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Original Article

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An international multicentre randomised controlled trial of *en bloc* resection of bladder tumour vs conventional transurethral resection of bladder tumour: first results of the *en bloc* resection of urothelium carcinoma of the bladder (EBRUC) II trial

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Objectives

To determine the safety and oncological advantages of *en bloc* resection of bladder tumour (ERBT) vs conventional transurethral resection of bladder tumour (cTURBT) in terms of resection quality, staging quality, and safety.

Patients and Methods

We conducted a single-blinded randomised controlled trial at seven European hospitals with the following inclusion criteria: first diagnosis of non-muscle-invasive bladder cancer, no singular carcinoma *in situ*, and tumour size >4.3 mm. Patients were randomised intraoperatively in a 1:1 ratio to either the ERBT or cTURBT group. Outcome analysis was performed using the chi-square test, *t*-test, and multivariate regression analysis.

Results

A total of 97 patients were randomised into the study (cTURBT = 40, ERBT = 57). A switch to cTURBT was necessary in two patients (3.5%) and 11.5% of the screened patients were preoperatively excluded for ERBT. There was no difference in the specimen presence of detrusor muscle with 73.7% in cTURBT and 67.3% in ERBT specimens ($P = 0.69$). There were no significant differences in mean operative time (ERBT 27.6 vs cTURBT 25.4 min, $P = 0.450$) or mean resection time (ERBT 16.3 vs cTURBT 15.5 min, $P = 0.732$). Overall the complication rate did not differ significantly (ERBT 18.2% vs cTURBT 7.5%, $P = 0.142$). Bladder perforations occurred significantly more often in the ERBT group (ERBT seven vs cTURBT none, $P = 0.020$). R0 status was reported more often after ERBT, whilst a second resection was significantly less frequent after ERBT ($P = 0.018$). Recurrence rates were comparable for both techniques after 6 months of follow-up.

Conclusion

The feasibility of ERBT is higher than previously reported. Whereas other perioperative and safety parameters are comparable to cTURBT, bladder perforations occurred significantly more often in the ERBT group and raised safety concerns. This is why this trial was terminated.

Keywords

bladder cancer, *en bloc* resection, non-muscle-invasive bladder cancer, transurethral resection of bladder tumour, EBRUC II

Introduction

High-quality transurethral resection of bladder tumour (TURBT) is the main tool for the treatment of non-muscle-invasive bladder cancer (NMIBC) [1]. Conventional TURBT (cTURBT) with fractioning of the tumour remains the standard surgical approach for NMIBC to date. However, it has come under criticism because it contradicts the 'no touch' principle of oncological surgery [2]. Also, cTURBT causes cauterisation artefacts and thermal damage, which impairs the staging of bladder cancer [3].

Thermal damage to tumour tissue can lead to difficulties in assessing the tumour stage and may result in under-staging and under-treatment of patients [3,4]. Previous studies have demonstrated the importance of sub-staging by dividing pT1 tumours into pT1a and pT1b [5], defined by lamina muscularis mucosae infiltration. Rouprêt et al. [5] demonstrated the prognostic significance of T1 sub-staging, in which patients with pT1b disease underwent radical cystectomy 6 months earlier than patients with pT1a disease because the disease progressed earlier. An *en bloc* resection of bladder tumour (ERBT) seeks to overcome this limitation.

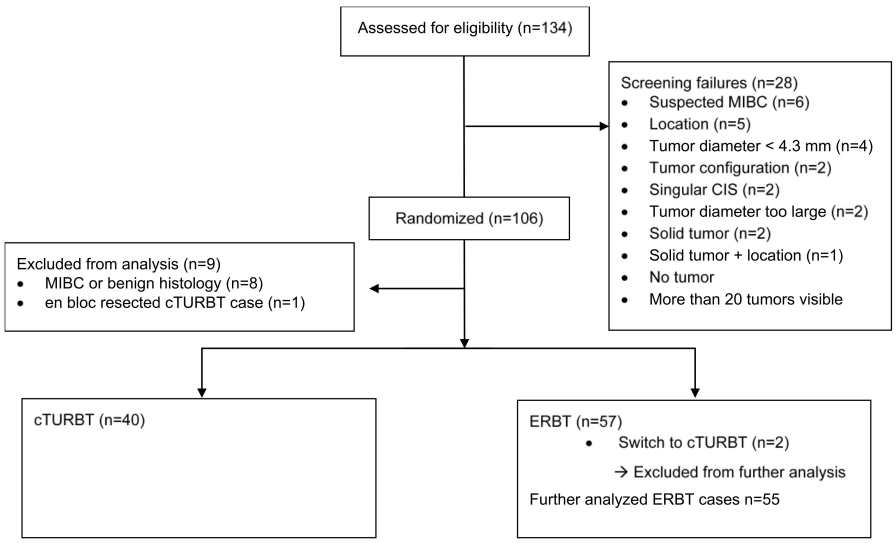
The ERBT is an emerging resection method for the treatment of NMIBC. In ERBT, the tumour is marked circumferentially before being incised to the detrusor muscle (DM) layer, and this depth is maintained until the tumour is resected *en bloc* [6]. Previous studies on ERBT suggested more accurate staging, fewer complications, and lower recurrence rates compared to cTURBT; however, most studies comparing ERBT with cTURBT have been limited by either retrospective or single-centre study design.

Patients and Methods

We performed a single-blinded randomised controlled trial (RCT) in seven European hospitals (Luebeck, Wolfsburg, Heilbronn, Berlin, Germany; Salzburg, Austria; Prague, Czech Republic; and Modena, Italy, German clinical trial register: DRKS00020738) from June 2019 until March 2022. Primary endpoints were non-inferiority in recurrence rate and superiority in the presence of DM in the sample for ERBT. Secondary endpoints included progression rate, perioperative safety, and residual tumour rate at 2–6 weeks, tumour extraction method, long-term recurrence at 24 months, and feasibility of histopathological staging (resection margins and T1 sub-staging). Inclusion criteria were the initial diagnosis of NMIBC and tumour size >4.3 mm (which is the standard diameter of a Karl Storz resection sling to prevent *en bloc* resection during cTURBT). There were no restrictions on the number of tumours, tumour location, or maximum tumour diameter. All surgeons were required to perform a cystoscopy intraoperatively but before the resection procedure. If all tumours were potentially eligible for ERBT, patients were randomised intraoperatively in a 1:1 ratio to either the cTURBT or the ERBT group. Randomisation was performed with an on-line randomisation tool (https://www.randomizer.org). Randomisation envelopes that contained the allocated group were concealed and placed in the operating room. If the surgeon determined that the tumour was not ERBT eligible, a screening failure was reported with justification (i.e., location, tumour size), and patients were not randomised (Fig. 1).

All visualisation methods and energy sources were eligible for this study. Exclusion criteria were recurrent NMIBC, solid,

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the EBRUC II study.



broad-based tumours, as this study aimed to evaluate the ERBT of papillary urothelial carcinoma of the bladder, tumour diameter <4.3 mm, or singular carcinoma *in situ*. If a change in surgical method ('switch') to cTURBT was required, these cases were excluded from perioperative statistical analysis as per modified intention-to-treat approach to avoid confounding in statistical analysis. Study sites were provided with a guideline for the evaluation of *en bloc* tumours by the Institute of Pathology in Luebeck, Germany. Surgeons were free to obtain additional biopsies from the tumour ground/base of the tumour. The Institute of Biometry at Hannover Medical School (Germany) performed a statistical power analysis prior to the study. Sample size calculation for non-inferiority in recurrence rate was based on a meta-analysis by Sylvester et al. [7]. As per inclusion criteria, we focused on prognosis scores 1–9. Assuming H0: odds ratio (OR) $\geq \delta$ vs alternative hypothesis H1: OR $< \delta$, with δ being defined as 1.5, significance level being $\alpha = 0.025$ and statistical power of 0.9 we calculated a sample size of $n = 177$ patients per group. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 26 (IBM Corp., Armonk, NY, USA). As per study protocol we performed an interim analysis after 36 months being the planned time point for the final analysis, which was at ~27% of recruitment. Due to a significantly higher rate of bladder perforations in the intervention (ERBT) group, this study was terminated before the targeted patient number could be reached to ensure patient safety, as pre-defined in study protocol. This study was approved by all ethics committees of the participating sites.

Results

A total of 134 patients were screened, of whom 97 were successfully enrolled (cTURBT $n = 40$, ERBT $n = 57$) from June 2019 to March 2022. There were 28 screening failures reported.

Patient and Tumour Characteristics

Tumours in the cTURBT group were 0.6 cm larger than ERBT tumours. In both groups, the tumours were mainly located on the lateral bladder walls (cTURBT 66.0%, ERBT 57.9%). In the ERBT group, 23.2% of tumours were located in the trigonal region and 2.9% on the anterior wall (Table 1). In two patients, a switch from ERBT to cTURBT was required, with the reasons being tumour diameter (4.0 cm in one) and tumour extension into a bladder diverticulum (in one). No complications were reported in these cases. The mean diameter of ERBT tumours extracted after intravesical fragmentation was 3.3 cm. The largest tumour extracted *en bloc* measured 4.0 cm. An *en bloc* extraction was feasible in 83.6% of ERBT, while 16.4% of ERBT tumours were fragmented within the bladder and subsequently extracted ($P < 0.001$). The mean (SD) drop of haemoglobin in the cTURBT group was 4.2 (0.1) g/L, while in the ERBT group it was 5.8 (0.102) g/L ($P = 0.488$). The mean (SD) irrigation time was 21.2 (15.9) h in the cTURBT group and 21.6 (19.1) h in the ERBT group ($P = 0.898$). The mean (SD) catheterisation time was 1.97 (0.87) days in the cTURBT group and 2.44 (2.29) days in the ERBT group ($P = 0.173$). The overall intraoperative complication rate did not differ significantly between groups ($P = 0.142$); however, more bladder perforations were observed in the ERBT group (none for cTURBT, seven [12.7%] for ERBT; $P = 0.020$).

The postoperative complication rate did not differ significantly between groups (four [10.5%] in the cTURBT group and seven [12.7%] in the ERBT group, $P = 1.000$). Clavien–Dindo Grade I complications occurred in two patients in each group (5.3% in the cTURBT and 3.7% in the ERBT group). There were no Clavien–Dindo Grade II complications in any group. Clavien–Dindo Grade IIIa, IIIb, and IVa complications were observed (one patient each) in the ERBT group. No complications of Grade ≥III were observed in the cTURBT group. The Grade IVa complication was cardiac decompensation in an 81-year-old female patient (American Society of Anesthesiologists score of 1 [8], Eastern Cooperative of Oncology Group performance status of 1) after a holmium laser resection. Prolonged bladder irrigation was required in two (5.3%) of the cTURBT and three (5.6%) of the ERBT group ($P = 1.000$). One patient (1.8%) in the ERBT required ureteric stenting and percutaneous nephrostomy after resection of a ureteric orifice ($P = 1.000$). Two patients had postoperative bleeding, with one requiring transfusion after ERBT who had tumours located at the anterior wall.

Bladder Perforations

Bladder perforations occurred in seven patients who underwent ERBT in multiple participating centres (Tables 1 and 2). Bladder perforations were defined macroscopically by visible fat during resection, without mandatory radiographic measurement. Tumour size in these patients ranged from 1.0 to 6 cm, with tumours being mainly located at the left side wall and trigonal area (Table S1). When compared to ERBT without perforation, bladder perforations did not lead to prolonged irrigation time ($P = 0.449$) or hospitalisation time ($P = 0.993$); however, there was evidence of longer catheterisation time, although this was not statistically significant (2.26 vs 3.71 days $P = 0.058$). Additionally, bladder perforations occurred in three out of 11 holmium cases (27.2%). There was no significant accumulation for study centres ($P = 0.721$) or specific surgeons ($P = 0.504$).

Table 1 Patient and tumour characteristics at baseline, used energy sources and visualisation techniques, localisations were individually registered for each tumour.

Characteristic	cTURBT (*n* = 40)	ERBT (*n* = 57)	*P*
Baseline patient and tumour characteristic			
Male, *n* (%)	32 (80.0)	38 (66.7)	
Female, *n* (%)	8 (20.0)	18 (31.6)	
N/A, *n* (%)		1 (1.8)	
Age, years, mean (SD)	69.4 (10.37)	70.2 (11.09)	
Non-smoker, *n* (%)	14 (35.0)	20 (35.7)	
Smoker, *n* (%)	16 (40.0)	26 (46.4)	
Pack-years, mean (SD)	24.0 (12.9)	39.2 (20.0)	
Pack-years, median (IQR)	25 (10)	40 (28)	
Former smoker, *n* (%)	10 (25.0)	10 (17.9)	
Pack-years, mean (SD)	24.7 (12.4)	24.4 (19.8)	
Pack-years, median (IQR)	20 (25)	16 (27)	
Tumour diameter, cm, mean (SD)	2.6 (1.2)	2.01 (1.13)	
Multifocality, *n* (%)	9 (22.5)	15 (27.3)	
Number of resected tumours if presented with multifocality mean (SD)	2 (0)	2.3 (0.7)	
Localisation, *n* (%)			
Left wall	13 (26)	28 (40.6)	
Right wall	20 (40)	12 (17.4)	
Trigonum	7 (14)	16 (23.2)	
Posterior wall	6 (12)	3 (4.4)	
Bladder bottom	–	4 (5.8)	
Bladder neck	2 (4)	3 (4.4)	
Prostate middle lobe	–	1 (1.5)	
Anterior wall	1 (2)	2 (2.9)	
Dome	1 (2)	–	
Resection and visualisation methods, *n* (%)			
Bipolar current	39 (95.1)	41 (71.9)	
Monopolar current	1 (2.5)	3 (5.3)	
Holmium laser		11 (19.3)	
White light	25 (62.5)	34 (59.6)	
Narrow-band imaging (NBI)	8 (20.0)	20 (35.1)	
Photodynamic diagnostics (HEXVIX®)	4 (10.0)	2 (3.5)	
Storz professional image enhancement system (SPIES)®	2 (5.0)		
SPIES® + PDD (HEXVIX®)	1 (2.5)	1 (1.8)	
Perioperative variables	(*n* = 40)	(*n* = 55)	
Surgical duration, min, mean (SD)	25.4 (13.6)	27.6 (14.5)	0.450
Resection duration, min, mean (SD)	15.5 (11.4)	16.3 (12.8)	0.732
Tumour retrieval, *n* (%)			
En bloc	–	46 (83.6)	<0.001
Fragmented	40 (100)	9 (16.4)	
Tumour size for ERBT tumours, cm, mean (SD)			
Fragmented		3.33 (1.43)	
En bloc		1.69 (0.81)	
Bladder irrigation period, h, mean (SD)	21.15 (15.97)	21.62 (19.08)	0.898
Catheterisation period, days, mean (SD)	1.9 (0.87)	2.44 (2.29)	0.173
Hospitalisation period, days, mean (SD)	2.4 (1.22)	2.7 (2.7)	0.389
Intraoperative complications, *n* (%)	(*n* = 40)	(*n* = 55)	
Overall complications	3 (7.5)	11 (20)	0.142
Bladder perforation	0	7	0.020
Strong bleeding	1	3	0.636
Resection of ureteric orifice	0	1	1.000
False passage	1	0	0.421
N/A	1	0	0.421
Haemoglobin drop, g/L, mean	4.2	5.8	0.488
Postoperative complications using Clavien–Dindo classification system*, *n* (%)			
Grade I	2 (5.3)	2 (3.7)	
Fever w/o antibiotic use	–	1	
Bleeding w/o transfusion	1	1	
N/A	1	–	
Grade II:	2 (5.3)	2 (3.7)	
Bleeding requiring transfusion	1	1	
Fever requiring antibiotics	1	1	
Grade IIIa	–	1 (1.8)	
Urinary retention requiring Foley catheter	–	1	
Grade IIIb	–	1 (1.8)	
N/A	–	1	

Table 1 (continued)

Characteristic	cTURBT (*n* = 40)	ERBT (*n* = 57)	*P*
Grade IVa		1 (1.8)	
Cardiac decompensation	–	1	
Pathological and oncological measures, *n* (%)			
pT stage			
Ta	25 (62.5)	44 (80)	0.075
T1	12 (30)	9 (16.4)	
T1 and CIS	1 (2.5)	–	
PUNLMP	–	2 (3.6)	
N/A	2 (5)	–	
Grading			
Low grade	20 (50)	28 (50.9)	0.530
High grade	18 (45)	24 (43.6)	
PUNLMP	–	2 (3.6)	
N/A	2 (5)	1 (1.8)	
EAU risk group			
Low risk	15 (37.5)	24 (43.6)	
Intermediate risk	8 (20)	17 (30.9)	0.113
High risk	15 (37.5)	12 (21.8)	
N/A	2 (5)	–	
DM proof			
Yes	28 (70)	37 (67.3)	0.687
No	10 (25)	16 (29.1)	
N/A	2 (5)	2 (3.6)	
LMP proof			
Yes	19 (47.5)	28 (50.9)	0.667
No	14 (35)	25 (45.5)	
N/A	7 (17.5)	2 (3.6)	
T1 sub-staging feasible	*n* = 13	*n* = 9	
Yes	5 (38.5)	9 (100)	0.006
No	8 (61.5)	–	
Recurrence within 6 months	*n* = 25	*n* = 39	
Yes	6 (24)	7 (17.9)	0.625
No	19 (76)	31 (79.5)	
Patient death (other cause)	–	1 (2.6)	
Second resection			
Yes	11 (44)	6 (15.8)	0.010
No	13 (52)	32 (84.2)	
N/A	1 (4)	–	

CIS, carcinoma in situ; EAU, European Association of Urology; N/A, not available; PUNLMP, papillary urothelial neoplasm of low malignant potential; w/o, without.
Perioperative outcomes were analysed for all ERBT cases that were completed with ERBT. T1 sub-staging feasibility analysis was performed only for T1 tumours. **Significance levels for postoperative complications were not assessed due to the low number of postoperative complications.*

Table 2 Multivariate regression analysis on (a) predictors for an intraoperative complication showing age and resection duration as significant factors and (b) predictors for a second resection after 6 weeks showing the resection method (ERBT vs cTURBT) and R0 status as significant factors.

Variable	*B*	Standard error	*P*	Odds ratio (95% CI)
(a) Intraoperative complication				
Age	0.142	0.058	0.015	1.153 (1.028–1.292)
ASA score	−0.494	0.674	0.463	0.610 (0.163–2.284)
ECOG performance status	−2.438	1.292	0.059	0.087 (0.007–1.100)
Resection duration	0.093	0.046	0.043	1.098 (1.003–1.202)
Resection method	1.328	0.948	0.161	3.773 (0.588–24.207)
Tumour localisation	−0.166	0.098	0.089	0.847 (0.700–1.025)
Tumour size	−0.005	0.408	0.990	0.995 (0.447–2.215)
Number of tumours	−0.564	0.810	0.486	0.569 (0.116–2.783)
(b) Second resection				
Resection method	−2.26	0.131	0.024	0.163 (0.034–0.784)
pT stage	0.39	0.837	0.694	1.290 (0.361–4.600)
DM proof	−0.89	0.378	0.376	0.534 (0.134–2.138)
R0 status	−3.45	0.060	0.001	0.084 (0.020–0.343)

ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative of Oncology Group; pT, pathological T stage.

Table 3 Endpoint comparison of main large prospective ERBT trials.

Endpoint	Prospective ERBT trials											
	EBRUC II		Gakis et al., 2020 [10]		Gallioli et al., 2022 [13]		Teoh et al., 2021 [16]		D'Andrea et al., 2023 [11]		Teoh et al., 2024 [12]	
	cTURBT (*n* = 46)	ERBT (*n* = 55)	cTURBT (*n* = 59)	ERBT (*n* = 56)	cTURBT (*n* = 108)	ERBT (*n* = 140)	cTURBT (*n* = 36)	ERBT (*n* = 99)	cTURBT (*n* = 178	ERBT (*n* = 179)	cTURBT (*n* = 133)	ERBT (*n* = 143)
Perioperative variables												
Surgical duration, min, mean (SD) /median (IQR)	25.4 (13.6)	27.6 (14.5)	N/A	N/A	30 (20–35)	30 (20–40)	N/A	N/A	25 (17–35)	26 (20–38)	22 (15–30)	28 (20–45)
Resection duration, min, mean (SD)	15.5 (11.4)	16.3 (12.8)	22.4 (14.5)	37.1 (22.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tumour retrieval rate, *n* (%)			N/A	N/A			N/A	N/A	N/A	N/A	N/A	N/A
En bloc	–	46 (83.6)	N/A	N/A		138 (99)	N/A	N/A	N/A	N/A	N/A	N/A
Fragmented	40 (100)	9 (16.4)	N/A	N/A		2 (1)	N/A	N/A	N/A	N/A	N/A	N/A
Tumour size, cm					N/A	N/A			N/A	N/A	N/A	N/A
<3			41	46								
≤1							5.6%	33.3%				
1.01–2							22.2%	37.4%				
2.01–3			10	2			19.4%	21.2%				
>3			N/A				52.8%	8.1%				
Fragmented, mean		3.33 cm	N/A	N/A	N/A	N/A	N/A	N/A				
En bloc, mean		1.69 cm	N/A	N/A	N/A	N/A	N/A	N/A				
Bladder irrigation, h, mean (SD)	21.15 (15.97)	21.62 (19.08)	N/A	N/A	12 (median)	12 (median)	N/A	N/A				
Catheterisation time, days, mean (SD)	1.9 (0.87)	2.44 (2.29)	2.0 (1.4)	2.0 (0.8)	2 (median)	2 (median)	N/A	N/A				
Hospitalisation time, days, mean (SD) / median (IQR)	2.4 (1.22)	2.7 (2.7)	2.5 (0.8)	2.6 (1.4)	2 (median)	2 (median)	N/A	N/A			2 (2–3)	2 (2–2)
Intraoperative complications, *n* (%)												
Overall complications	3 (7.5)	11 (20)	N/A	N/A			2 (5.6)	7 (7.1)			17 (13)	21 (15)
Bladder perforation rate	0	7	1	1	18 (17)	28 (20)	0	0	10 (5.6)	22 (12.3)		
Extraperitoneal	0	7	1	1	N/A	N/A			9 (5.1)	21 (11.7)		
Intraperitoneal	0	0	0	0	N/A	N/A			1 (0.5)	1 (0.6)		
Strong bleeding	1	3					1	5				
Resection of ureteric orifice	0	1					0	0				
False passage	1	0					0	0				
N/A	1	0										
Haemoglobin drop, g/L, mean	4.2	5.8	N/A	N/A	5.5	6.0	N/A	N/A				
Postoperative complications, *n* (%)												
Grade I	2 (5.3)	2 (3.7)	N/A	N/A	Grade I–II 23 (21)		1				Grade I–II 17 (13)	Grade I–II 21 (15)
Fever w/o antibiotic use	-	1										
Bleeding w/o transfusion	1	1	1	0								
N/A	1	-					1	0				
Grade II	2 (5.3)	2 (3.7)	N/A	N/A			0	0				
Bleeding requiring transfusion	1	1			2 (1.9)	0						
Fever requiring antibiotics	1	1										
Grade IIIa	–	1 (1.8)	0	0	3 (3)	6 (5)	0	2			Grade III –IV 0	Grade III –IV 2 (1.4)
Urinary retention requiring Foley catheter	–	1					0	2				
Grade IIIb	–	1 (1.8)	0	0			0	0				
N/A	–	1										
Grade IVa		1 (1.8)	0	0			0	0				
Cardiac decompensation	–	1										

IQR, interquartile range; N/A, not available; w/o, without.

Pathological and Oncological Outcomes

Presence of DM was observed in 73.7% of cTURBT and 67.3% of ERBT specimens ($P = 0.69$). R0 status was reported in 72.2% after ERBT vs 45% after cTURBT ($P = 0.006$), whilst resection margins were not assessable (Rx) in 45% of cTURBT cases vs 25.5% after ERBT ($P = 0.047$). R1 status was reported in four cTURBT cases (10%) and one ERBT case (1.8%) but showed no statistical significance ($P = 0.158$; Table 2). Second resection was less likely to be performed after ERBT ($P = 0.010$). Multivariate regression showed only R0 status and ERBT to be independent predictors for no second resection after 6 weeks (Table 3). There was no statistical difference in recurrence rates ($P = 0.625$) after 6 months as shown in Table 2. Sub-staging feasibility was reported in 100% of T1 tumours undergoing ERBT, compared to 38% of cTURBT cases ($P = 0.006$).

Discussion

This study was initially designed to evaluate 360 patients (180 per group). Due to the increased risk of bladder perforations and subsequent safety concerns for ERBT, this study had to be terminated after the enrolment and analysis of 97 patients. Thus, these data should be considered, knowing that statistical power is lower than initially planned. Of the 28 failed screenings, 15 patients (11.2% of screened patients) were explicitly excluded for ERBT based on the following criteria: localisation, tumour configuration, tumour size, solid tumours, or number of tumours, meaning that ERBT was potentially feasible in nearly 90% of the screened cases. In a 2017 meta-analysis, our group reported an overall feasibility rate of 70% for ERBT [9]. The HYBRIDBLUE study (German clinical trials register ID: DRKS00004414) by Gakis et al. [10] showed an exclusion rate for *en bloc* hydrodissection of 69.06%, with more restrictive inclusion criteria. Our RCT seems to be in favour of ERBT compared with previous data. Recent RCTs comparing cTURBT and ERBT showed conversion rates of 3.4% (D'Andrea et al. [11]) up to 10% [12] (4.3%, Gallioli et al. [13]). The reasons given for the conversions were suspected detrusor infiltration, resection of the ureteric meatus, laser failure, perforation, tumour size and localisation [13].

In our study, two (3.5%) patients in the ERBT group required conversion to cTURBT, which is consistent with the data from D'Andrea et al. [11] and lower than in the RCT by Teoh et al. [12]. Hurle et al. [14] conducted an observational study at a single centre and found a low conversion rate of 0.97%. While the selection for ERBT cases was more stringent in these trials than ours, excluding tumours >3 cm in diameter [11,12,14]. Gallioli et al. [13] also excluded multiple tumours. A systematic review by Naselli and Puppo [15] found a conversion rate of 6.5%. Teoh et al. [16] reported decreasing rates of successful ERBT with increasing tumour size, reaching 29.6% for tumours >3 cm. Our results lie between these findings and show that ERBT is feasible in 96.5% of cases without the need for intraoperative modification of the surgical method, after proper preoperative tumour assessment.

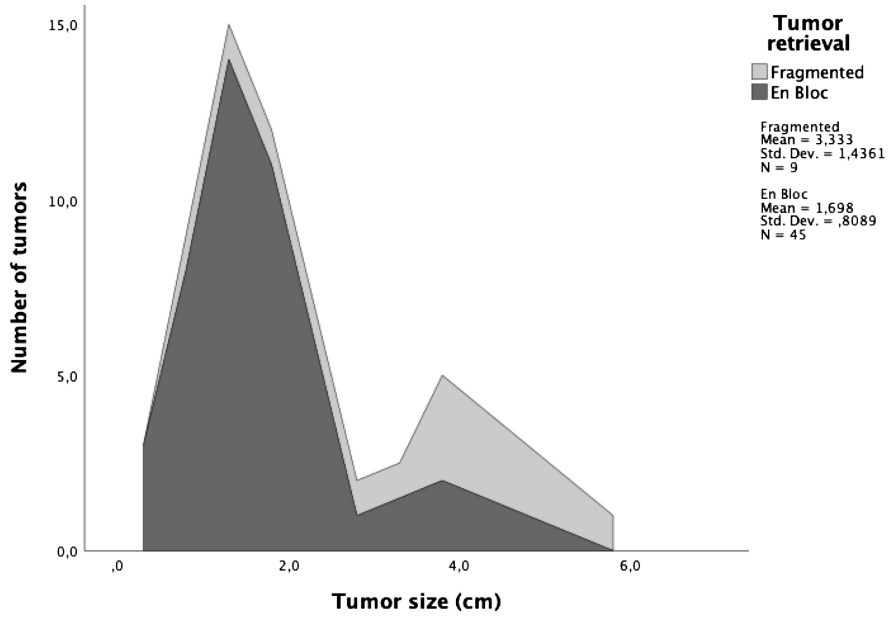
Previous studies have shown that *en bloc* tumour extraction may be limited to ~3 cm [11,14,16]. In our study, we did not set an upper limit for tumour size in the inclusion criteria. The average tumour size for tumours that were fragmented intravesically before extraction was 3.3 cm, whereas the largest tumour that was retrieved *en bloc* measured 4 cm. Figure 2 shows the increasing rate of ERBT tumours that were fragmented intravesically, with an increase in the fragmented fraction at 3.5 cm. In only one case, tumour size was the reason for an intraoperative change of the resection method. Our findings confirm that tumour size is not a contraindication for successful ERBT, whereas larger tumours still pose a problem for intact recovery.

The results of previous studies on operation time are inconsistent. The recent larger RCT of Gallioli et al. [13], D'Andrea et al. [11] and Teoh et al. [12] found no difference in median operative time, whilst a retrospective analysis from Li et al. [17] showed a shorter duration for thulium laser ERBT (25.96 min) compared to cTURBT (37.18 min) ($P = 0.018$). Meanwhile, Gakis et al. [10] reported significantly longer operative time using a HybridKnife® (37.1 vs 22.4 min for cTURBT; $P < 0.001$). In our study and in congruence to the other reported RCTs, no significant difference in mean operative time was observed ($P = 0.450$), thus, the operation time seems to be dependent on the energy source and the technique used for ERBT.

In a previous observational study, ERBT was described to have an advantage over cTURBT concerning DM inclusion rate [14]. In the RCT conducted by D'Andrea et al. [11] a significantly higher rate of DM was reported in favour of the ERBT group (80.7% vs 71.1%). Other RCTs [10,12,13] and non-randomised prospective trials [16] failed to prove significant differences for either one of the two methods regarding DM inclusion rate. Our results confirm these findings and found no benefit for either cTURBT or ERBT ($P = 0.69$).

In our study, ERBT showed a significantly higher rate of R0 assessability ($P = 0.006$), and a significant reduction of necessary second resection ($P = 0.010$). Multivariate regression showed ERBT and R0 status to be significant predictors for a second resection. This confirms the findings by Gakis et al. [10], where hydrodissection ERBT showed superiority in R0 status. Additionally, the RCTs by D'Andrea et al. [11] and Teoh et al. [12] reported higher margin assessability for the ERBT group [11,12]. This seems to be a significant advantage for ERBT, especially when a second

Fig. 2 Tumour retrieval *en bloc* vs fragmented retrieval after ERBT depending on tumour size showing an increased number of tumours being fractioned intravesically starting at ~3 cm.



resection is performed due to uncertainty of complete resection. As reported in the RCT by Gallioli et al. [13], in our study sub-staging was assessable in 100% of T1 cases (P = 0.006) showing superiority in staging quality of ERBT.

In this early data, there was no significant difference in recurrence rate after the 6-month follow-up period. Most previous RCTs showed no significant advantage for ERBT [10,13]. However, Teoh et al. [12] recently found a significant advantage for ERBT regarding the 1-year recurrence rate, with a hazard ratio of 0.57, especially for patients with 1–3 cm tumours, a single tumour, Ta disease, or intermediate-risk NMIBC. They did not detect any significant difference in the 1-year progression rate between the ERBT and cTURBT groups (P = 0.065). Our own long-term follow up is still ongoing at this point.

In a previous meta-analysis, our group reported a significantly higher drop of haemoglobin with electrical ERBT compared to laser ERBT (4.6 vs 1.5 g/L, P = 0.0013) [18]. The *en bloc* resection of urothelium carcinoma of the bladder (EBRUC) II study showed no statistical difference between the two groups (P = 0.488). A mean haemoglobin drop averaged 4.2 g/L in the cTURBT group and 5.8 g/L in the ERBT group, and the difference can be considered clinically insignificant. In further studies, the use of haemoglobin levels as a standard value for comparison of TURBT should be evaluated critically. Mean irrigation time was not significantly different between groups (P = 0.898). Our results confirm those of previous studies with an average irrigation time after ERBT of <24 h [14,18].

Surprisingly, bladder perforations were observed more frequently after ERBT (P = 0.02). Previous studies showed either no significant difference between the methods or an advantage for ERBT (5.6% vs 12%, D'Andrea et al. [11]), whilst perforation in the RCT performed by Gallioli et al. [13] was defined as resection reaching the perivesical fat. In a single-centre study by Hurle et al. [14], cystography was performed after macroscopic detection of bladder perforation. Other studies did not define bladder perforation or performed cystography routinely [6,10,11,13,14,16].

Limitations

Although the presented EBRUC II study was started by a pro-ERBT group, the planned interim analysis showed a significantly increased perforation rate. It should be mentioned that in our study, bladder perforations were documented by the surgeon according to subjective assessment. The perforations did not occur in a single, but in multiple study sites. No objective measurements (i.e., cystography) were systematically implemented in the initial EBRUC II study protocol. Although the systematic use of cystograms was discussed during the initial development of the study protocol, it could not be implemented in a multicentre setting. Even if this limits the data quality, it was no longer possible to continue the study in a protocol-compliant manner. As there are virtually no data on a comparison of perforation rates in the multicentre setting, we believe that these are worth reporting. In our view, this reflects the clinical reality in which bladder perforations are

often defined macroscopically by visible fat during deep resection. This definition is also covered by the DEpth of Endoscopic Perforation (DEEP) scale reported by Breda et al. [19]. Additionally, it is consistent with other trials. Although ERBT showed a perforation rate of 20% (28 cases) compared to 17% for cTURBT, no cystographic evidence was mentioned in the trial of Gallioli et al. [13] (Table 3) [10–13,16]. Radiographic confirmation is left to the discretion of the surgeon and is not mandatory in the case of safe extraperitoneal perforations. They can usually be managed conservatively with longer catheter placement time and sparing bladder irrigation. A follow-up study with the systematic use of cystograms would certainly be interesting for the final clarification of the perforation question.

Fortunately, the perforations described in our trial occurred extraperitoneally, yet the increased risk of bladder perforation must be considered and evaluated when performing ERBT. In our case, it led to a prolongation of catheterisation time although not statistically significant. Additionally, early bladder instillations could not be administered. Multivariate analysis for intraoperative complication showed that patient age and duration of resection were predictors of intraoperative complication, but resection method was not a significant predictor (Table 2). Bebane et al. [20] showed a correlation between surgeon experience and complication rate when performing TURBT. Surgeon experience should be considered when conducting further studies on ERBT. This is a major limitation of this study, because ERBT is a relatively new procedure compared with cTURBT. Because surgeon identity was assessed without assessing the number of ERBTs conducted by each surgeon, intraoperative complications such as perforations and assessment of resection quality may be limited due to inexperienced surgeons.

Bladder perforations occurred in three out of 11 holmium cases (27.2%), two on the left sidewall and one in the trigonal region. Gallioli et al. [13] reported an overall perforation rate of 20% for ERBT vs 17% for cTURBT without statistical significance ($P = 0.9$). They mentioned a 17% perforation rate for thulium laser ERBT, compared to 29% for bipolar and 14% for monopolar ERBT. Other trials did not show a higher perforation risk for laser ERBT [11,16,21]. Laser resection techniques were originally developed for TURP. Whereas prostate resection ends at the compact and dense capsule where the adenoma can be cut off and torn out of the capsule, there is no such natural boundary in bladder tumour resection. Therefore, deep laser resection may carry a higher risk of bladder perforation, especially in inexperienced hands, although a lower rate of obturator nerve reflexes has been reported [21]. The fact that the DM detection rates were comparable in both arms invalidates the assumption that cTURBT may not have been performed deeply enough or insufficiently (73.7% of cTURBT and 67.3% of ERBT specimens; $P = 0.69$).

No standardised tumour ground biopsy was performed in the cTURBT arm, which limits the power to directly compare resection margin information. Nevertheless, resection margin information can be provided more frequently after ERBT if no additional biopsies are taken. However, this is the first multicentre RCT on ERBT in a real-world setting without limitations regarding tumour localisation, tumour size or energy source.

Conclusion

This is the first European multicentre prospective RCT of ERBT compared to cTURBT in a real-world setting, with no restrictions on tumour size, number of tumours, or energy sources. The feasibility of ERBT in our trial is higher than previously reported. Overall perioperative and safety parameters are comparable to cTURBT. Nevertheless, ERBT appears to carry an increased risk of bladder perforation, especially with laser and sidewall resections, which should be considered when performing ERBT. Preoperative assessment of the tumour size and location is essential for successful ERBT. Staging quality is superior in ERBT specimens resulting in lesser rates of second resections after initial ERBT. Recurrence rates after a 6-month follow-up are comparable. With longer follow-up available, we intend to report on oncological outcomes focusing on in- and out-field recurrence rates.

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Disclosure of Interests

None declared.

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Abbreviations: DM, detrusor muscle; EBRUC, *en bloc* resection of urothelium carcinoma of the bladder (study); ERBT, *en bloc* resection of bladder tumour; NMIBC, non-muscle-invasive bladder cancer; OR, odds ratio; RCT, randomised controlled trial; (c)TURBT, (conventional) transurethral resection of bladder tumour.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Surgical technique and main characteristics of patients who had a bladder perforation.

