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En Bloc Versus Conventional Transurethral Resection of Bladder Tumors: A Single-center Prospective Randomized Noninferiority Trial

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Abstract

Background: It has been proposed that en bloc resection of bladder tumor (ERBT) improves the quality of tumor resection. A recent international collaborative consensus statement on ERBT underlined the lack of high-quality prospective studies precluding the achievement of solid conclusion on ERBT.

Objective: To compare conventional transurethral resection of bladder tumor (cTURBT) and ERBT.

Design, setting, and participants: This study (NCT04712201) was a prospective, randomized, noninferiority trial enrolling patients diagnosed with bladder cancer (BC) undergoing endoscopic intervention. Inclusion criteria were: tumor size ≤3 cm, three or fewer lesions, and no sign of muscle invasion and/or ureteral involvement. For a noninferiority rate in BC staging of 5% (α risk 2.5%; β risk 20%), a total of 300 subjects were randomized to ERBT treatment at a 1:1.5 allocation ratio.

Intervention: TURBT and ERBT.

Outcome measurements and statistical analysis: The primary outcome was the presence of detrusor muscle at final histology. Secondary outcomes include BC staging, T1 substaging, artifacts, complications, the rate of adjuvant treatment, and oncological outcomes.

Results and limitations: From April 2018 to June 2021, 300 patients met the inclusion criteria. Of these, 248 (83%) underwent the assigned intervention: 108 patients (44%) underwent cTURBT and 140 (57%) underwent ERBT. The rate of detrusor muscle presence for ERBT was noninferior to that for TURBT (94% vs 95%; $p = 0.8$). T1 substaging was feasible in 80% of cTURBT cases versus 100% of ERBT cases ($p = 0.02$). Complication rates, rates of postoperative adjuvant treatment, catheterization time, and hospital stay were comparable between the two groups ($p > 0.05$). The recurrence rate at median follow-up of 15 mo (interquartile range 7–28) was 18% for cTURBT versus 13% for ERBT ($p = 0.16$). Limitations include the single high-volume institution and the short-term follow-up.

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Conclusions: Our study has the highest level of evidence for comparison of ERBT versus TURBT. ERBT was noninferior to TURBT for BC staging. The rate of T1 substaging feasibility was significantly higher with ERBT.

Patient summary: We compared two techniques for removing tumors from the bladder. The en bloc technique removes the tumor in one piece and is not inferior to the conventional method in terms of the quality of the surgical resection and cancer staging assessment.

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1. Introduction

Transurethral resection of bladder tumor (TURBT) is the gold standard for the diagnosis and local staging of bladder cancer (BC) [1]. Although it is considered a basic urological procedure, TURBT is a crucial step in the management of non–muscle-invasive BC (NMIBC); it defines the patient's risk class and prognosis, from which indications for adjuvant intravesical therapies and follow-up schedules can be drawn. Conventional TURBT (cTURBT) involves a piece-by-piece resection of the tumor using monopolar or bipolar energy. This procedure violates one of the key principles of oncological surgery, the preservation of tumor integrity, raising some concerns regarding the risk of tumor cell scattering and seeding and thus local recurrence. Moreover, although the presence of detrusor muscle (DM) in the histopathological specimen is crucial to ensure correct staging and it is considered a surrogate for resection quality, DM can be missed in up to 30–35% of cTURBT procedures [2,3]. In addition, the pathologist may be unable to provide reliable information about disease staging and T1 substaging because of a fragmented, non-orientable specimen [4]. En bloc resection of bladder tumor (ERBT) was introduced in an attempt to improve cTURBT outcomes [5-7]. In ERBT, the bladder tumor is resected as a single piece comprising both its exophytic and endophytic parts, which reduces tumor cell dispersion, allows precise resection, facilitates DM sampling in proximity to the tumor base, and yields a more informative pathological specimen. Several retrospective studies have suggested multiple advantages for ERBT over cTURBT, although these were not confirmed in a subsequent randomized controlled trial (RCT) [3,7-12]. In 2020, an international collaborative consensus statement confirmed the feasibility of ERBT without providing solid conclusions regarding its indications and advantages, as the high-quality data required for robust recommendations are limited [7]. Thus, the consensus underlines the need for a high-quality prospective RCT.

The aim of our study was to provide the highest level of evidence for comparison of cTURBT versus ERBT by analyzing surgical, pathological, and oncological outcomes for these two techniques, using all the energy sources available.

2. Patients and methods

2.1. Study design and endpoints

This was a single-center, prospective, randomized, controlled, noninferiority trial analyzing patients undergoing ERBT or cTURBT for BC. All the patients were prospectively enrolled and randomized to receive one of the following treatments: ERBT using monopolar (m-ERBT), bipolar (b-ERBT), or thulium laser (l-ERBT) energy; or cTURBT using monopolar (m-cTURBT) or bipolar (b-cTURBT) energy. The primary endpoint of the study was DM presence in the pathological specimen. Secondary endpoints included: staging of BC, evaluated according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system and the World Health Organization classification [13]; the feasibility of T1 subclassification (T1a/b/c) according to the depth of invasion in the muscularis mucosae-vascular plexus [4]; the rate of artifacts in the pathological specimen; the rate of treatment with a single instillation of mitomycin/epirubicin postoperatively according to the European Association of Urology (EAU) guidelines [1]; operative and postoperative variables (operative time, irrigation and catheterization time, hospital length of stay, hemoglobin decrease, and postoperative complications scored according to the Clavien-Dindo classification [14]); and early oncological outcomes (3-mo recurrence rate, recurrence-free survival, overall survival). The study was carried out according to the principles of the Declaration of Helsinki and was approved by the institutional review board (2017/09c). The study is registered on ClinicalTrials.gov as NCT04712201. All participants were adequately informed and provided written consent.

2.2. Study population

The target population included patients undergoing TURBT for the diagnosis and treatment of BC according to the EAU guidelines on NMIBC [1]. Preoperative evaluation included recording of anthropometric variables, comorbidities, and history of NMIBC; bladder ultrasound and/or flexible cystoscopy; and urine cytology. An abdominal computed tomography scan was performed in cases with suspicion of muscle-invasive bladder cancer (MIBC) or upper urinary tract involvement. We included patients affected by primary or recurrent BC, located anywhere in the bladder, with a maximum of three separated lesions and/or a maximum size of 3 cm for each lesion. Patients were excluded from the study if there was preoperative evidence of MIBC, ureteral involvement, and/or nodal/metastatic extension of the disease.

The sample size was calculated using the primary outcome of the rate of DM presence in the specimen as a surrogate for resection quality. Previous studies have shown that approximately 90% of specimens were suitable for correct staging using conventional approaches [15,16]. For this noninferiority clinical trial we estimated that 95% of specimens would have DM presence and a minimum noninferiority margin of 5% for ERBT in comparison to cTURBT. Accepting a one-sided α risk of 2.5%, a β risk of 20%, and an anticipated dropout rate of 12%, a minimum of 120 patients per group for randomization (107 after dropouts) was foreseen for an adequately powered analysis. Two energy types were used in the cTURBT group (m-cTURBT and b-cTURBT) and three in the ERBT group (m-ERBT, b-ERBT, and l-ERBT). Thus, patients were allocated to the ERBT or cTURBT group in a 3:2 ratio using computer-generated randomization tables during operating room planning on the day before surgery. Thus, 180 patients were randomized to the ERBT group (60 patients each in the m-ERBT, b-ERBT, and l-ERBT subgroups) and 120 to the cTURBT control group (60 patients each in the m-cTURBT and b-cTURBT subgroups). The study was suspended between March and September 2020 because of the COVID-19 pandemic, when no patients were considered for eligibility.

2.3. Surgical procedure and follow-up

Every procedure was performed by the uro-oncology team of Fundació Puigvert, which consists of seven senior urologists (>5 yr of experience), four junior urologists (<5 yr of experience), and 3rd-5th-year residents supervised by at least one urologist from the team. The patient was positioned in a standard lithotomy position under spinal or general anesthesia. A 28 Ch resectoscope (Karl Storz, Tuttlingen, Germany) was used with saline or glycine solution as the distension medium. m-cTURBT and b-cTURBT were performed using standard loop monopolar and bipolar electrodes. A Collins knife was used for m-ERBT and rectangular bipolar loop (Karl Storz) electrodes for b-ERBT. l-ERBT was performed using of a 550-μm fiber connected to a thulium laser generator (Revolix Duo; LisaLaser, Katlenburg-Lindau, Germany) set to 10–20 W of power. At the start of the procedure, the bladder was carefully inspected to verify the inclusion or exclusion status of the patient. For cases not meeting the inclusion criteria, dropout status was recorded and the patient was excluded from the per-protocol analysis.

ERBT, regardless of the energy used, involved a circular incision around the tumor base, cutting through macroscopically healthy mucosa with a safety margin of 5–10 mm and bluntly dissecting the tumor from the bladder wall at the desired depth.

The specimen was extracted by grabbing it with the electrode or using a glass Toomey evacuator; subsequent processing for pathological evaluation was according to a standard internal protocol. All samples were examined by an expert uropathologist (F.A.). For T1 tumors, T1 substaging (T1a/b/c [4]) was performed if feasible. The presence of artifacts was recorded and graded as focal or extensive. Perforation was defined as a resection depth reaching the perivesical fat and beyond. A 20–22 Ch three-way bladder catheter was inserted at the end of the procedure, and continuous bladder irrigation was started. An early one-shot instillation of 40 mg of mitomycin C or 50 mg of epirubicin was administered according to current guidelines for primary tumors or recurrent tumors detected more than 1 yr after the previous TURBT (2006 European Organisation for Research and Treatment of Cancer recurrence score <5) [17]. In cases of perforation or bleeding, no single instillation was performed. Patient care was in accordance with the postoperative and follow-up protocols of our institution, which are in line with the current EAU NMIBC guidelines [1].

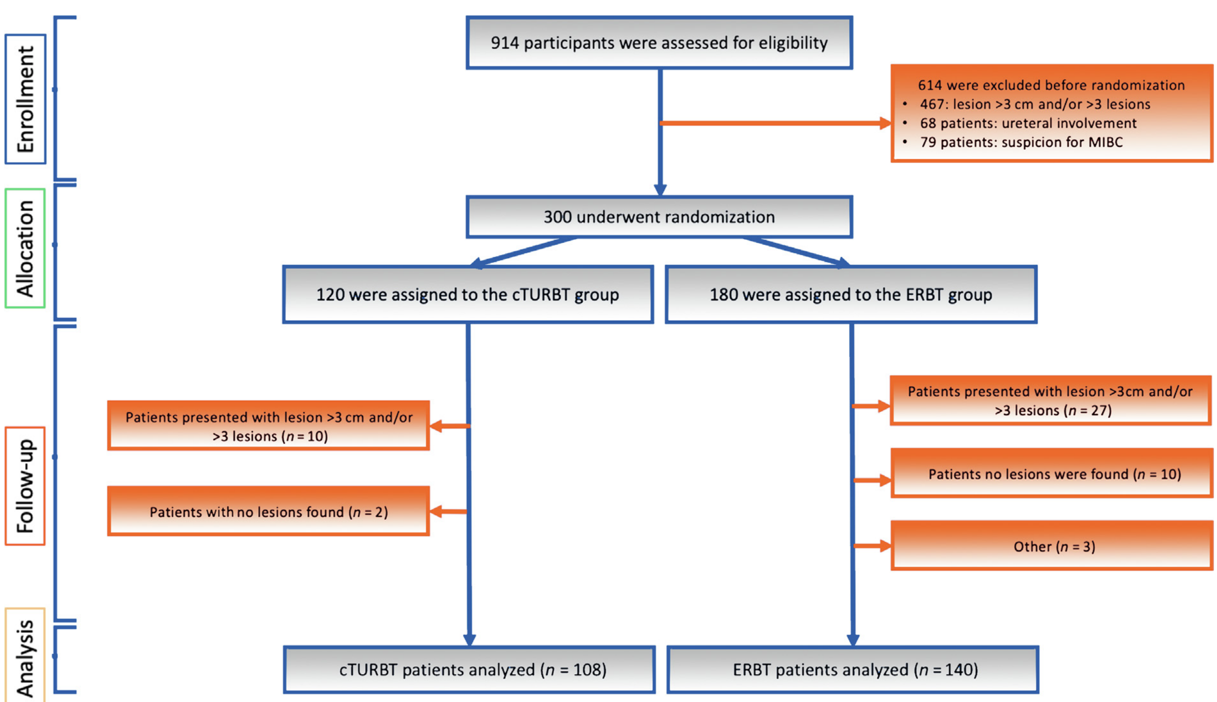

Fig. 1 – CONSORT flowchart showing the assessment, inclusion/exclusion, and randomization of patients in the study. cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; MIBC = muscle-invasive bladder cancer.

Table 1 – Population demographics by technique (ERBT vs cTURBT)

	cTURBT	ERBT	p value*
Patients, n (%)	108 (44)	140 (56)	
Males, n (%)	91 (84)	109 (78)	0.2
Median age, yr (interquartile range)	73 (65–79)	72 (61–80)	0.7
Median hemoglobin, g/l (interquartile range)	142.5 (129–154)	144 (135–154)	0.6
Tobacco use, n (%)			0.8
Active smoker	33 (30.5)	49 (35)	
Former smoker	33 (30.5)	40 (29)	
Nonsmoker	42 (39)	51 (36)	
Hypertension, n (%)	63 (58)	76 (54)	0.5
Diabetes, n (%)	28 (26)	34 (24)	0.8
History of myocardial infarction, n (%)	12 (11)	20 (14)	0.5
History of stroke, n (%)	6 (5.6)	5 (3.6)	0.5
Anticoagulant therapy, n (%)	14 (13)	17 (12)	0.9
Antiplatelet therapy, n (%)	19 (18)	25 (18)	1
Positive urine culture before surgery, n (%)	5 (4.6)	5 (3.6)	0.7
Radiation-induced cystitis, n (%)	4 (3.7)	1 (0.7)	0.1
History of bladder cancer, n (%)	48 (44)	50 (36)	0.2
Low-grade bladder cancer	28 (26)	31 (22)	0.5
High-grade bladder cancer	21 (19)	24 (17)	0.6
Preoperative urine cytology, n (%)			0.9
Positive	18 (17)	20 (14)	
Negative	84 (78)	109 (78)	
Suspicious	4 (4)	8 (6)	
Not performed	2 (1)	3 (2)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

2.4. Statistical analysis

A descriptive statistical analysis of all data was performed. Analysis for quantitative variables included measures of central tendency and measures of dispersion and position. Differences between study groups in baseline variables were analyzed using a χ^2 test for categorical or nominal variables (or Fisher's test) and a t test (U Mann-Whitney U test) for continuous variables. Kaplan-Meier curves were generated to assess recurrence-free survival and overall survival. All the tests were conducted at a significance level of $p = 0.05$. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA).

3. Results

We enrolled a total of 300 patients between April 2018 and June 2021 (Fig. 1). Fifty-two patients (17%) were excluded after randomization because they did not meet the inclusion criteria at the time of the surgical procedure, leaving 248 patients for the analysis, 140 in the ERBT group and 108 in the cTURBT group. Population characteristics are summarized in Table 1. There were no significant differences between the two study groups (all $p > 0.05$).

3.1. Intraoperative and postoperative outcomes

Intraoperative and postoperative data are shown in Table 2. In the ERBT group, the specimen was extracted inside the resectoscope in 127/140 cases (91%). The median irrigation

Table 2 – Intraoperative and postoperative outcomes by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs laser)

Parameter	cTURBT			ERBT				p value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Patients, n (%)	108 (44)	57 (23)	51 (21)	140 (56)	49 (20)	45 (18)	46 (18)	
Surgeon, n (%)								0.1
Senior urologist	16 (15)	11 (19)	5 (10)	30 (21)	4 (8)	12 (27)	14 (30)	
Junior urologist	31 (29)	17 (30)	17 (33)	52 (37)	25 (51)	14 (31)	15 (33)	
Resident	61 (56)	29 (51)	29 (57)	58 (42)	20 (41)	19 (42)	17 (37)	
Median surgery time, min (IQR)	30 (20–35)	30 (20–40)	30 (20–30)	30 (20–40)	30 (20–40)	30 (20–40)	30 (20–45)	0.1
Conversion to cTURBT, n (%)	–	–	–	6 (4.3)	2 (4.1)	2 (4.4)	2 (4.3)	–
Obturator nerve reflex, n (%)	7 (6.5)	3 (5.3)	4 (7.8)	15 (11)	5 (10)	10 (22)	0 (0)	0.3
Perforation, n (%)	18 (17)	8 (14)	10 (20)	28 (20)	7 (14)	13 (29)	8 (17)	0.9
Specimen extraction, n (%)	–	–	–					–
cTURBT				6 (5)	2 (4)	2 (4)	2 (4.5)	
Inside resectoscope				127 (91)	45 (92)	40 (89)	42 (91)	
With resectoscope				5 (4)	0 (0)	3 (7)	2 (4.5)	
Lesion splitting				2 (1)	2 (4)	0 (0)	0 (0)	
Early CTx installation, n (%)								
Planned	43 (40)	21 (37)	22 (43)	69 (49)	26 (53)	22 (49)	21 (46)	0.1
Performed	37 (86)	20 (95)	17 (77)	65 (94)	26 (100)	20 (91)	19 (86)	0.1
Complications, n (%)								0.5
No complications	82 (76)	43 (75)	39 (77)	111 (79)	43 (88)	23 (73)	35 (76)	
Clavien-Dindo 1–2	23 (21)	12 (21)	11 (22)	23 (16)	5 (10)	8 (18)	10 (22)	
Clavien-Dindo 3	3 (3)	2 (4)	1 (1)	6 (5)	1 (2)	4 (9)	1 (2)	
Blood transfusion, n (%)	2 (1.9)	1 (1.8)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0.2
Median irrigation time, d (IQR)	0.5 (0.5–1)	1 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.1
Median vesical catheter time, d (IQR)	2 (2–3)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–2)	2 (1–2)	2 (2–3)	0.2
Median hospitalization, d (IQR)	2 (2–2)	2 (2–2.5)	2 (1–2)	2 (1.3–2)	2 (1–2)	2 (1–2)	2 (2–2)	0.6
Median postoperative Hb, g/l (IQR)	137 (120–147)	135 (119–146)	138 (121–149)	137 (123–144)	137 (125–137)	139 (122–148)	132 (119–144)	0.9

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; IQR = interquartile range; CTx = chemotherapy; Hb = hemoglobin.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

and catheterization times were 0.5 d (interquartile range [IQR] 0.5-1) and 2 d (IQR 1–3) days in the ERBT group versus 0.5 d (IQR 0.5–1) and 2 d (IQR 2–3) in the cTURBT group, respectively (all $p > 0.05$). The median hospitalization time was 2 d (IQR 1.3–2) in the ERBT group and 2 d (IQR 2–2) in the cTURBT group ($p = 0.6$). Adjuvant treatment was planned for 69/140 patients (49%) in the ERBT group and 43/108 (40%) in the cTURBT group ($p = 0.1$) and was actually performed in 65/69 (94%) and 37/43 (86%), respectively ($p = 0.1$). Six patients (4.3%) undergoing ERBT had a conversion to cTURBT. Five of these six patients had anterior wall lesions for which ERBT was not feasible and one patient had a lesion in close proximity to the meatus so the surgeon decided to perform cTURBT.

Complications were reported for 29/140 patients (21%) in the ERBT group and 26/108 (24%) in the cTURBT group ($p = 0.5$). Clavien-Dindo >2 complications occurred in 6/140 patients (5%) in the ERBT group and 3/108 (3%) in the cTURBT group ($p = 0.5$). Only two patients in the cTURBT group received a blood transfusion. Obturator nerve reflex was reported for 15 patients (11%) in the ERBT group and seven (6.5%) in the TURBT group ($p = 0.2$).

3.2. *Pathological outcomes*

Per-patient analysis for the ERBT and cTURBT groups revealed similar rates of DM presence (95% vs 94%; $p = 0.8$; difference 1.5%, 95% confidence interval [CI] −0.01% to 3%), Tx stage (4% vs 3%; $p = 0.8$), and artifacts (7.9% vs 7.4%; $p = 0.8$) between the groups (Table 3). T1 substaging feasibility rate was significantly superior in the ERBT group: all 40 pT1 cases could be subclassified, in comparison to 34/37 cases in the cTURBT group (100% vs 80%; $p = 0.02$). These findings were confirmed in per-lesion anal-

Table 3 – Per-patient analysis of pathological outcomes for endoscopic resection by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs and laser)

Parameter	cTURBT			ERBT				*p* value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Patients, *n* (%)	108 (44)	57 (23)	51 (21)	140 (56)	49 (20)	45 (18)	46 (18)	
Bladder SBx, *n* (%)	85 (78.7)	48 (84.2)	37 (72.6)	116 (82.9)	40 (81.6)	35 (77.8)	41 (89.1)	0.4
Positive bladder SBx, *n* (%)	16 (19)	11 (23)	5 (14)	22 (19)	7 (18)	6 (17)	9 (22)	1
Stage on BSM, *n* (%)								1
Tx	2 (13)	2 (18)	0 (0)	3 (13)	1 (14)	1 (17)	1 (11)	
Ta	1 (6)	0 (0)	1 (20)	1 (5)	1 (14)	0 (0)	0 (0)	
Carcinoma in situ	13 (81)	9 (82)	4 (80)	18 (82)	5 (72)	5 (83)	8 (89)	
Grade on BSM, *n* (%)								0.9
Low grade	2 (13)	1 (9)	1 (20)	2 (9)	1 (14)	1 (17)	0 (0)	
High grade	1 (6)	1 (9)	0 (0)	1 (5)	1 (14)	0 (0)	0 (0)	
Carcinoma in situ	13 (81)	9 (81)	4 (80)	18 (81)	5 (72)	5 (83)	8 (89)	
Unspecified	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (11)	
Artifacts, *n* (%)	8 (7.4)	3 (5.3)	5 (9.8)	11 (7.9)	2 (4.1)	6 (13)	3 (6.5)	0.8
Detrusor muscle, *n* (%)								0.8
Yes	101 (94)	52 (96)	49 (96)	133 (95)	47 (96)	42 (93)	44 (96)	
No	7 (6)	5 (4)	2 (4)	7 (5)	2 (4)	3 (7)	2 (4)	
Tumor stage, *n* (%)								0.9
Tx	3 (3)	1 (2)	2 (4)	6 (4)	2 (4)	1 (2)	3 (7)	
Tis	2 (2)	2 (4)	0 (0)	2 (2)	0 (0)	2 (4)	0 (0)	
Ta	76 (70)	39 (68)	37 (72)	90 (64)	32 (65)	29 (65)	29 (63)	
T1	15 (14)	9 (16)	6 (12)	25 (18)	9 (19)	8 (18)	8 (17)	
T2	5 (5)	3 (5)	2 (4)	6 (4)	3 (6)	0 (0)	3 (6.5)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (6.5)	
T1 substage feasibility, *n* (%)								**0.02**
Yes	12 (80)	7 (78)	5 (83)	25 (100)	9 (100)	8 (100)	8 (100)	
No	3 (20)	2 (22)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
T1 substage, *n* (%)								0.1
1a	9 (60)	5 (56)	4 (66)	20 (80)	9 (100)	6 (75)	5 (62)	
1b	1 (7)	1 (11)	0 (0)	5 (20)	0 (0)	2 (25)	3 (38)	
1c	2 (13)	1 (11)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
Not feasible	3 (20)	2 (22)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor grade, *n* (%)								0.9
Low grade	56 (52)	30 (53)	26 (51)	70 (50)	26 (53)	20 (44)	24 (52)	
High grade	41 (38)	20 (35)	21 (41)	55 (39)	20 (41)	16 (36)	19 (41)	
Carcinoma in situ[a]	4 (4)	4 (7)	0 (0)	4 (3)	0 (0)	4 (9)	0 (0)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (7)	
Risk category, *n* (%)[a]								0.4
Low	12 (11)	8 (14)	4 (8)	11 (8)	3 (6)	3 (7)	5 (11)	
Intermediate	42 (39)	19 (33)	23 (45)	71 (51)	15 (31)	18 (40)	14 (30)	
High	47 (44)	27 (48)	20 (39)	47 (33)	28 (57)	19 (42)	24 (52)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (7)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; SBx = systematic biopsy; BSM = bladder systematic mapping.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.
[a] Patients were stratified according to the risk categories in the 2018 European Association of Urology guidelines.

Table 4 – Per-lesion analysis of pathological outcomes after endoscopic resection by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs laser)

Parameter	cTURBT			ERBT				p value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Lesions, n (%)	147 (43)	76 (22)	71 (21)	194 (57)	61 (18)	73 (21)	60 (18)	
Tumor dimension, n (%)								0.07
<10 mm	84 (57)	46 (61)	38 (54)	92 (47)	33 (54)	32 (44)	27 (45)	
10–30 mm	63 (43)	30 (39)	33 (46)	102 (53)	28 (26)	41 (56)	33 (55)	
Tumor location, n (%)								0.7
Trigone	24 (16)	16 (21)	8 (11)	24 (12)	7 (11)	12 (16)	5 (8)	
Posterior wall	26 (18)	10 (13)	16 (23)	29 (15)	12 (20)	8 (11)	9 (16)	
Right wall	27 (19)	15 (19)	12 (17)	51 (26)	14 (23)	19 (26)	18 (30)	
Left wall	43 (29)	19 (25)	24 (33)	56 (29)	17 (28)	20 (27)	19 (32)	
Anterior wall	8 (5)	6 (8)	2 (3)	11 (6)	5 (8)	4 (6)	2 (3)	
Dome	10 (7)	5 (7)	5 (7)	12 (6)	3 (5)	4 (6)	5 (8)	
Bladder neck	9 (6)	5 (7)	4 (6)	11 (6)	3 (5)	6 (8)	2 (3)	
Tumor location, n (%)								0.7
Trigone	24 (16)	16 (21)	8 (11)	24 (12)	7 (11)	12 (17)	5 (8)	
Posterior wall	26 (18)	10 (13)	16 (22)	29 (15)	12 (20)	8 (11)	9 (15)	
Lateral walls	70 (48)	34 (45)	36 (51)	107 (55)	31 (51)	39 (53)	37 (62)	
Anterior wall/dome	18 (12)	11 (14)	7 (10)	23 (12)	8 (13)	8 (11)	7 (12)	
Bladder neck	9 (6)	5 (7)	4 (6)	11 (6)	3 (5)	6 (8)	2 (3)	
Artifacts, n (%)								0.2
Absent	135 (92)	71 (93)	64 (90)	180 (93)	58 (95)	66 (90)	56 (94)	
Present	3 (2)	2 (3)	1 (1)	8 (4)	3 (5)	3 (4)	2 (3)	
Extensive	9 (6)	3 (4)	6 (9)	6 (3)	0 (0)	4 (6)	2 (3)	
DM presence, n (%)	137 (93.2)	69 (90.8)	68 (95.8)	180 (92.8)	58 (95.1)	65 (89)	57 (95)	0.9
Tumor stage, n (%)								0.8
Tx	6 (4)	3 (4)	3 (4)	12 (6)	3 (5)	5 (7)	4 (7)	
Carcinoma in situ	3 (2)	3 (4)	0 (0)	4 (2)	0 (0)	4 (5)	0 (0)	
Ta	101 (69)	50 (66)	51 (72)	124 (64)	38 (62)	47 (64)	39 (65)	
T1	19 (13)	11 (14)	8 (11)	30 (16)	11 (18)	10 (14)	9 (15)	
T2	7 (5)	3 (4)	4 (6)	7 (3)	4 (7)	0 (0)	3 (5)	
T0/Benign/other	11 (7)	6 (8)	5 (7)	17 (9)	5 (8)	7 (10)	5 (8)	
T1 substage feasibility, n (%)								**0.03**
Yes	15 (84)	9 (82)	6 (86)	30 (100)	11 (100)	10 (100)	9 (100)	
No	3 (16)	2 (18)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
T1 substage, n (%)	18	11	7	30	11	10	9	0.2
1a	10 (55)	5 (46)	5 (72)	23 (77)	11 (100)	7 (70)	5 (56)	
1b	3 (17)	3 (27)	0 (0)	7 (23)	0 (0)	3 (30)	4 (44)	
1c	2 (11)	1 (9)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
Not feasible	3 (17)	2 (18)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor grade, n (%)								0.9
Low grade	75 (51)	39 (51)	36 (51)	94 (49)	32 (53)	34 (46)	28 (47)	
High grade	56 (38)	26 (34)	30 (42)	76 (39)	24 (39)	26 (36)	26 (43)	
Carcinoma in situ	5 (3)	5 (7)	0 (0)	6 (3)	0 (0)	6 (8)	0 (0)	
T0/benign/other	11 (8)	6 (8)	5 (7)	18 (9)	5 (8)	7 (10)	6 (10)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; DM = detrusor muscle.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

ysis, which showed a statistically significant difference in T1 substaging feasibility in favor of ERBT (100% vs 84%; p = 0.03). Similar results were achieved in the per-lesion analysis, as shown in Table 4. Out of 248 patients, eight (3.2%) underwent second-look TURB: 1/5 patients in the ERBT group had residual tumor (T1a + carcinoma in situ), while 1/3 patient in the cTURBT group had residual tumor (T1b) and one patient was lost to follow-up.

3.3. *Oncological outcomes*

Median follow-up was 15 mo (IQR 7–28). The risk of death was similar for the cTURBT and ERBT groups (hazard ratio [HR] 1.43, 95% CI 0.41–4.95; p = 0.6), as was the risk of recurrence (HR 1.53, 95% CI 0.80–2.91; p = 0.2). Kaplan-Meier analysis revealed that recurrence-free survival was similar between the groups (p = 0.2); the survival curves are shown in Figure 2.

4. Discussion

This study provides the highest level of evidence for comparison of ERBT and cTURBT regarding operative, pathological, and short-term oncological outcomes and exploring all energy types available for the two techniques.

The literature contains controversial results from comparative RCTs on ERBT. This may reflect the heterogeneity study design, since the majority of the RCTs compared the two techniques using two different types of energy (laser ERBT versus electric TURBT) and different endpoints were assessed [18]. As reported by Teoh et al [7] in the international consensus statement, the current quality of evidence does not allow solid conclusions to be drawn.

The presence of DM has been considered a marker of a high-quality resection as it allows the pathologist to evaluate the extent of the disease and the urologist to give indications [2,3,19]. Our study demonstrated that ERBT was noninferior

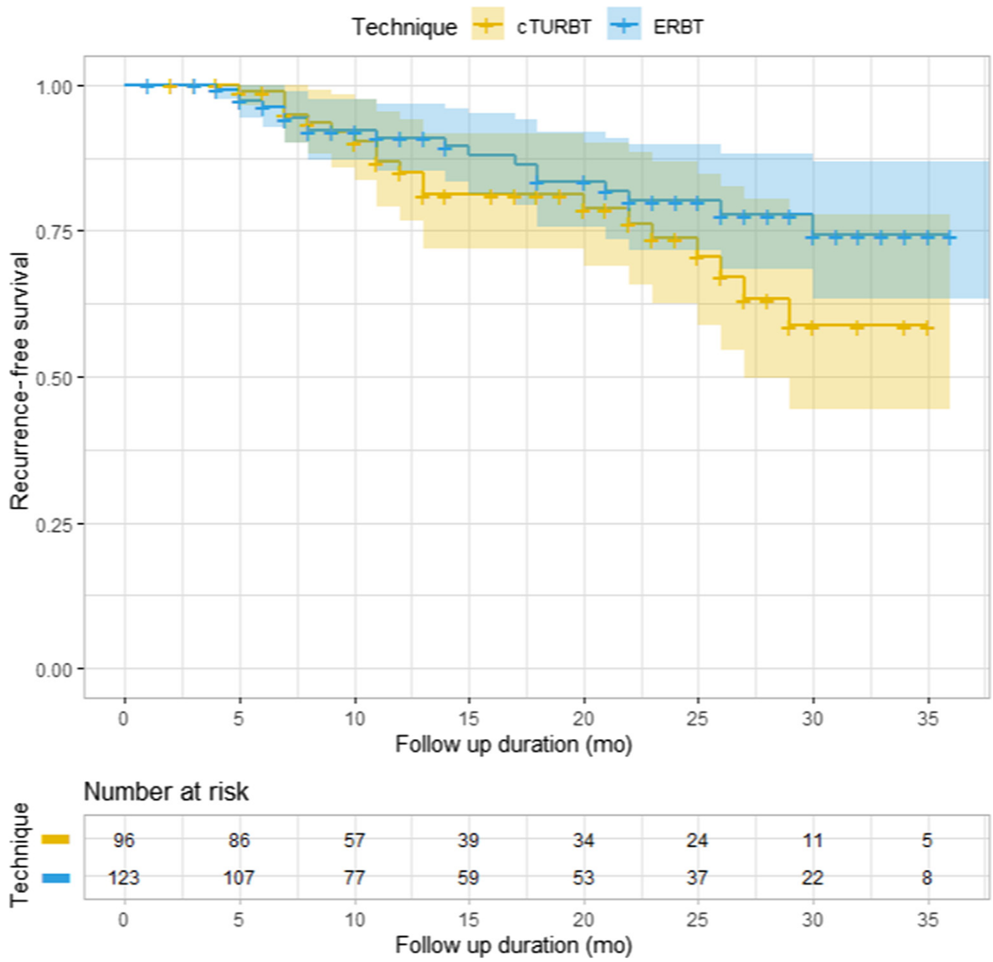

Fig. 2 – Kaplan-Meier analysis of recurrence-free survival. There was no statistically significant difference in survival rates between the cTURBT and ERBT groups (p = 0.2). cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor.

to cTURBT in terms of rates of DM presence (94% for cTURBT and 95% for ERBT; p = 0.84) and Tx stage (3% for cTURBT and 4% for ERBT; p = 0.85) at final histology. Therefore, ERBT guarantees a resection quality comparable to that with cTURBT, provided the latter is performed according to the best surgical practice [19]. This finding is somewhat surprising, as an improvement in resection quality has been considered the most important advantage of ERBT [6]. In fact, retrospective studies show an absence of DM in the specimen in up to 51% of cTURBT procedures [3,8,9].

Hashem et al [10] reported a DM rate of 62% with cTURBT versus 98% with laser ERBT, with a statistically significant difference between the groups (p < 0.001). Similarly, Cheng et al [20] reported that the rate of DM presence was 97.1% with green-light laser ERBT and 80% with cTURBT (p = 0.04). By contrast, other studies reported a DM rate that did not significantly differ between ERBT and cTURBT (p > 0.05) [11,12,21].

T1 substaging was possible in all ERBT cases, while the rate of T1 substaging feasibility was significantly lower in our cTURBT group (80%; p = 0.02). Just one previous study investigated the rate of T1 substaging feasibility and also found a significant difference (68.2% for laser ERBT vs 18.4% for cTURBT; p < 0.001) [10]. However, the definition of T1 BC was not clear, as the rate of T1 tumors was 95.5% in the ERBT and 93.9% in the cTURBT group, with DM absence rates of 2% and 38%, respectively (p < 0.001) [10]. Thus, a significant percentage of the T1 BC cases were actually Tx. Nonetheless, these findings underline the higher accuracy of ERBT for T1 substaging, which is currently recommended by the EAU guidelines [4,22,23].

The advantage of ERBT over cTURBT in terms of operative outcomes is debated. Resection time was longer for cTURBT in two studies, ranging from 13 to 19 min in comparison to 10–13 min for ERBT (p < 0.05). Conversely, two other RCTs found a significantly shorter operative time for cTURBT (22–30 min) than for ERBT (35–37 min; p < 0.05) [12,20]. Results for catheterization time were more uniform, with significantly longer times for cTURBT [10-12,20,21,24]. Hospitalization time was significantly shorter for ERBT in three RCTs [11,12,24] and comparable in two studies [10,20]. Despite these results, similar perforation rates were reported in these RCTs. In our study, there was no significant difference between ERBT and cTURBT in operative time, the rate of adjuvant instillation, catheterization time, or hospital stay. These findings represent the logical consequence of comparable rates of perforation and postoperative complications between the groups. Regarding oncological outcomes, both disease persistence at 3 mo and recurrence-free survival at median follow-up of 12 mo were comparable between the groups. These results are in line with the literature [7].

Our study is not devoid of limitations. This was a single-center study in an academic hospital. Our center is highly experienced in NMIBC treatment and thus the results may potentially not reflect current treatment outcomes. However, the heterogeneity of the operators, including supervised residents, means that the current results are generalizable and underline that a high rate of DM presence should be considered standard, regardless of the surgeon or resection technique [25,26]. Other limitations are the lack of specific analysis of tumor margins and the short follow-up, which precludes solid conclusions regarding oncological outcomes; long-term follow-up is foreseen to evaluate the definitive oncological results. Finally, we only tested EBRT in patients with a limited number of lesions that were ≤3 cm. Therefore, in translating these results to our daily practice, ERBT is only indicated for the clinical scenario considered in our study. Nonetheless, our results demonstrate why ERBT should be considered a standard surgery worth employing. The ERBT technique preserves tumor integrity, providing a high-quality specimen that increases pathological substaging accuracy without significant drawbacks in comparison to cTURBT. Further subanalysis will provide new insights regarding the different energy sources for ERBT.

5. Conclusions

This is the largest RCT of ERBT and demonstrates that ERBT is noninferior to cTURBT in the staging of BC. The rate of T1 substaging feasibility was significantly higher in the ERBT group. The intraoperative and postoperative outcomes were comparable between the groups. With median follow-up of 15 mo, oncological outcomes were comparable.

Author contributions: Pietro Diana 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.

Study concept and design: Breda, Palou, Gallioli.
Acquisition of data: Diana, Fontana, Piana, Algaba.
Analysis and interpretation of data: Diana, Gallioli, Gaya.
Drafting of the manuscript: Diana, Gallioli, Territo.
Critical revision of the manuscript for important intellectual content: Breda, Palou, Sanguedolce.
Statistical analysis: Diana, Gallioli, Rodriguez-Faba.
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