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European Association of Urology

Urothelial Cancer

Editorial by Marko Babjuk on pp. 112–113 of this issue

Transurethral En Bloc Resection Versus Standard Resection of Bladder Tumour: A Randomised, Multicentre, Phase 3 Trial

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Article info

Article history:
Accepted April 10, 2024

Associate Editor:
Sarah P. Psutka

Keywords:
Non–muscle-invasive bladder cancer
Bladder cancer
En bloc resection
En bloc resection of the bladder tumour

Abstract

Background and Objective: Conventionally, standard resection (SR) is performed by resecting the bladder tumour in a piecemeal manner. En bloc resection of the bladder tumour (ERBT) has been proposed as an alternative technique in treating nonmuscle-invasive bladder cancer (NMIBC). The objective of this study is to investigate whether ERBT could improve the 1-yr recurrence rate of NMIBC, as compared with SR.
Methods: A multicentre, randomised, phase 3 trial was conducted in Hong Kong. Adults with bladder tumour(s) of $\leq$3 cm were enrolled from April 2017 to December 2020, and followed up until 1 yr after surgery. Patients were randomly assigned to receive either ERBT or SR in a 1:1 ratio. The primary outcome was 1-yr recurrence rate. A modified intention-to-treat analysis on patients with histologically confirmed NMIBC was performed. The main secondary outcomes included detrusor muscle sampling rate, operative time, hospital stay, 30-d complications, any residual or upstaging of disease upon second-look transurethral resection, and 1-yr progression rate.

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https://doi.org/10.1016/j.eururo.2024.04.015

Transurethral resection of bladder tumour

Key Findings and Limitations: A total of 350 patients underwent randomisation, and 276 patients were histologically confirmed to have NMIBC. At 1 yr, 31 patients in the ERBT group and 46 in the SR group developed recurrence; the Kaplan-Meier estimate of 1-yr recurrence rates were 29% (95% confidence interval, 18–37) in the ERBT group and 38% (95% confidence interval, 28–46) in the SR group (p = 0.007). Upon a subgroup analysis, patients with 13 cm tumour, single tumour, Ta disease, or intermediate-risk NMIBC had a significant benefit from ERBT. None of the patients in the ERBT group and three patients in the SR group developed progression to muscle-invasive bladder cancer; the Kaplan-Meier estimates of 1-yr progression rates were 0% in the ERBT group and 2.6% (95% confidence interval, 0–5.5) in the SR group (p = 0.065). The median operative time was 28 min (interquartile range, 20–45) in the ERBT group and 22 min (interquartile range, 15–30) in the SR group (p < 0.001). All other secondary outcomes were similar in the two groups.

Conclusions and Clinical Implications: In patients with NMIBC of ≤3 cm, ERBT resulted in a significant reduction in the 1-yr recurrence rate when compared with SR. The study results support ERBT as the first-line surgical treatment for patients with bladder tumours of ≤3 cm.

ADVANCING PRACTICE

What does this study add?
This is the first randomised trial adequately powered to detect a significant difference in 1-year recurrence rate between ERBT and SR in patients with NMIBC. Regarding the primary outcome, we found that the 1-year recurrence rates were 29% (95% confidence interval, 18–37) in the ERBT group, and 38% (95% confidence interval, 28–46) in the SR group. There was no significant difference in 1-year progression rates, which were 0% in the ERBT group and 2.6% (95% confidence interval, 0-5.5) in the SR group (p=0.065). There was also no significant difference in 30-day complications between the two groups.

Clinical Relevance
The authors present a multicentre phase III randomized controlled trial of en bloc transurethral resection (EBRT) compared to standard resection for nonmuscle invasive bladder cancer. This article provides Level 1 evidence demonstrating that EBRT resulted in a statistically significant reduction in recurrence of NMIBC at one year. EBRT was able to be completed by participating surgeons per protocol in 88% of patients randomized to the intervention arm, and there were no significant differences in complication rates between arms.

Patient Summary
En bloc resection, that is, removal of the bladder tumour in one piece, could reduce 1-year recurrence rate of non-muscle-invasive bladder cancer. En bloc resection should be considered as the first-line surgical treatment for bladder tumours of ≤ 3cm.

1. Introduction

Bladder cancer is a common urological cancer, with approximately 610 000 new cases and 220 000 deaths in 2022 [1]. About 75% of bladder cancer patients present with non–muscle-invasive bladder cancer (NMIBC) [2]. Conventionally, standard resection (SR) can be performed transurethrally by resecting the bladder tumour(s) in a piecemeal manner [3]. However, the oncological control of NMIBC is unsatisfactory, with 1-yr recurrence rates ranging from 15% to 61% and 5-yr recurrence rates ranging from 31% to 78% [4]. Patients often require other adjunct treatments including single-dose intravesical mitomycin C instillation, second-look transurethral resection, and intravesical bacillus Calmette-Guerin (BCG) therapy [5–7].

Upon SR, piecemeal resection of the bladder tumour(s) results in floating tumour cells. Tumour cells may reimplant on to the bladder wall and lead to disease recurrence [8]. Tumour specimens are also fragmented, and it is not possible to assess the resection margin. Whether a "complete resection" has been achieved is dependent on the surgeon's experience. Second-look transurethral resection has been shown to detect residual disease in 17–67% in Ta disease and 20–71% in T1 disease [9].

Transurethral en bloc resection of the bladder tumour (ERBT) has been proposed as an alternative technique in

bladder tumour resection [10–12]. By removing the tumour in one piece, the risk of tumour reimplantation may be reduced [8]. Complete tumour resection can also be ascertained by histological means, as clear resection margins can be achieved in 94–99% of the cases [8,13,14]. In this phase 3, multicentre, randomised trial, we investigated whether ERBT would reduce the 1-yr recurrence rate in patients with NMIBC of $\leq$3 cm.

2. Patients and methods

2.1. Trial design

In this multicentre, randomised trial, we enrolled patients from 13 hospitals in Hong Kong. The trial protocol is available with the full text of this article (Supplementary material), and it was approved by our local Clinical Research Ethics Committee (CRE-2016.553-T). This study was registered with ClinicalTrials.gov (NCT02993211), and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

2.2. Patients

Adult patients who were found to have bladder tumour(s) upon flexible cystoscopy were screened for study eligibility. The exclusion criteria included bladder tumour base maximal dimension of >3 cm, bladder tumour detected during intravesical BCG therapy, histological diagnosis other than NMIBC (ie, patients with benign histology, muscle-invasive bladder cancer [MIBC], or nonurothelial carcinoma of the bladder), presence or prior history of upper urinary tract malignancy, Eastern Cooperative Oncology Group performance status of $\geq$3, American Society of Anesthesiologists physical status classification of III or above, history of bleeding disorder or use of anticoagulants, pregnancy, presence of other active malignancy, and life expectancy of <1 yr. Tumour size was determined by the surgeon's endoscopic judgement. There were no exclusion criteria on the number of bladder tumours. In Hong Kong, the standard BCG regimen is one induction course (six doses of BCG) plus three maintenance courses (three doses of BCG for each maintenance course) across a 1-yr time period. In our study, patients with any bladder tumours detected during the 1-yr BCG treatment period were excluded, as they would typically undergo radical cystectomy as the definitive treatment. Intravesical maintenance chemotherapy and other investigational drugs were not given in all participating centres. All patients had upper tract imaging to rule out concomitant upper tract urothelial carcinoma.

2.3. Randomisation

Patients were randomised to receive either transurethral ERBT or SR with an allocation ratio of 1:1. Central randomisation was performed with computer-generated random sequence numbers in permuted blocks of random sizes. In order to ensure allocation concealment, block sizes were not disclosed and randomisation codes were obtained through a web-based Internet application by the participating site. The urologist performing the surgery could not be blinded due to the nature of the intervention. Patients receiving the treatment and investigators assessing for any disease recurrence were blinded to the allocated treatment arm.

2.4. Interventions

All interventions were performed by urology specialists with a minimum experience of 50 cases of SR/ERBT combined, and they were advised to perform the interventions in a standardised and systematic manner as follows. All patients underwent bipolar transurethral resection with white-light cystoscopy, under spinal or general anaesthesia. In the ERBT group, the circumferential resection margin was first marked 5 mm from the bladder tumour using the cauterisation mode. An incision was made along the circumferential margin down to the detrusor muscle layer, using the cutting mode with an intermittent burst technique. The remaining central part of the tumour was further excised at the level of the detrusor muscle. For bladder tumours that were judged to be too large to retrieve en bloc, modified ERBT (ie, piecemeal resection of the exophytic part of the tumour followed by en bloc resection of the tumour base) was allowed [15]. In case of technical difficulty encountered during ERBT, the urologist was allowed to crossover to SR. In the SR group, bladder tumour was resected in a piecemeal manner. Once the bladder tumour has been resected in a piecemeal manner, crossover to ERBT is no longer feasible. In both groups, additional sampling of the resection bed was performed routinely in all cases according to the European Association of Urology (EAU) guidelines [16]. A urethral catheter was inserted at the end of the procedure, and the need of bladder irrigation postoperatively was left to the discretion of the operating surgeon. Postoperatively, a single dose of intravesical mitomycin C was instilled if the bladder tumour was judged to be completely resected endoscopically without any evidence of bladder perforation.

2.5. Subsequent management and follow-up schedule

Patients with benign histology, MIBC, or nonurothelial carcinoma of the bladder were excluded. For patients with histologically confirmed NMIBC, second-look transurethral resection was arranged within 2–6 wk after the first operation should there be any indications as stated in the EAU guidelines [16]. Upon the inception of the study in 2016, the EAU NMIBC guidelines [16] recommended that repeat transurethral resection should be offered (1) after incomplete initial transurethral resection of the bladder tumour; (2) if there is no muscle in the specimen after initial resection, with the exception of TaG1 tumours and primary carcinoma in situ (CIS); (3) in all T1 tumours; or (4) in all HG/G3 tumours except primary CIS. Patients were also stratified into low-, intermediate-, and high-risk groups according to the EAU risk group stratification for consideration of intravesical BCG [16]. For patients in the low-risk group, intravesical BCG was not offered. For patients in the intermediate- or high-risk group, induction and 1-yr maintenance course of intravesical BCG were offered. Surveillance flexible cystoscopy was performed once every 3 mo for up to 1 yr. Transurethral resection was offered if any suspicious tumour recurrence was noted during surveillance cystoscopy. For patients with normal or atypical cells but negative cystoscopy, they would continue regular surveillance cystoscopy without additional treatment. For patients with suspicious or malignant cells but negative

cystoscopy, they would be treated for CIS and managed by intravesical BCG therapy.

2.6. Outcome measures

The primary outcome was 1-yr recurrence rate. Histological diagnosis of urothelial carcinoma is mandatory to define disease recurrence. Time to recurrence was defined as the time interval between the date of allocated treatment and the date of disease recurrence. Secondary outcomes included detrusor muscle sampling rate, occurrence of obturator reflex, operative time, rate of postoperative mitomycin C instillation, hospital stay, 30-d complications, any residual disease or upstaging of disease upon second-look transurethral resection, and 1-yr progression rate. Upstaging of disease was defined as the presence of MIBC upon second-look transurethral resection. Disease progression was defined as progression of NMIBC to MIBC. Time to progression was defined as the time interval between the date of allocated treatment and the date of disease progression. In addition, for the ERBT group, resection margin and successful en bloc resection rate were also assessed.

2.7. Statistical analyses

According to the en bloc resection of urothelium carcinoma of the bladder (EBRUC) study [17], the 1-yr recurrence rates of patients with EAU low-, intermediate-, and high-risk NMIBC following ERBT were 11%, 16%, and 26%, respectively. We previously conducted a randomised trial on monopolar versus bipolar SR [18], and the 1-yr recurrence rate in patients with NMIBC following bipolar SR was 36%. By stratifying our patients into the EAU risk groups and utilising the reported 1-yr recurrence rates for the different risk groups from the EBRUC study, the expected overall 1-yr recurrence rate following ERBT was calculated to be 19%. With an estimated 17% difference (19% in the ERBT group vs 36% in the SR group) in the 1-yr recurrence rate with a significance level of 0.05 and a power of 80%, 118 patients with NMIBC will be required in each group to show a significant treatment effect. In the same randomised trial that we conducted [18], 76% of the patients were histologically confirmed to have NMIBC and the remaining 24% had benign histology, MIBC, or nonurothelial carcinoma of the bladder. Taking these into account and assuming a 10% dropout rate, 174 patients would be required in each group. Therefore, we aimed to recruit 350 patients in total.

All outcome measurements will be analysed with a modified intention-to-treat principle. Patients who were assigned to receive ERBT and eventually underwent SR were still included and analysed as the ERBT group. Only study participants with histologically confirmed non–muscle-invasive urothelial carcinoma of the bladder were included in the final analyses. The 1-yr recurrence and 1-yr progression rates were analysed with the Kaplan-Meier method, and significance was determined by the log-rank test. Regarding the primary outcome, a further subgroup analysis was performed and presented as a forest plot. A multivariable Cox regression analysis was also performed for the primary outcome. Operative time and hospital stay were compared using the Mann-Whitney *U* test. Detrusor muscle sampling, occurrence of obturator reflex, postoperative bladder irrigation, postoperative mitomycin C instillation, overall complication, haematuria, and urinary retention rates were compared using the chi-square test. The rate of residual disease, urinary tract infection, delirium, and grade 3–4 complications were compared using Fisher's exact test. A two-sided p value of <0.05 is considered to be statistically significant. All statistical analyses were performed with SPSS Statistics software, version 27 (IBM Corp., Armonk, NY, USA), and R software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

From April 2017 to December 2020, we enrolled 350 patients; a total of 175 patients in the ERBT group and

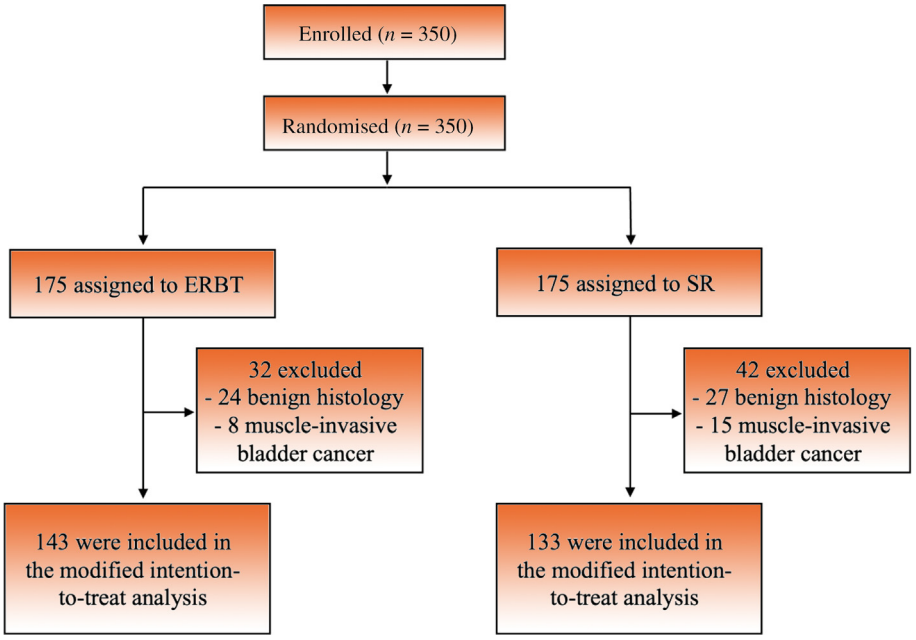

Fig. 1 – Enrolment, randomisation, and analysis. ERBT = en bloc resection of bladder tumour; SR = standard resection.

175 in the SR group. According to our predefined criteria, 74 patients were excluded due to benign histology or MIBC, resulting in 143 patients in the ERBT group and 133 in the SR group (Fig. 1). The baseline characteristics were similar between the two groups (Table 1). Regarding the EAU risk stratification, among the 143 patients in the ERBT group, 45 (31%) had low-risk NMIBC, 65 (45%) had intermediate-risk NMIBC, and 33 (23%) had high-risk NMIBC; among the 133 patients in the SR group, 34 (26%) had low-risk NMIBC, 75 (56%) had intermediate-risk NMIBC, and 24 (18%) had high-risk NMIBC. In the ERBT group, 126 patients (88%) underwent ERBT successfully, two patients (1.4%) underwent modified ERBT, and 15 patients failed ERBT and crossed over to SR. Complete macroscopic resection was achieved in all cases after the first surgery. Regarding the subsequent treatment, 27 of 143 patients (19%) in the ERBT group and 18 of 133 patients (14%) in the SR group underwent second-look transurethral resection; 20 of 143 patients (14%) in the ERBT group and 23 of 133 patients (17%) in the SR group received intravesical BCG therapy. At 1 yr, 12 of 143 patients (8.4%) in the ERBT group and 9 of 133 patients (6.8%) in the SR group were lost to follow-up.

Table 1 – Baseline characteristics of the patients

	ERBT (n = 143)	SR (n = 133)
Age (yr)	70 (63–78)	69 (62–79)
Male	108 (76)	110 (83)
ASA 2	125 (87)	121 (91)
ECOG 1	15 (10)	10 (7.5)
General anaesthesia	62 (43)	64 (48)
Recurrent tumour	52 (36)	55 (41)
Multiple tumours	46 (32)	47 (35)
Tumour size (cm) [a]	1.5 (1.0–2.0)	2.0 (1.0–2.0)
Tumour location [a]		
Anterior	7 (4.9)	12 (9.0)
Posterior	18 (13)	20 (15)
Left lateral	39 (27)	35 (26)
Right lateral	47 (33)	34 (26)
Dome	16 (11)	13 (9.8)
Trigone	6 (4.2)	3 (2.3)
Bladder neck	10 (7.0)	16 (12)
T stage [a]		
Ta	110 (77)	112 (84)
Tis [b]	2 (1.4)	3 (2.3)
T1	31 (22)	18 (14)
Presence of CIS	7 (4.9)	6 (4.5)
Tumour grade [a]		
PUNLMP	6 (4.2)	3 (2.3)
Low grade	92 (64)	93 (70)
High grade	45 (31)	37 (28)
EAU risk group		
Low risk	45 (31)	34 (26)
Intermediate risk	65 (45)	75 (56)
High risk	33 (23)	24 (18)
Successful en bloc resection	126 (88)	–
Successful modified en bloc resection	2 (1.4)	–
Crossed over to standard resection	15 (10)	–
Clear resection margin [c]	105 (82)	–
Subsequent treatment		
Second-look transurethral resection	27 (19)	18 (14)
Intravesical BCG therapy	20 (14)	23 (17)

ASA = American Society of Anaesthesiologists; BCG = bacillus Calmette-Guerin; CIS = carcinoma in situ; EAU = European Association of Urology; ECOG = Eastern Cooperative Oncology Group; ERBT = en bloc resection of bladder tumour; PUNLMP = papillary urothelial neoplasm of low malignant potential; SR = standard resection.
Continuous variables are presented as median (interquartile range), while categorical variables are presented as count (percentage).
[a] Most representative bladder tumour.
[b] Tis refers to patients with primary CIS.
[c] Among 128 patients with successful en bloc or modified en bloc resection.

3.2. Primary outcome

The primary outcome was the recurrence rate at 1 yr. In the ERBT group, 31 patients developed recurrence by 1 yr, and the Kaplan-Meier estimate of the 1-yr recurrence rate was 29% (95% confidence interval, 18–37). In the SR group, 46 patients developed recurrence by 1 yr, and the Kaplan-Meier estimate of the 1-yr recurrence rate was 38% (95% confidence interval, 28–46). A significant difference was detected in the 1-yr recurrence rate between the two groups (p = 0.007; Fig. 2).

Upon a subgroup analysis (Fig. 3), patients with 1–3 cm tumours, a single tumour, Ta disease, or intermediate-risk NMIBC had a significant benefit from ERBT. No significant difference was detected for all other subgroups. Upon a multivariable analysis, after adjusting for age and EAU risk group, ERBT was significantly associated with a lower risk of tumour recurrence, with a hazard ratio of 0.57 (95% confidence interval, 0.36–0.91; p = 0.017).

3.3. Secondary outcomes

None of the patients in the ERBT group developed disease progression. In the SR group, three patients developed disease progression to MIBC, and the Kaplan-Meier estimate of the 1-yr progression rate was 2.6% (95% confidence interval, 0–5.5; Fig. 4). No significant difference was detected in the 1-yr progression rate between the two groups (p = 0.065; Fig. 4). The ERBT group had a longer median operative time (28 min, interquartile range, 20–45) than the SR group (22 min, interquartile range, 15–30; p < 0.001). Other perioperative outcomes, including the detrusor muscle sampling rates, occurrence of obturator reflex, need of bladder irrigation, rates of postoperative mitomycin C instillation, and hospital stay, were similar between the two groups (Table 2). Among the 128 patients who underwent ERBT/modified ERBT successfully, 105 (82%) were able to achieve clear resection margins. Upon second-look transurethral resection surgery, the rates of residual disease in the ERBT group (seven of 27 patients; 26%) and the SR group (four of 18 patients; 22%) were similar (Table 2). In both groups, none of the patients had upstaging of disease upon second-look transurethral resection.

A more detailed flow diagram on the 27 patients in the ERBT group who received second-look transurethral resection is shown in Figure 5. Among the 27 patients who were assigned to receive ERBT, 19 underwent ERBT or modified ERBT, and the remaining eight failed ERBT and crossed over to SR. Among the 19 patients who had ERBT or modified ERBT, 11 had positive resection margins and the remaining eight had negative resection margins. Among the 11 patients with positive resection margins, five had residual disease upon second-look transurethral resection. None of the patients with negative resection margins had residual disease upon second-look transurethral resection. Among the eight patients who failed ERBT and crossed over to SR, two had residual disease upon second-look transurethral resection.

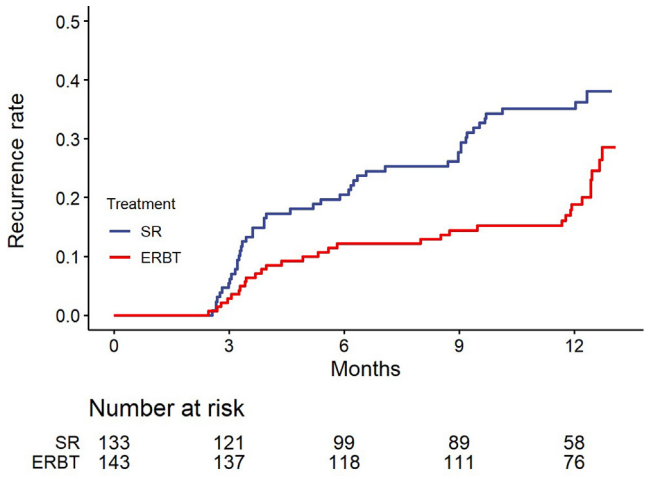

Fig. 2 – Kaplan-Meier analysis of disease recurrence. ERBT = en bloc resection of bladder tumour; SR = standard resection.

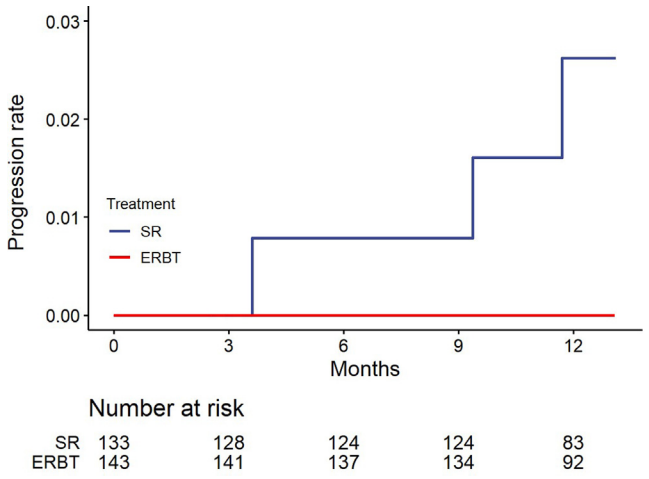

Fig. 4 – Kaplan-Meier analysis of disease progression. ERBT = en bloc resection of bladder tumour; SR = standard resection.

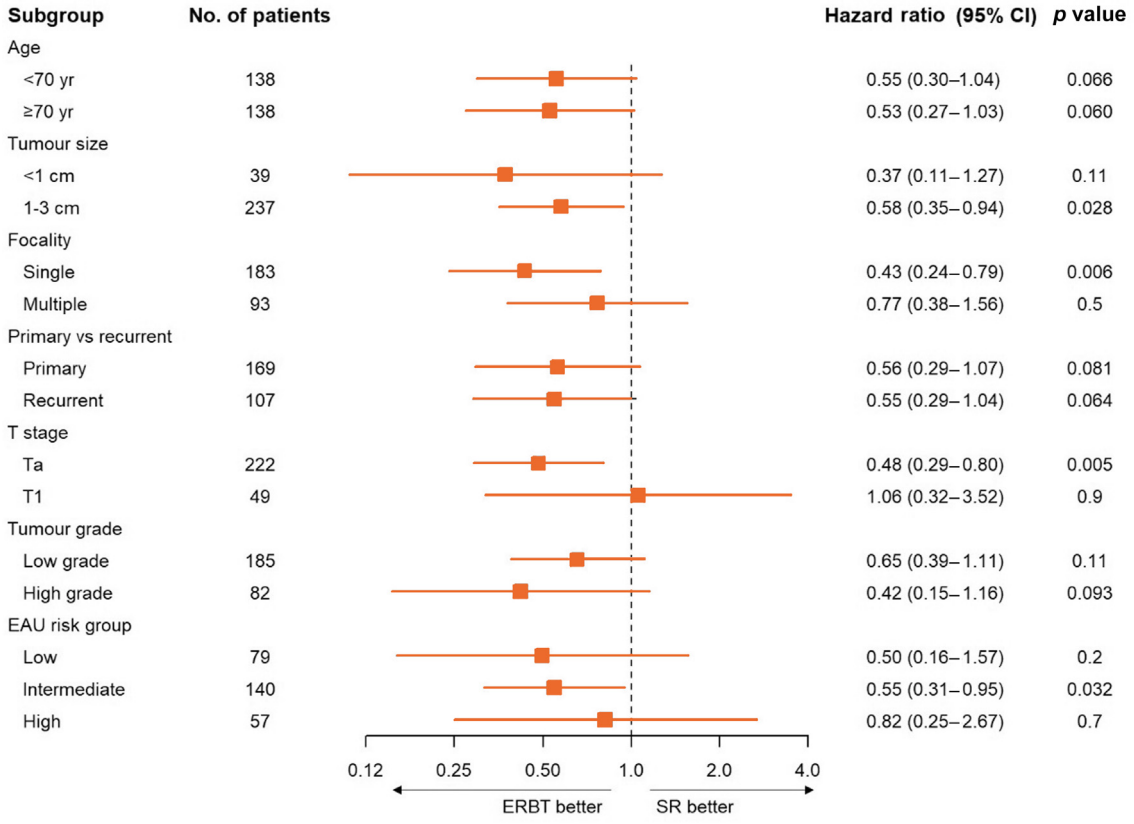

Fig. 3 – Forest plot of hazard ratio and 95% confidence intervals for tumour recurrence by patient and disease characteristics. CI = confidence interval; EAU = European Association of Urology; ERBT = en bloc resection of bladder tumour; SR = standard resection.

3.4. *Safety outcomes*

Within 30 d of operation, the rates of any-grade complications, minor complications (grade 1–2), and major complications (grade 3–4) were similar in the two groups (Table 3). Of note, among the 143 patients in the ERBT group, one patient (0.70%) developed acute coronary syndrome and one (0.70%) developed pulmonary embolism after surgery. None of the patients in the SR group developed major complications. There was no bladder perforation or mortality in the two groups.

4. Discussion

In this multicentre, randomised trial on patients with bladder tumours of ≤3 cm, ERBT resulted in a significant reduc-

Table 2 – Secondary outcomes of the study

	ERBT	SR	*p* value
Perioperative outcomes	*n* = 143	*n* = 133	
Detrusor muscle sampling rate, *n* (%)	119 (83)	112(84)	0.8
Occurrence of obturator reflex, *n* (%)	37 (26)	25 (19)	0.16
Operative time (min), median (IQR)	28 (20–45)	22 (15–30)	<0.001
Postoperative bladder irrigation, *n* (%)	26 (18)	18 (14)	0.3
Rate of mitomycin C instillation, *n* (%)	106 (74)	102 (77)	0.6
Hospital stay (d), median (IQR)	2 (2–2)	2 (2–3)	0.8
Second-look transurethral resection, *n* (%)	*n* = 27	*n* = 18	
Residual disease	7 (26)	4 (22)	1
Upstaging of disease	0	0	–

ERBT = en bloc resection of bladder tumour; IQR = interquartile range; SR = standard resection.

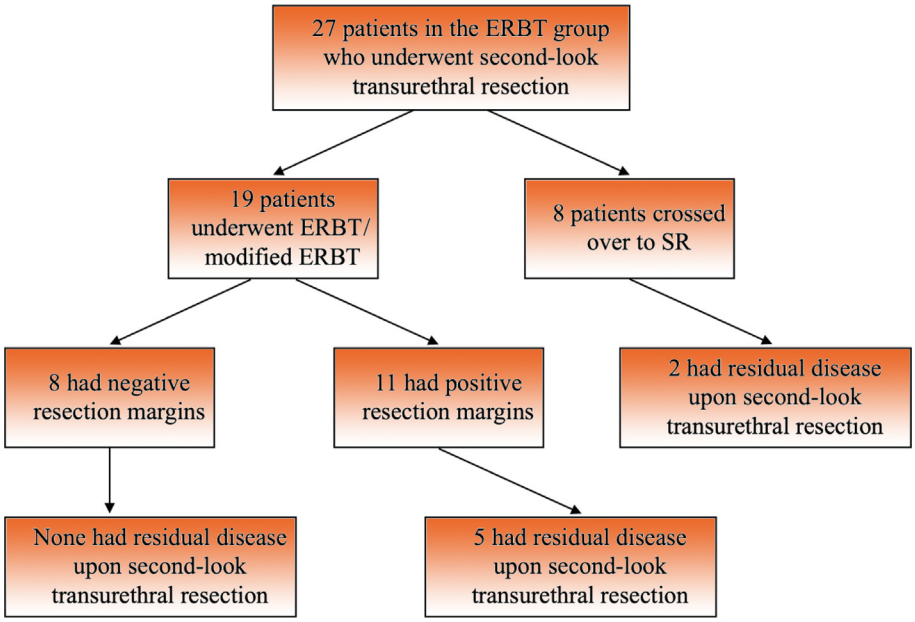

Fig. 5 – Flow diagram of the 27 patients in the en bloc resection group who received second-look transurethral resection. ERBT = en bloc resection of bladder tumour; SR = standard resection.

Table 3 – Safety outcomes of the study

	ERBT (*n* = 143)	SR (*n* = 133)	*p* value
Any complications, *n* (%) [a]	21 (15)	17 (13)	0.6
Grade 1–2 complications, *n* (%) [a]	19 (13)	17 (13)	0.9
Haematuria	6 (4.2)	7 (5.3)	0.7
Urinary retention	11 (7.7)	7 (5.3)	0.4
Urinary tract infection	2 (1.4)	4 (3.0)	0.4
Delirium	0	1 (0.75)	0.5
Grade 3–4 complications, *n* (%)	2 (1.4)	0	0.5
Acute coronary syndrome	1 (0.70)	0	1
Pulmonary embolism	1 (0.70)	0	1

ERBT = en bloc resection of bladder tumour; SR = standard resection.
[a] A total of 19 grade 1–2 complications occurred in 17 patients in the standard resection arm.

tion in the 1-yr recurrence rate. ERBT aims to ensure complete tumour resection and minimise the risk of tumour seeding [8], and this might explain the observable difference in recurrence rate as early as 3 mo [8]. In our study, the technical success rate of ERBT was 88%, and this is compatible with the literature [19]. Although 12% of the patients in the ERBT group eventually underwent SR due to technical difficulty (eg, bladder dome tumours, solid and sessile tumours, etc.), the significant difference in the 1-yr recurrence rate was maintained in the modified intention-to-treat analysis. Our study did not detect any significant difference in the 1-yr progression rate between the ERBT and SR groups ($p = 0.065$), but we should take note that the sample size was not calculated based on this secondary outcome. The ERBT group had a longer median operative time than the SR group (difference of 6 min), but other perioperative and safety outcomes were similar between the two groups. Overall, the results showed that ERBT is

safe, technically feasible, and generalisable in a multicentre setting.

Recently, Gallioli et al [20] published the results of a randomised noninferiority trial comparing ERBT with conventional SR. A total of 300 patients were included, of whom 248 underwent the assigned intervention. The authors found that the rate of detrusor muscle presence for the ERBT group was noninferior to that of the SR group (94% vs 95%, $p = 0.8$). With a median follow-up of 15 mo, the recurrence rates were 13% for the ERBT group and 18% for the conventional SR group, but it did not reach statistical significance ($p = 0.16$). In another trial by D'Andrea et al [21], 384 patients were included, and a total of 452 bladder tumours were resected and analysed for the primary outcome of detrusor muscle presence. The authors found that ERBT was superior to SR in terms of detrusor muscle presence (81% vs 71%, $p = 0.01$). However, with a median follow-up of 13 mo, there was no difference in tumour recurrence (18% in the ERBT group vs 17% in the SR group, $p = 0.6$). Variations in the quality of surgery and postoperative management such as the use of single-dose intravesical chemotherapy instillation and intravesical BCG therapy could exist, and these might explain why the results of recurrence rates were different.

The adoption of ERBT allows surgeons to perform the surgery in a more systematic manner. By defining the circumferential margin and the depth of incision early in the surgery, the surgeons would be able to perform a more uniform resection throughout the whole resection procedure. Any incomplete resection could also be reflected by the resection margins of the bladder tumour specimen. In the ERBT group, 27 patients underwent second-look transurethral resection, and seven of them were found to have residual disease (26%). Interestingly, among the seven patients with residual disease, five had positive resection margins in the ERBT tumour specimens, and the remaining two failed ERBT and crossed over to SR. None of the patients with negative resection margins had residual disease upon second-look transurethral resection. While data are limited, the authors believe that the presence of a positive resection margin in the ERBT specimens should prompt the need of second-look transurethral resection. On the contrary, second-look transurethral resection should be avoided in patients with clear resection margins.

ERBT avoids tumour fragmentation during the resection procedure. Together with the use of intravesical mitomycin C instillation, any minute floating tumour cells within the bladder could thus be eliminated. In a previous systematic review and individual patient meta-analysis, single-dose intravesical mitomycin C instillation was shown to be useful only in NMIBC patients with a prior recurrence rate of one or fewer recurrences per year, and those with a European Organisation for Research and Treatment of Cancer recurrence score of <5 [22]. However, all the included patients received SR instead of ERBT. Whether these results still apply in patients following ERBT remains to be explored in future trials.

To our knowledge, this is the first randomised trial with the recurrence rate at 1 yr as the primary outcome. This is also the only multicentre trial that has demonstrated a significant difference in the 1-yr recurrence rate between ERBT and SR. The multicentre setting is important to demonstrate the generalisability of ERBT across different surgeons and centres. However, this study has several limitations. First, although we follow the EAU guidelines in offering second-look transurethral resection surgery and intravesical BCG therapy, the actual decision to undergo treatment is largely a shared decision-making between the urologist and the patient, and this resulted in low rates of second-look transurethral resection surgery and intravesical BCG therapy in our study. Moreover, urology centres in Hong Kong typically do not offer intravesical maintenance chemotherapy, and this could be different from the clinical practice elsewhere. The readers should take note of these limitations and decide whether the study results are generalisable to their own clinical practices. Second, due to the low rates of second-look resection surgery in our study, there is a possibility of understaging, especially in those with T1 disease. This could affect our secondary outcome on disease progression. Third, there is no central pathology review. There could be interobserver variability in the histology assessment and reporting, and this might affect the interpretation of our results. Fourth, our sample size was calculated based on the primary outcome of 1-yr recurrence rate, and it is likely to be underpowered for other secondary outcomes including the 1-yr progression rate. Whether ERBT could lead to any benefit in disease progression should be explored in future clinical trials.

Last but not least, it is of utmost importance to ensure proper training and education as we disseminate the ERBT technique. A porcine bladder training model can be an effective tool for ERBT training [23]. The international consensus statement on ERBT has been published in 2020 [24], and it serves as a standard reference for any health care professionals who would like to adopt ERBT in their clinical practice. A collaborative effort is needed to standardise the ERBT procedure, ensure the quality of the surgery, and translate our clinical trial results into real-world benefit.

5. Conclusions

In patients with NMIBC of $\leq$3 cm, ERBT resulted in a significant reduction in the 1-yr recurrence rate when compared with SR. This multicentre study also showed that ERBT is generalisable with a comparable safety profile to SR. The study results support ERBT as the first-line surgical treatment for patients with bladder tumours of $\leq$3 cm.

***Author contributions*:** Jeremy Yuen-Chun Teoh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Other: None.

Financial disclosures: Jeremy Yuen-Chun Teoh certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: J.Y.-C. Teoh has previously received honorarium from Olympus HK & China Limited as an invited speaker. Other authors have no conflict of interest to declare.

***Funding/Support and role of the sponsor*:** This work was funded by GRF/ECS, Research Grants Council, HKSAR (reference no.: 24116518).

***Data sharing*:** Individual, deidentified participant data used in these analyses will be shared on request from any qualified investigator after the approval of a protocol and signed data access agreement via both the EB-StaR Study Group and the Chinese University of Hong Kong (Hong Kong, China).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.04.015.

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