%	61.7%	121	1	Not reached
89	In studies of ERBT, the occurrence of ureteric stricture is an important outcome to measure	11.2%	21.6%	67.2%	135	1	Not reached	5.8%	13.3%	80.8%	121	1	Agree
90	In studies of ERBT, the successful en bloc resection rate (i.e. removal of bladder tumour in one piece) is an important outcome to measure	0.7%	3.0%	96.3%	135	1	Agree	0%	0.8%	99.2%	121	1	Agree
91	In studies of ERBT, presence of detrusor muscle in the ERBT specimen is an important outcome to measure	0.7%	2.2%	97.0%	135	1	Agree	0%	2.5%	97.5%	121	1	Agree
92	In studies of ERBT, presence of clear circumferential resection margin in the ERBT specimen is an important outcome to measure	2.3%	5.3%	92.5%	135	2	Agree	3.3%	2.5%	94.2%	121	1	Agree

93	In studies of ERBT, presence of clear deep resection margin in the ERBT specimen is an important outcome to measure	0%	3.7%	96.3%	135	1	Agree	0%	0.8%	99.2%	121	1	Agree
94	In studies of ERBT, whether post-operative intravesical instillation of chemotherapy is given is an important outcome to report	0.8%	15.9%	83.3%	135	3	Agree	0.8%	10.9%	88.2%	121	2	Agree
95	In studies of ERBT, whether second look transurethral resection is performed is an important outcome to report	3.0%	9.0%	88.0%	135	2	Agree	1.7%	6.7%	91.6%	121	2	Agree
96	In studies of ERBT, any residual disease is detected upon second look transurethral resection is an important outcome to report	1.5%	3.8%	94.7%	135	2	Agree	0%	2.5%	97.5%	121	2	Agree
97	In studies of ERBT, any upstaging of disease is detected upon second look transurethral resection is an important outcome to report	1.5%	4.5%	94.0%	135	2	Agree	0%	3.4%	96.6%	121	2	Agree
98	In studies of ERBT, whether intravesical BCG therapy is given is an important outcome to report	3.8%	18.0%	78.2%	135	2	Agree	1.7%	9.2%	89.1%	121	2	Agree
99	In studies of ERBT, 3-month recurrence rate is an important outcome to measure	0.7%	4.5%	94.8%	135	1	Agree	0%	1.7%	98.3%	121	1	Agree
100	In studies of ERBT, 1-year recurrence rate is an important outcome to measure	0%	2.3%	97.7%	135	2	Agree	0%	0.8%	99.2%	121	1	Agree
101	In studies of ERBT, 1-year progression rate is an important outcome to measure	0%	1.5%	98.5%	135	1	Agree	0%	0.8%	99.2%	121	1	Agree
102	In studies of ERBT, 5-year recurrence rate is an important outcome to measure	1.5%	6.7%	91.8%	135	1	Agree	0%	2.5%	97.5%	121	1	Agree
103	In studies of ERBT, 5-year progression rate is an important outcome to measure	1.5%	6.0%	92.5%	135	1	Agree	0%	2.5%	97.5%	121	1	Agree

EAU = European Association of Urology; ERBT = En bloc resection of bladder tumour; TURBT = Transurethral resection of bladder tumour.

^a In columns showing percentages agree/equivocal/disagree, red shaded cells indicate $\geq 70\%$.

^b Green shaded cell indicate $\geq 15\%$ of disagree despite $\geq 70\%$ of agree in the same statement.

^c This statement was added after first round of Delphi survey.

Table 5. Summary of the statements that were discussed and re-voted, and their consensus status after the voting session.

Domains and statements	Voting session ^a			Total N	Unable to score N	Consensus status
	% Disagree (1-3)	% Equivocal (4-6)	% Agree (7-9)			
<i>Definitions and objectives of ERBT</i>						
7 ERBT should be considered for treatment of muscle-invasive bladder cancer	80.0%	6.7%	13.3%	15	0	Disagree
8 ERBT should be considered to treat carcinoma in-situ of the bladder to optimize subsequent treatment	73.3%	13.3%	13.3%	15	0	Disagree
<i>Case selection</i>						
11 ERBT is feasible for patients with bladder tumour size of more than 3cm	0.0%	6.7%	93.3%	15	0	Agree
12 Number of bladder tumours is a major limitation in performing ERBT	86.7%	6.7%	6.7%	15	0	Disagree
14 If tumour size is not an issue, ERBT is feasible for patients with more than 4 bladder tumours	0.0%	0.0%	100.0%	15	0	Agree
15 Tumour location is a major limitation in performing ERBT	73.3%	20.0%	6.7%	15	0	Disagree
21 ERBT is feasible for bladder tumour located at the bladder dome	0.0%	0.0%	100.0%	15	0	Agree
<i>Surgical procedure</i>						
25 Narrow-band imaging, Image 1S or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	20.0%	33.3%	46.7%	15	0	Not reached
31 After ERBT, additional biopsy of the tumour base should be performed routinely	86.7%	6.7%	6.7%	15	0	Disagree
32 After ERBT, additional biopsy of the tumour edge should be performed routinely	100.0%	0.0%	0.0%	15	0	Disagree
<i>Different modalities of ERBT</i>						
46 HybridKnife (hydrodissection) is the safest modality in performing ERBT	86.7%	6.7%	6.7%	15	0	Disagree
47 There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	0.0%	21.4%	78.6%	14	1	Agree
<i>Specimen preparation and reporting of histological findings</i>						
59 For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	40.0%	33.3%	26.7%	15	0	Not reached

60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	20.0%	26.7%	53.3%	15	0	Not reached
<i>Data reporting and outcome measures</i>							
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	13.3%	46.7%	40.0%	15	0	Not reached

ERBT = En bloc resection of bladder tumour.

^a In columns showing percentages agree/equivocal/disagree, red shaded cells indicate $\geq 70\%$.

Table 6. Final consensus statements on en bloc resection of bladder tumour.

Domains and statements	Consensus stage (Delphi/meeting)	Direction of consensus (Agree/disagree)
<i>Definitions and objectives of ERBT</i>		
1 Removal of bladder tumour in one piece is the most appropriate definition for ERBT	Delphi	Agree
2 The depth of ERBT must include the detrusor muscle layer in the specimen	Delphi	Agree
3 One of the main goals of ERBT is to ensure complete local resection of bladder tumour	Delphi	Agree
4 One of the main goals of ERBT is to ensure proper local staging of the disease	Delphi	Agree
5 One of the main goals of ERBT is to reduce the risk of tumour re-implantation	Delphi	Agree
6 ERBT should always be considered for treatment of non-muscle-invasive bladder cancer	Delphi	Agree
7 ERBT should be considered for treatment of muscle-invasive bladder cancer	Meeting	Disagree
8 ERBT should be considered to treat carcinoma in-situ of the bladder to optimize subsequent treatment	Meeting	Disagree
<i>Case selection</i>		
9 Size of bladder tumour is a major limitation in performing ERBT	Delphi	Agree
10 ERBT is feasible for patients with bladder tumour size of less than 3cm	Delphi	Agree
11 ERBT is feasible for patients with bladder tumour size of more than 3cm	Meeting	Agree
12 Number of bladder tumours is a major limitation in performing ERBT	Meeting	Disagree
13 If tumour size is not an issue, ERBT is feasible for patients with less than 4 bladder tumours	Delphi	Agree
14 If tumour size is not an issue, ERBT is feasible for patients with more than 4 bladder tumours	Meeting	Agree
15 Tumour location is a major limitation in performing ERBT	Meeting	Disagree
16 ERBT is feasible for bladder tumour located at the posterior wall	Delphi	Agree
17 ERBT is feasible for bladder tumour located at the anterior wall	Delphi	Agree
18 ERBT is feasible for bladder tumour located at the right lateral wall	Delphi	Agree
19 ERBT is feasible for bladder tumour located at the left lateral wall	Delphi	Agree
20 ERBT is feasible for bladder tumour located at the trigone	Delphi	Agree
21 ERBT is feasible for bladder tumour located at the bladder dome	Meeting	Agree
22 ERBT is feasible for bladder tumour located at the bladder neck	Delphi	Agree
23 ERBT is feasible for bladder tumour located near the ureteric orifice	Delphi	Agree
<i>Surgical procedure</i>		
24 A thorough cystoscopic examination must be performed before any ERBT	Delphi	Agree
25 Narrow-band imaging, Image 1S or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	Meeting	Not reached

26	The bladder should be distended enough to facilitate ERBT	Delphi	Agree
27	The bladder should not be over-distended to avoid bladder perforation upon ERBT	Delphi	Agree
28	The planned circumferential margin should be marked first to facilitate subsequent ERBT	Delphi	Agree
29	Upon ERBT, the planned circumferential margin should be at least 5mm from any visible bladder tumour	Delphi	Agree
30	Upon ERBT, the incision should be made deep into the detrusor muscle layer	Delphi	Agree
31	After ERBT, additional biopsy of the tumour base should be performed routinely	Meeting	Disagree
32	After ERBT, additional biopsy of the tumour edge should be performed routinely	Meeting	Disagree
33	If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered	Delphi	Agree
34	If the size of bladder tumour is too big, after ERBT, dividing the specimen into 2-3 pieces for retrieval can be considered	Delphi	Agree
35	Should there be any technical difficulty being encountered upon ERBT, conversion to conventional TURBT should be considered	Delphi	Agree
36	Special extraction methods (Endobag, laparoscopic instrument through nephroscope, etc.) can be considered in retrieving large ERBT specimens	Delphi	Agree
<i>Different modalities of ERBT</i>			
37	It is technically feasible to use monopolar energy for ERBT	Delphi	Agree
38	It is technically feasible to use bipolar energy for ERBT	Delphi	Agree
39	It is technically feasible to use holmium laser for ERBT	Delphi	Agree
40	It is technically feasible to use thulium laser for ERBT	Delphi	Agree
41	It is technically feasible to use HybridKnife (hydrodissection) for ERBT	Delphi	Agree
42	ERBT using monopolar energy allows conversion to piecemeal resection readily when technical difficulty arises	Delphi	Agree
43	ERBT using bipolar energy allows conversion to piecemeal resection readily when technical difficulty arises	Delphi	Agree
44	Holmium laser eliminates the risk of obturator nerve reflex during ERBT	Delphi	Agree
45	Thulium laser eliminates the risk of obturator nerve reflex during ERBT	Delphi	Agree
46	HybridKnife (hydrodissection) is the safest modality in performing ERBT	Meeting	Disagree
47	There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	Meeting	Agree
<i>Reporting of intra-operative findings for patients undergoing ERBT</i>			
48	The modality used for ERBT must be documented	Delphi	Agree
49	Whether ERBT has been successfully performed, or any need of conversion to conventional TURBT,	Delphi	Agree

	must be documented		
50	Whether additional biopsy of the tumour base has been performed must be documented	Delphi	Agree
51	Whether additional biopsy of the tumour edge has been performed must be documented	Delphi	Agree
52	The EAU guidelines stated that the operative record of TURBT must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection	Delphi	Agree
53	Any occurrence of obturator nerve reflex and the laterality of obturator nerve reflex being encountered during ERBT must be documented	Delphi	Agree
54	Any occurrence of extraperitoneal or intraperitoneal bladder perforation during ERBT must be documented	Delphi	Agree
55	The method of tumour extraction must be documented	Delphi	Agree
56	Any difficulty in tumour extraction must be documented	Delphi	Agree
57	Whether the ERBT specimen has been divided for extraction must be documented	Delphi	Agree
	<i>Specimen preparation and reporting of histological findings</i>		
58	Every ERBT specimen must be prepared and sent for histological assessment separately	Delphi	Agree
59	For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	Meeting	Not reached
60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	Meeting	Not reached
61	For the ERBT specimen, it should be serially sectioned at 2mm intervals	Delphi	Agree
62	The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of carcinoma-in-situ and detrusor muscle	Delphi	Agree
63	Upon histological assessment of the ERBT specimen, the maximal dimension of bladder tumour must be documented	Delphi	Agree
64	Upon histological assessment of the ERBT specimen, T1 substage must be assessed	Delphi	Agree
65	Upon histological assessment of the ERBT specimen, circumferential resection margin must be assessed	Delphi	Agree
66	Upon histological assessment of the ERBT specimen, deep resection margin must be assessed	Delphi	Agree
	<i>Post-operative management and follow-up schedule</i>		
67	It is safe to give single dose of intravesical chemotherapy immediately after ERBT	Delphi	Agree
68	The indications of single-dose of intravesical chemotherapy immediately after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
69	It is safe to perform second look TURBT after the first ERBT	Delphi	Agree
70	The indications of second look TURBT after ERBT should follow the EAU guidelines recommendation	Delphi	Agree

	as in the case of conventional TURBT		
71	It is safe to give intravesical BCG therapy after ERBT	Delphi	Agree
72	The indications of intravesical BCG therapy after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
73	The flexible cystoscopy surveillance protocol after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
74 ^a	Upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in-field and out-of-field recurrence	Delphi	Agree
	<i>Data reporting and outcome measures</i>		
75	In studies of ERBT, both per patient and per tumour analyses should be performed for different outcomes	Delphi	Agree
76	In studies of ERBT, the operative time is an important outcome to measure	Delphi	Agree
77	In studies of ERBT, the presence of obturator nerve reflex an important outcome to measure	Delphi	Agree
78	In studies of ERBT, the need for bladder irrigation is an important outcome to measure	Delphi	Agree
79	In studies of ERBT, the duration of urethral catheterization is an important outcome to measure	Delphi	Agree
80	In studies of ERBT, hospital stay is an important outcome to measure	Delphi	Agree
81	In studies of ERBT, the complication rate is an important outcome to measure	Delphi	Agree
82	In studies of ERBT, the Clavien-Dindo grading system is the preferred system to measure the severity of complication	Delphi	Agree
83	In studies of ERBT, the need for blood transfusion is an important outcome to measure	Delphi	Agree
84	In studies of ERBT, the occurrence of urethral stricture is an important outcome to measure	Delphi	Agree
85	In studies of ERBT, the occurrence of bladder perforation is an important outcome to measure	Delphi	Agree
86	In studies of ERBT, the occurrence of urinary tract infection is an important outcome to measure	Delphi	Agree
87	In studies of ERBT, the occurrence of transurethral resection syndrome is an important outcome to measure	Delphi	Agree
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	Meeting	Not reached
89	In studies of ERBT, the occurrence of ureteric stricture is an important outcome to measure	Delphi	Agree
90	In studies of ERBT, the successful en bloc resection rate (i.e. removal of bladder tumour in one piece) is an important outcome to measure	Delphi	Agree
91	In studies of ERBT, presence of detrusor muscle in the ERBT specimen is an important outcome to measure	Delphi	Agree
92	In studies of ERBT, presence of clear circumferential resection margin in the ERBT specimen is an important outcome to measure	Delphi	Agree
93	In studies of ERBT, presence of clear deep resection margin in the ERBT specimen is an important	Delphi	Agree

	outcome to measure		
94	In studies of ERBT, whether post-operative intravesical instillation of chemotherapy is given is an important outcome to report	Delphi	Agree
95	In studies of ERBT, whether second look transurethral resection is performed is an important outcome to report	Delphi	Agree
96	In studies of ERBT, any residual disease is detected upon second look transurethral resection is an important outcome to report	Delphi	Agree
97	In studies of ERBT, any upstaging of disease is detected upon second look transurethral resection is an important outcome to report	Delphi	Agree
98	In studies of ERBT, whether intravesical BCG therapy is given is an important outcome to report	Delphi	Agree
99	In studies of ERBT, 3-month recurrence rate is an important outcome to measure	Delphi	Agree
100	In studies of ERBT, 1-year recurrence rate is an important outcome to measure	Delphi	Agree
101	In studies of ERBT, 1-year progression rate is an important outcome to measure	Delphi	Agree
102	In studies of ERBT, 5-year recurrence rate is an important outcome to measure	Delphi	Agree
103	In studies of ERBT, 5-year progression rate is an important outcome to measure	Delphi	Agree

EAU = European Association of Urology; ERBT = En bloc resection of bladder tumour; TURBT = Transurethral resection of bladder tumour.

^a This statement was added after first round of Delphi survey.

Take home message

An international collaborative consensus statement on en bloc resection of bladder tumour has been developed. The consensus statement serves as a standard reference for practising en bloc resection of bladder tumour and conducting future research work in this area.

Appendix 1. Supplementary data.

	Page
Table of contents	
1. Search strategy of the systematic review	2
2. Study characteristics of included non-randomised studies	3
3. Risk of bias assessment of included non-randomised studies	7
4. Other findings of the meta-analysis results from randomised controlled trials	9
5. Summary of the results from non-randomised studies	10
6. GRADE summary for randomised controlled trials	14
7. GRADE summary for non-randomised studies	16
8. References - List of studies included in the effectiveness review	18
9. References - List of studies included in the uncertainties review	22

1. Search strategy of the systematic review

Database: Embase <1974 to 2019 June 04>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 5, 2019>

Search Strategy:

- 1 exp *Urinary Bladder Neoplasms/ or exp *bladder tumor/ (96660)
- 2 ((bladder or vesical) adj5 (cancer* or carcin* or malign* or tumor* or tumour* or neoplas* or papilloma*)).tw,kw. (133952)
- 3 exp *Carcinoma, Transitional Cell/ or *exp transitional cell carcinoma/ (30028)
- 4 ((transitional cell or urothelial or urothelium) adj3 (carcinoma* or cancer*)).tw,kw. (50931)
- 5 or/1-4 (167520)
- 6 (en bloc or ERBT or EBTUR or EBTURBT or RERBT or ETURBT).mp. (25957)
- 7 5 and 6 (793)
- 8 limit 7 to english language [Limit not valid in CDSR; records were retained] (680)
- 9 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10475381)
- 10 8 not 9 (665)
- 11 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or paediatric* or infant* or infancy or neonat* or newborn* or new born* or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4140342)
- 12 10 not 11 (662)
- 13 gall bladder.ti. (4842)
- 14 12 not 13 (658)

2. Study characteristics of included non-randomised studies

Study	Country	Study design	Eligibility criteria	Comparison	Total	ERBT arm	TURBT arm
Altobelli et al. (2016)	Italy	Retrospective cohort study	Newly diagnosed bladder cancer Not locally advanced	Thulium laser ERBT vs TURBT ^c	120	60	60
Chen et al. (2016)	China	Prospective cohort study	Primary NMIBC Not MIBC No distant metastasis No upper urinary tract tumours No medical conditions contradicting surgery	Greenlight laser ERBT vs Monopolar TURBT	158	83	75
Cheng et al. (2017)	China	Retrospective cohort study	Primary NMIBC <=3cm in diameter <=3 tumours No cT2 or higher disease No distant metastases At least 12 months of follow up or until death	Greenlight laser ERBT vs TURBT ^c	64	34	30
Cheng et al. (2018)	China	Retrospective cohort study	Primary NMIBC Not MIBC or CIS >18 years old ECOG 0-1 No pregnancy	HybridKnife ERBT vs Monopolar TURBT	193	95	98
D'Souza et al. (2016)	India	Prospective cohort study	Localised papillary tumour Not MIBC Not >3cm <5 tumours No extravesical extension, lymphatic metastasis or invasion of adjacent organs	Holmium laser ERBT vs Monopolar TURBT	50	23	27
Dymov et al. (2018) and Kogan et al. (2018) ^a	Russia	Non-randomised study ^b	cT1 bladder cancer	Thulium laser ERBT vs TURBT ^c	26	16	10

Hayashida et al. (2019)	Japan	Retrospective cohort study	Monopolar EMR + bipolar ERBT group: >=1.5cm in diameter <= 3 tumours TURBT group: <1.5cm or >6cm in diameter >3 tumours NMIBC without metastasis No neoadjuvant chemotherapy and radiotherapy	Monopolar EMR + bipolar ERBT vs TURBT ^c	70	39	31
Huang et al. (2016) ^d	China	Retrospective cohort study	Primary NMIBC Not MIBC No distant metastasis No upper urinary tract tumours Not MIBC	Thulium laser ERBT vs Monopolar TURBT	140	70	70
Introini et al. (2012)	Italy	Prospective matched cohort study		ERBT ^c vs TURBT ^c	76	26	50
Jiang et al. (2018)	China	Non-randomised study ^b	NMIBC	Bipolar ERBT vs TURBT ^c	31	13	18
Li et al. (2019)	China	Retrospective cohort study	Primary NMIBC No cT2 or higher disease Not CIS No distant metastasis Not >85 years Not ASA 4 or above	Thulium laser ERBT vs Bipolar TURBT	256	136	120
Liang et al. (2019)	China	Retrospective cohort study	Primary NMIBC Excluded specimens without muscularis propria	Greenlight laser ERBT vs Bipolar TURBT	158	88	70
Migliari et al. (2015)	Italy	Retrospective cohort study	Primary papillary bladder tumour Single tumour >1 cm in diameter	Thulium laser ERBT vs Monopolar TURBT	119	58	61

Rezac et al. (2017)	Czech Republic	Retrospective cohort study	Primary Ta/T1 NMIBC or CIS EORTC intermediate risk group for recurrence	ERBT ^c vs TURBT ^c	270	39	231
Mandhani et al. (2011), Upadhyay et al. (2012) and Sureka et al. (2014) ^a	India	Prospective cohort study	Primary tumour Single tumour 2-4cm in size No pedunculated tumours No tumour with associated hydroureteronephrosis No prior TURBT Excluded patients with absence of detrusor muscle in specimen ^c	Monopolar ERBT vs Monopolar TURBT	45	21	24
Teoh et al. (2017a) + Teoh et al. (2017b) ^a	Hong Kong	Retrospective cohort study	All patients undergoing ERBT or TURBT	Bipolar ERBT vs Bipolar TURBT	154	47	107
Xishuang et al. (2010)	China	Non-randomised study ^b	Primary NMIBC Not MIBC	Holmium laser ERBT vs Monopolar and bipolar TURBT	173	64	109
Xu et al. (2017)	China	Retrospective cohort study	Primary NMIBC without CIS Less than 4.5cm in diameter No upper urinary tract tumour	Vela laser ERBT vs TURBT ^c	70	26	44
Yanagisawa et al. (2018)	Japan	Retrospective cohort study	pT1 bladder cancer	ERBT ^c vs TURBT ^c	90	18	72
Zhang et al. (2017)	China	Retrospective cohort study	Primary NMIBC	Monopolar ERBT vs Monopolar TURBT	90	40	50
Zhong et al. (2010)	China	Retrospective cohort study	Newly diagnosed NMIBC Not MIBC Not locally advanced No distant metastases No concomitant benign prostatic hyperplasia	Holmium laser and thulium laser ERBT vs Monopolar TURBT	97	55	42
Zhu et al. (2008)	China	Retrospective cohort study	Primary NMIBC	Holmium laser ERBT vs TURBT ^c	212	101	111

ASA: American Society of Anaesthesiologists; CIS: Carcinoma in-situ; ECOG: Eastern Cooperative Oncology Group; EMR: Endoscopic mucosal resection; EORTC: European Organisation for Research and Treatment of Cancer; ERBT: En bloc resection of bladder tumour; MIBC: Muscle-invasive bladder cancer; NMIBC: Non-muscle-invasive bladder cancer; TURBT: Transurethral resection of bladder tumour.

^a Same study with numerous reports; report with the most complete data and longest follow-up was presented

^b Nature of study (i.e. retrospective vs prospective) was not mentioned

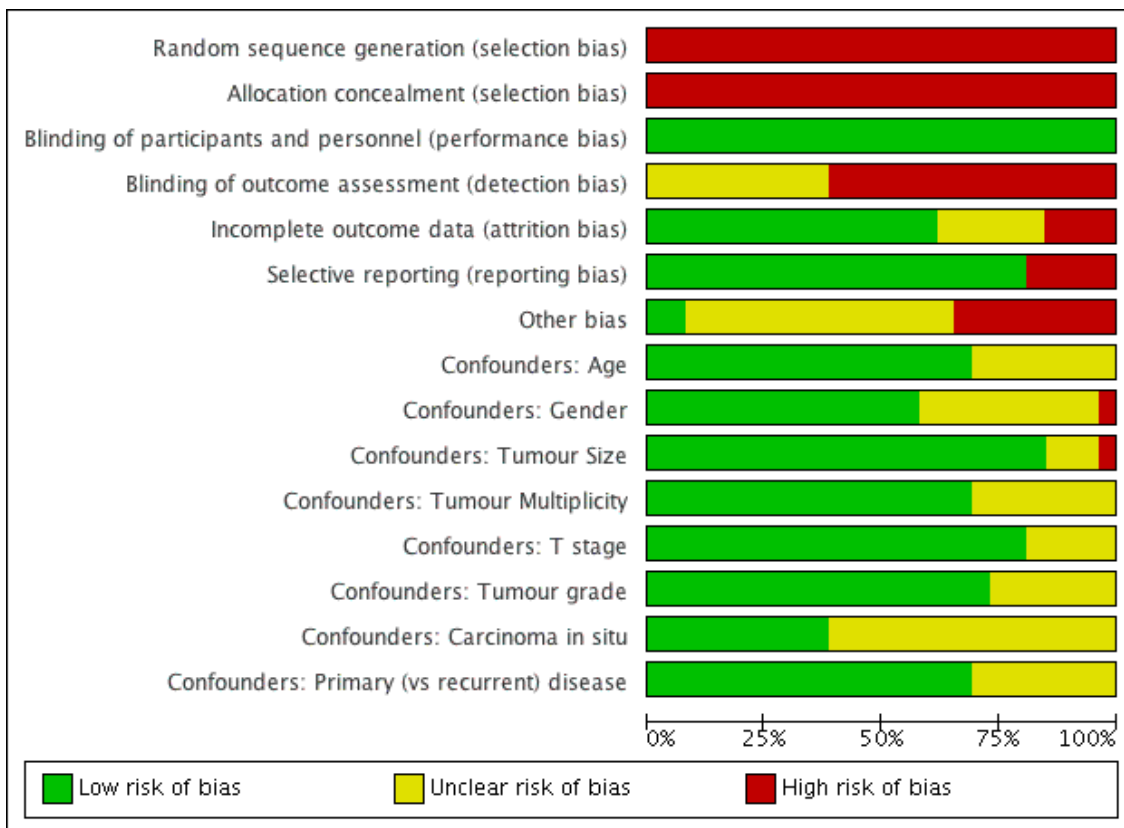
^c Unknown energy source

^d This is a three-arm study comparing between thulium laser ERBT, holmium laser vaporisation and monopolar TURBT. Data on the holmium laser vaporisation group was not presented.

^e This exclusion criteria was only mentioned in Sureka et al. (2014)

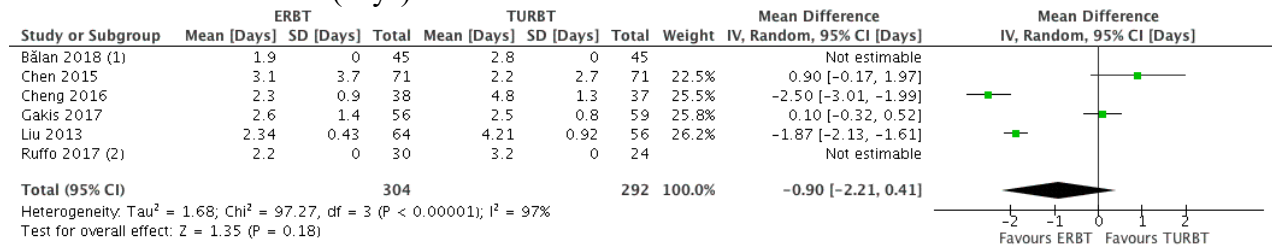
3. Risk of bias assessment of included non-randomised studies

	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	Confounders: Age	Confounders: Gender	Confounders: Tumour Size	Confounders: Tumour Multiplicity	Confounders: T stage	Confounders: Tumour grade	Confounders: Carcinoma in situ	Confounders: Primary (vs recurrent) disease
Altobelli 2016	+	+	-	+	+	+	?	?	?	+	?	?	?	?	?
Chen 2016	+	+	-	?	?	+	?	+	+	+	+	+	+	+	+
Cheng 2017	+	+	-	+	+	+	+	+	+	+	+	+	+	?	+
Cheng 2018	+	+	-	?	+	+	+	+	+	+	+	+	+	+	+
D'Souza 2016	+	+	-	?	+	+	?	+	+	+	+	+	+	?	+
Dymov 2018	+	+	-	?	+	+	?	?	?	?	?	?	?	?	?
Hayashida 2019	+	+	-	+	+	+	+	+	+	+	+	+	+	?	+
Huang 2016	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Introini 2012	+	+	-	?	+	+	?	+	+	+	+	+	?	?	+
Jiang 2018	+	+	-	?	?	+	?	?	?	?	?	?	?	?	?
Kogan 2018	+	+	-	?	+	+	?	?	?	?	?	?	?	?	?
Li 2019	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Liang 2019	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Mandhani 2011	+	+	-	?	+	+	?	?	?	+	?	?	?	?	?
Migliari 2015	+	+	-	+	+	+	+	+	+	+	+	+	+	?	+
Rezac 2017	+	+	-	+	+	+	?	?	?	+	+	+	+	+	+
Sureka 2014	+	+	-	?	+	+	+	?	?	+	+	+	+	?	+
Teoh 2017a	+	+	-	+	+	+	?	+	+	+	?	+	+	?	?
Teoh 2017b	+	+	-	+	+	+	?	+	+	+	?	+	+	?	?
Upadhyay 2012	+	+	-	?	+	+	?	?	?	+	+	+	+	?	+
Xishuang 2010	+	+	-	?	+	+	?	+	+	+	+	+	+	+	+
Xu 2017	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Yanagisawa 2018	+	+	-	?	+	?	?	?	?	+	?	+	?	?	?
Zhang 2017	+	+	-	?	+	+	+	+	+	+	+	+	+	?	+
Zhong 2010	+	+	-	+	+	+	+	?	?	+	+	+	+	+	+
Zhu 2008	+	+	-	?	+	+	?	+	+	+	+	+	+	+	+



4. Other findings of the meta-analysis results from randomised controlled trials

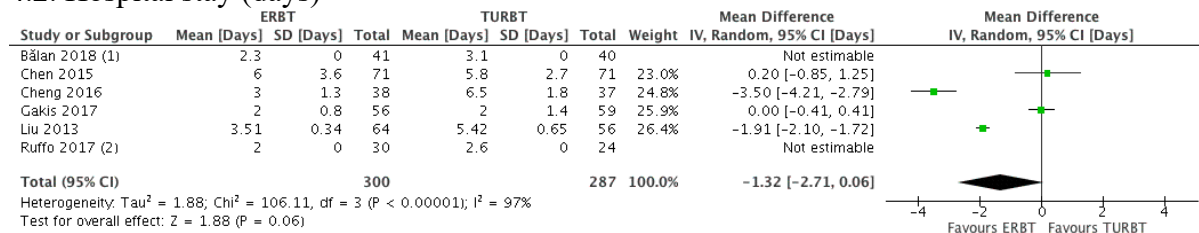
4.1. Catheterisation time (days)



Footnotes

- (1) Standard deviation was not provided
(2) Standard deviation was not provided

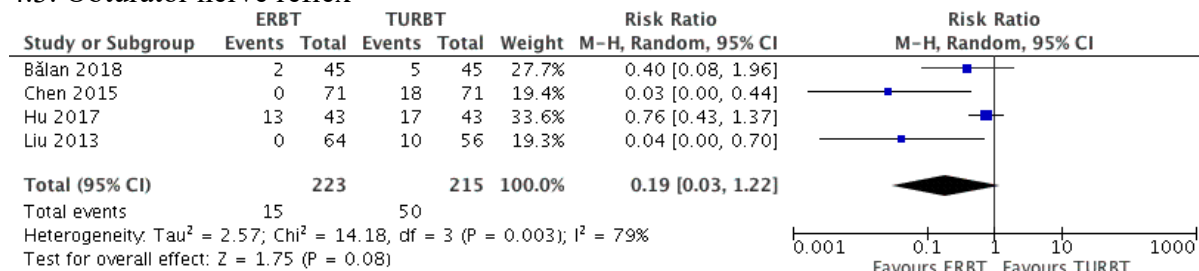
4.2. Hospital stay (days)



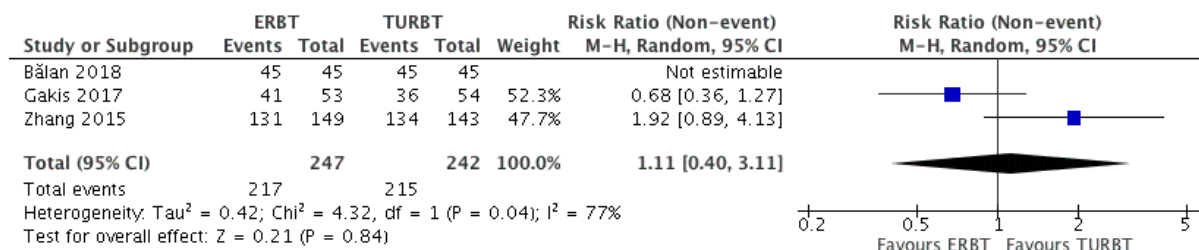
Footnotes

- (1) Standard deviation was not provided
(2) Standard deviation was not provided

4.3. Obturator nerve reflex

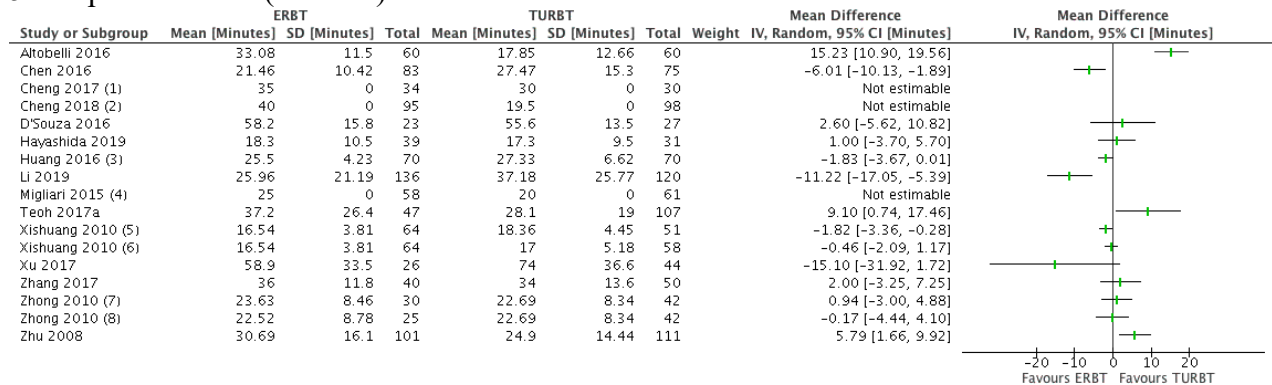


4.4. Presence of detrusor muscle in specimen



5. Summary of the results from non-randomised studies

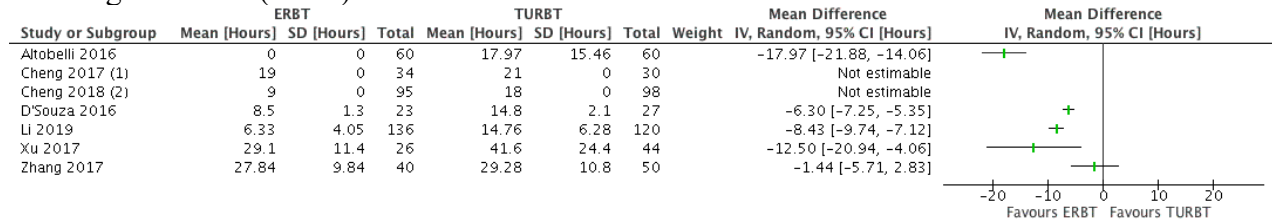
5.1. Operative time (minutes)



Footnotes

- (1) Standard deviation was not provided
- (2) Mean and standard deviation were not provided; Median value was presented
- (3) Thulium laser ERBT arm of the study
- (4) Standard deviation was not provided
- (5) Monopolar TURBT arm of the study; Data on 'resection time' was used.
- (6) Bipolar TURBT arm of the study; Data on 'resection time' was used
- (7) Thulium laser ERBT arm of the study
- (8) Holmium laser ERBT arm of the study

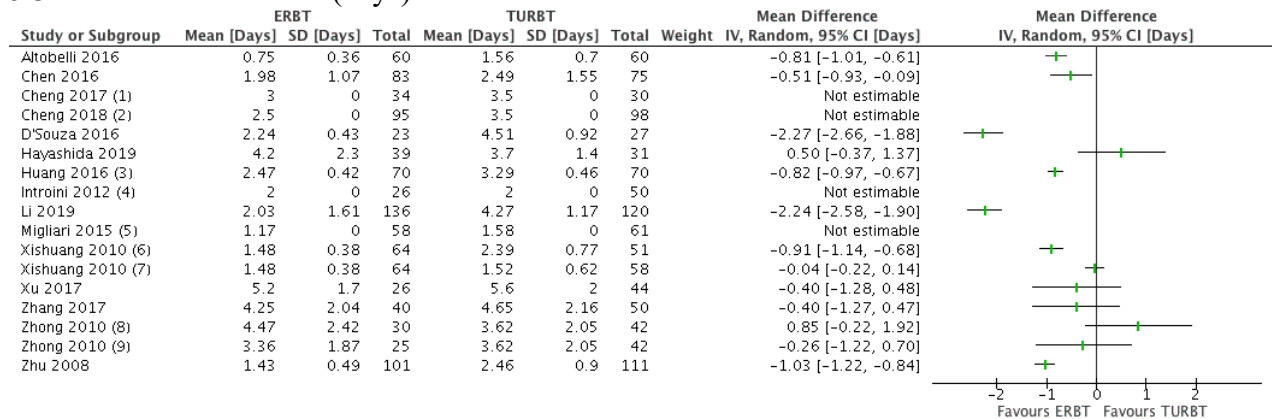
5.2. Irrigation time (hours)



Footnotes

- (1) Standard deviation was not provided
- (2) Mean and standard deviation were not provided; Median value was presented

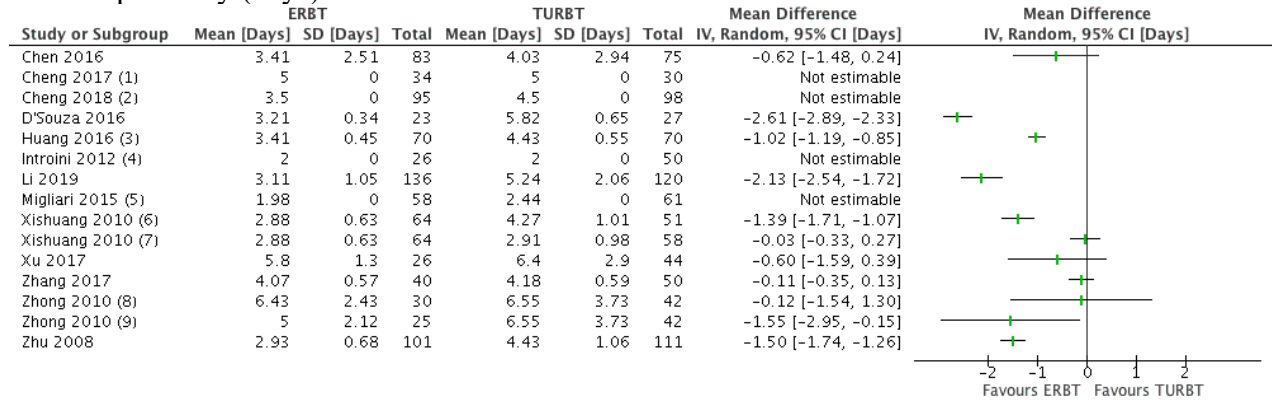
5.3. Catheterisation time (days)



Footnotes

- (1) Standard deviation was not provided
- (2) Mean and standard deviation were not provided; Median value was presented
- (3) Thulium laser ERBT arm of the study
- (4) Mean and standard deviation were not provided; Median value was presented
- (5) Standard deviation was not provided
- (6) Monopolar TURBT arm of the study
- (7) Bipolar TURBT arm of the study
- (8) Thulium laser ERBT arm of the study
- (9) Holmium laser ERBT arm of the study

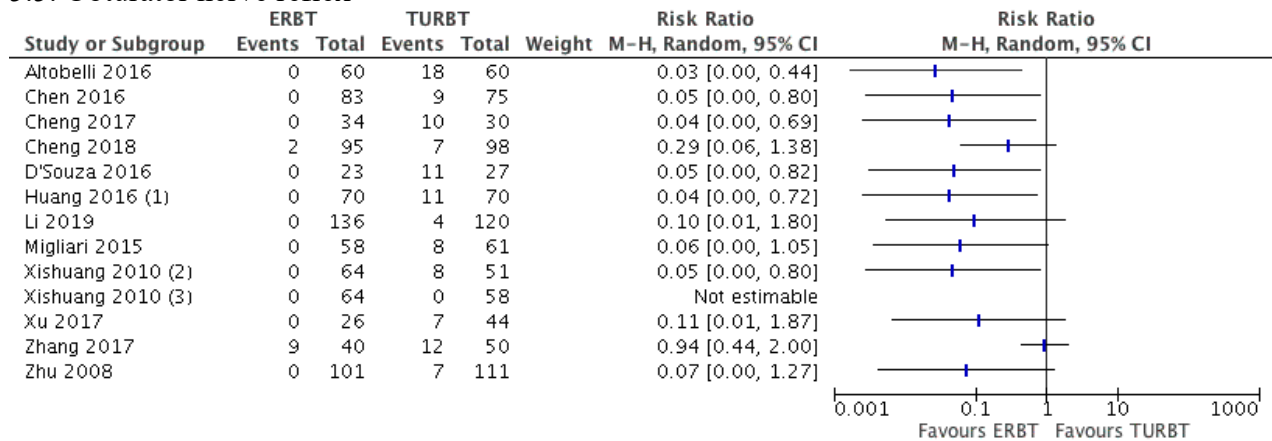
5.4. Hospital stay (days)



Footnotes

- (1) Standard deviation was not provided
- (2) Mean and standard deviation were not provided; Median value was presented
- (3) Thulium laser ERBT arm of the study
- (4) Mean and standard deviation were not provided; Median value was presented
- (5) Standard deviation was not provided
- (6) Monopolar TURBT arm of the study
- (7) Bipolar TURBT arm of the study
- (8) Thulium laser ERBT arm of the study
- (9) Holmium laser ERBT arm of the study

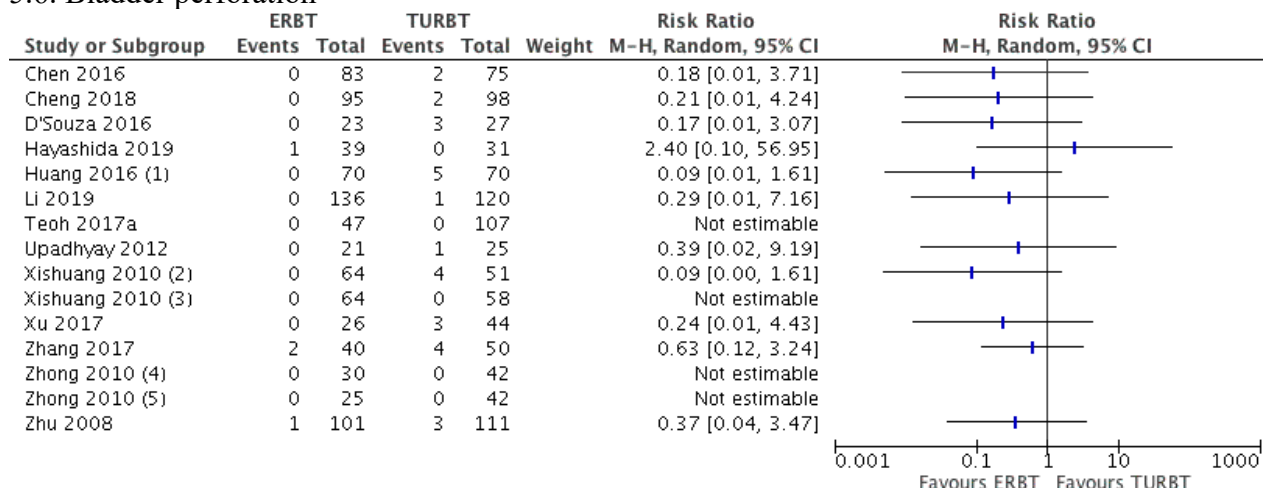
5.5. Obturator nerve reflex



Footnotes

- (1) Thulium laser ERBT arm of the study
- (2) Monopolar TURBT arm of the study
- (3) Bipolar TURBT arm of the study

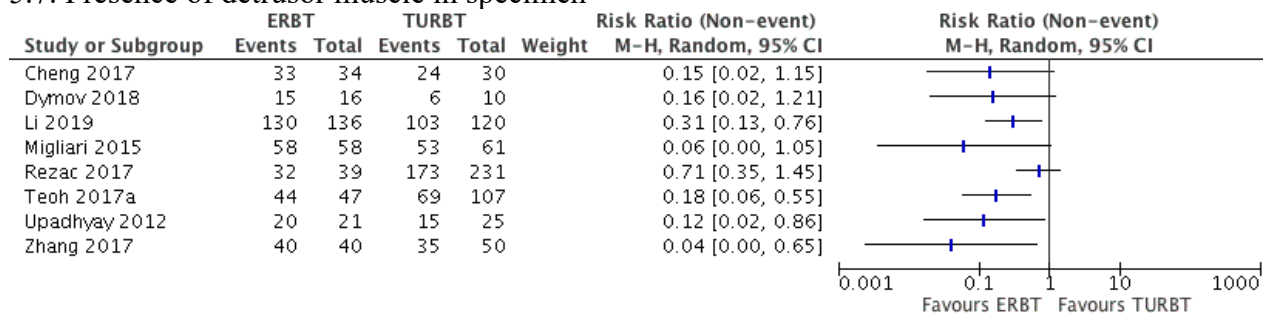
5.6. Bladder perforation



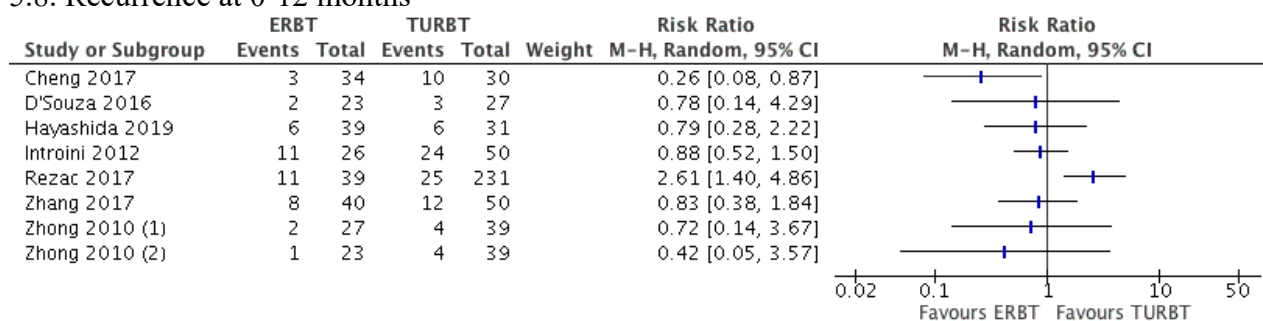
Footnotes

- (1) Thulium laser ERBT arm of the study
- (2) Monopolar TURBT arm of the study
- (3) Bipolar TURBT arm of the study
- (4) Thulium laser ERBT arm of the study
- (5) Holmium laser ERBT arm of the study

5.7. Presence of detrusor muscle in specimen



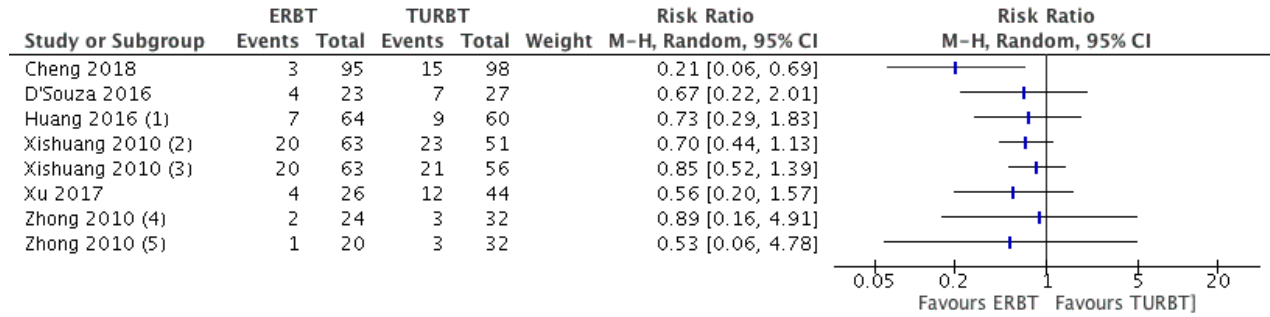
5.8. Recurrence at 0-12 months



Footnotes

- (1) Thulium laser ERBT arm of the study
- (2) Holmium laser ERBT arm of the study

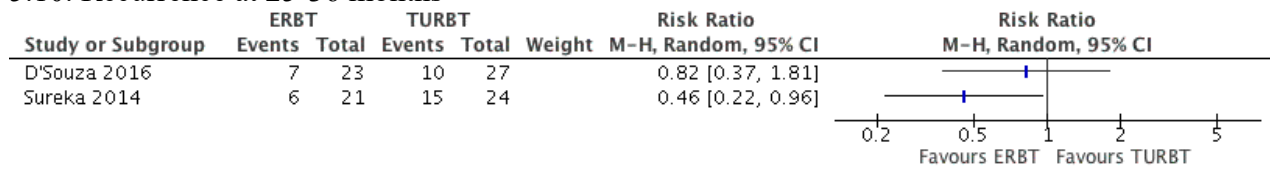
5.9. Recurrence at 13-24 months



Footnotes

- (1) Thulium laser ERBT arm of the study
- (2) Monopolar TURBT arm of the study
- (3) Bipolar TURBT arm of the study
- (4) Thulium laser ERBT of the study
- (5) Holmium laser ERBT of the study

5.10. Recurrence at 25-36 months




6. GRADE summary for randomised controlled trials


Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERBT	TURBT	Relative (95% CI)	Absolute (95% CI)		
Operative time												
10	randomised trials	serious ^{a,b}	serious ^c	not serious	serious ^d	none	586	569	-	MD 9.07 higher (3.36 higher to 14.79 higher)	⊕○○○ VERY LOW	IMPORTANT
Irrigation time												
2	randomised trials	serious ^{e,f}	not serious	not serious	not serious	none	102	93	-	MD 7.24 lower (9.29 lower to 5.2 lower)	⊕⊕⊕○ MODERATE	IMPORTANT
Catheterisation time												
6	randomised trials	serious ^{a,b}	serious ^c	not serious	not serious	none	304	292	-	MD 0.9 lower (2.21 lower to 0.4 higher)	⊕⊕○○ LOW	IMPORTANT
Hospital stay												
6	randomised trials	serious ^{a,b}	serious ^c	not serious	not serious	none	300	287	-	MD 1.32 lower (2.71 lower to 0.06 higher)	⊕⊕○○ LOW	IMPORTANT
Obturator nerve reflex												
4	randomised trials	serious ^{a,g}	serious ^c	not serious	very serious ^h	none	15/223 (6.7%)	50/215 (23.3%)	RR 0.19 (0.03 to 1.22)	188 fewer per 1,000 (from 226 fewer to 51 more)	⊕○○○ VERY LOW	IMPORTANT
Bladder perforation												
5	randomised trials	serious ^{a,b}	not serious	not serious	not serious	none	4/370 (1.1%)	18/353 (5.1%)	RR 0.30 (0.11 to 0.83)	36 fewer per 1,000 (from 45 fewer to 9 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERBT	TURBT	Relative (95% CI)	Absolute (95% CI)		


Presence of detrusor muscle in specimen

3	randomised trials	serious ^{a,b}	serious ^c	not serious	very serious ^h	none	217/247 (87.9%)	215/242 (88.8%)	RR 1.11 (0.40 to 3.11)	98 more per 1,000 (from 533 fewer to 1,000 more)	 VERY LOW	CRITICAL
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Recurrence at 0-12 months

5	randomised trials	serious ^{a,e}	not serious	not serious	very serious ^h	none	63/322 (19.6%)	72/300 (24.0%)	RR 0.82 (0.56 to 1.19)	43 fewer per 1,000 (from 106 fewer to 46 more)	 VERY LOW	CRITICAL
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Recurrence at 13-24 months

2	randomised trials	serious ^{a,f}	not serious	not serious	very serious ^h	none	17/135 (12.6%)	20/127 (15.7%)	RR 0.79 (0.44 to 1.42)	33 fewer per 1,000 (from 88 fewer to 66 more)	 VERY LOW	CRITICAL
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Recurrence at 25-36 months

3	randomised trials	serious ^{a,f}	not serious	not serious	very serious ^h	none	109/293 (37.2%)	112/277 (40.4%)	RR 0.89 (0.65 to 1.22)	44 fewer per 1,000 (from 142 fewer to 89 more)	 VERY LOW	CRITICAL
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. Sequence generation and allocation concealment unclear in most studies
- b. Blinding of outcome assessor unclear in most studies
- c. Important heterogeneity with high I square value
- d. Wide 95% CI
- e. Blinding of outcome assessors unclear in all studies
- f. Allocation concealment unclear in all studies
- g. High risk of bias for allocation concealment in one study and unclear in all others
- h. Very wide 95% CI; contains appreciable benefit and appreciable harm at extremes of the CI.

7. GRADE summary for non-randomised studies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERBT	TURBT	Relative (95% CI)	Absolute (95% CI)		
Operative time												
15	observational studies	serious ^a	serious ^b	not serious	not serious	none	995	1077	not pooled	see comment	⊕○○○ VERY LOW	IMPORTANT
Irrigation time												
7	observational studies	serious ^a	not serious	not serious	not serious	none	414	429	not pooled	see comment	⊕○○○ VERY LOW	IMPORTANT
Catheterisation time												
15	observational studies	serious ^a	serious ^b	not serious	not serious	none	974	1020	not pooled	see comment	⊕○○○ VERY LOW	IMPORTANT
Hospital stay												
13	observational studies	serious ^a	not serious	not serious	not serious	none	875	929	not pooled	see comment	⊕○○○ VERY LOW	IMPORTANT
Obturator nerve reflex												
12	observational studies	serious ^a	not serious	not serious	not serious	strong association	854	855	not pooled	see comment	⊕⊕○○ LOW	IMPORTANT
Bladder perforation												
13	observational studies	serious ^a	not serious	not serious	serious ^c	none	864	951	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Presence of detrusor muscle in specimen												
8	observational studies	serious ^a	not serious	not serious	not serious	none	391	634	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL

Recurrence at 0-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERBT	TURBT	Relative (95% CI)	Absolute (95% CI)		
7	observational studies	serious ^a	not serious	not serious	not serious	none	251	497	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Recurrence at 13-24 months												
6	observational studies	serious ^a	not serious	not serious	serious ^d	none	378	400	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Recurrence at 25-36 months												
2	observational studies	serious ^a	not serious	not serious	not serious	none	44	51	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. Potential for confounding bias (see risk of bias graphs)
- b. Wide variation in estimates between studies; some studies show benefit for TURBT, others show benefit for EBRT
- c. Low event rates contributing to uncertain estimates across studies
- d. Wide confidence intervals across studies, many including appreciable benefit and appreciable harm

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