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ORIGINAL ARTICLE

The safety and efficacy of total mesorectal excision (TME) surgery following dose-escalation: Surgical outcomes from the organ preservation in early rectal adenocarcinoma (OPERA) trial, a European multicentre phase 3 randomised trial (NCT02505750)

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Abstract

Aim: Nonsurgical treatment with chemoradiotherapy for rectal cancer is gaining interest as it avoids total mesorectal excision (TME) surgery and stoma. The OPERA trial aims to evaluate whether dose escalation with contact X-ray brachytherapy (CXB) boost improves organ preservation compared to external beam radiotherapy (EBRT) boost. It has been suggested that dose escalation adversely affects surgical outcomes and therefore we report outcomes following TME in OPERA at 36 months.

Methods: OPERA is a European multicentre phase 3 trial (NCT02505750) which randomises patients with cT2-3a-b, cN0-1, M0 to EBCRT (45 Gy in 25 fractions over 5 weeks with oral capecitabine 825 mg/m^2) followed by EBRT boost (9 Gy in 5 fractions over 5 days) versus EBCRT followed by CXB boost (90 Gy in 3 fractions over 4 weeks). Patients were assessed at 14, 20 and 24 weeks from the start of treatment. Watch and wait management was adopted for patients who achieved a clinical complete response (cCR) at 24 weeks following treatment. Either local excision (LE) or TME surgery was offered for residual disease or local regrowth, according to patient and surgeon preference. Surgical morbidity and mortality were recorded prospectively.

Results: Between July 2015 and June 2020, 148 patients were randomised of which 141 were evaluable in March 2022. At median follow-up of 38.2 months (range: 34.2–42.5), surgery was performed for 66 (47%) patients. A total of 27 (20%) patients had local excision and 39 (29%) had TME surgery, 22/39 (56%) underwent anterior resection and 17/39 (44%) underwent abdominoperineal excision of the rectum. The R0 resection rate was 87%. There were no deaths, and six patients (15%) had Clavien-Dindo IIIb complications.

[Correction added on 23 Oct 2023, after first online publication: The copyright line was changed.]

An abstract of this paper was selected for oral presentation at the GI ASCO meeting in San Francisco on 21 January 2023.

Whilst there was a statistically significant decrease in the TME rate following CXB boost (HR 0.38, 95% CI: 0.19–0.74, $p = 0.00419$) there was no difference in surgical outcomes between patients who received EBRT and CXB boost.

Conclusion: Dose escalation can facilitate nonsurgical treatment for cT2-3 rectal cancer patients who are fit but wish to avoid TME surgery and stoma. If TME surgery is required, then it can be performed safely and effectively.

KEYWORDS
contact X-ray brachytherapy, neoadjuvant treatment, organ preservation, rectal cancer

INTRODUCTION

The standard of care for cT2-3 nonmetastatic adenocarcinoma of the distal and middle rectum is total mesorectal excision (TME) [1]. When the circumferential resection margin is threatened or there are high-risk prognostic features, this is often preceded by neoadjuvant external beam chemoradiotherapy (EBCRT) [2, 3]. A proportion of patients can achieve a clinical complete response (cCR) after EBCRT, and planned surgery can be deferred or avoided with the adoption of a "watch and wait" (WW) strategy [4–7]. Several studies have demonstrated the safety of this strategy, pioneered by the São Paulo group in the early nineties [8]. It eliminates operative morbidity and mortality, delivers equivalent oncological outcomes, and preserves bowel continuity [4, 5, 9]. This is particularly appealing for patients who are reluctant to accept a permanent stoma, or the risks associated with surgery, or who are unable to undergo TME surgery because of comorbidities. Unfortunately, most patients who receive EBCRT alone will not achieve a cCR [4, 6] and approximately 25% of patients who achieved a cCR will develop local regrowth and need TME surgery [5, 6], reducing the organ preservation rate.

Dose-escalation, to improve organ preservation rate has been advocated by several groups [10–12]. While the cCR can be increased significantly with external beam dose-escalation from 24% to 49%, local regrowth remains a problem at 31% and approximately only one third of patients achieved organ preservation at the end of their treatment [10–12]. It has previously been reported that 50 kV contact X-ray brachytherapy (CXB) boost limits tissue penetration, due to its low energy, and can be used to escalate the targeted dose of radiation directly to the tumour with minimal damage to surrounding tissues [7, 13, 14]. CXB following EBCRT appears to result in higher cCR and lower regrowth rate [15–17]. The only direct comparison of CXB following EBRT, and EBRT alone, showed higher colostomy free survival rates [7]. However, the use of a historic EBRT regimen has made the relevance of this study unclear. Therefore, we performed the Organ Preservation for Early Rectal Adenocarcinoma (OPERA) trial (NCT02505750), a European phase III multicentre randomised controlled trial which seeks to define the role of dose escalation using CXB in the management of rectal cancer in contemporary practice. Three-year follow-up data suggest that the local regrowth is lower and the cCR and organ preservation rate is significantly better following CXB boost [18].

What does this paper add to literature?

Some surgeons are concerned about feasibility to offer salvage surgery after dose escalation with contact X-ray brachytherapy or external beam radiotherapy in patients who develop local failure either due to persistent disease or a regrowth. Our data confirmed the safety and feasibility of surgical salvage in those patients who need it.

It has been suggested that dose-escalation might result in worse outcomes following TME surgery and adversely affect the chance of long-term cure compared to TME following EBCRT alone. Specifically, it has been suggested that dose escalation may worsen fibrosis and oedema following radiotherapy, making surgical planes challenging, resulting in increased operative complications such as bleeding and anastomotic leak rate; reducing the oncological quality of surgery; and worsening longer-term functional outcomes [19].

Consequently, we reviewed our data and report the outcomes following TME surgery from the OPERA trial for patients who underwent TME following dose escalation with EBRT or CXB.

METHODS

OPERA is a European phase III multicentre open label randomised controlled trial comparing current standard of care, EBCRT (45 Gy in 25 fractions over 5 weeks, with oral capecitabine 825 mg/m^2 twice daily) and EBRT boost (9 Gy in 5 fractions over 5 days) (Arm A), versus EBCRT followed by CXB boost (90 Gy in 3 fractions over 4 weeks) (Arm B) (Figure 1). The full trial protocol has previously been described [18]; however, briefly, randomisation at a 1:1 ratio was performed centrally with stratification according to; (1) the trial centres (2) cT stage (cT2 vs. cT3a-b), (3) tumour site (distal rectum <6 cm from anal verge vs. ≥6 cm), and (4) tumour size (<3 cm vs. ≥3 cm).

Patients were assessed at 14, 20 and 24 weeks following the start of treatment. WW management was adopted for patients with cCR or near cCR (ncCR). A cCR is defined as no visible tumour (endoscopy) rectal wall, supple on DRE and on MRI TRG1 or 2. A ncCR can be split into three different clinical presentations

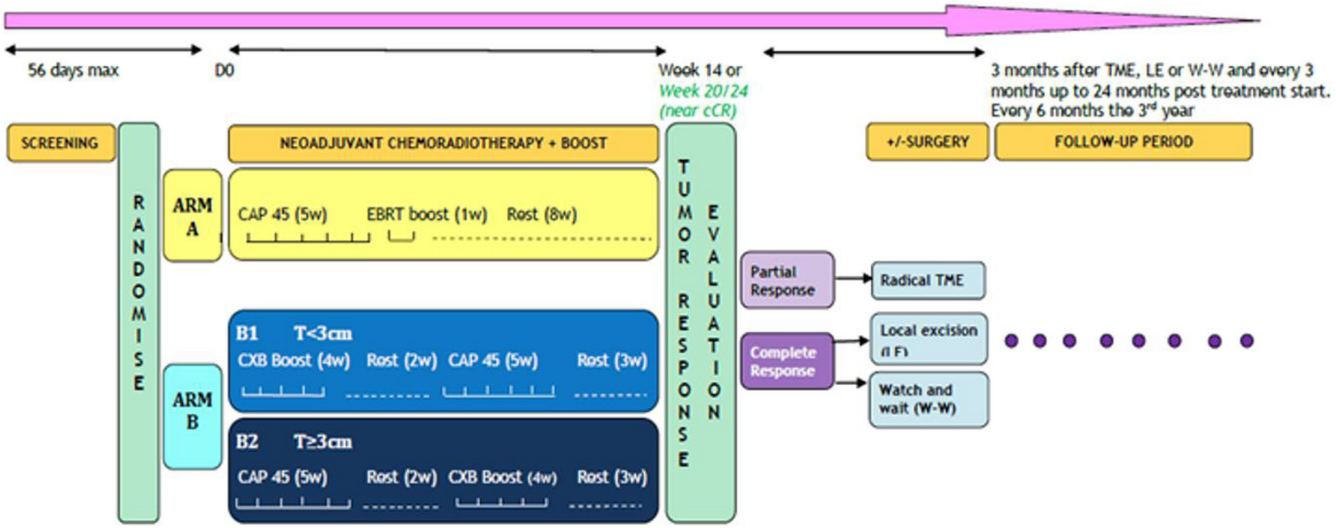

FIGURE 1 Trial design diagram.

of residual "suspicious" lesions: residual ulceration or residual "fibrotic" induration which is felt on DRE or residual polypoid lesion which looks benign and size <2 cm. If ncCR was observed at 14 weeks, we recommended reassessment 6 weeks later, and finally at 24 weeks to evaluate if these abnormalities continue to resolve and heal. If they persisted, surgery (TME or local excision) was offered for suspicious residual lesions. It was recommended that patients with cCR or ncCR can be managed with a WW approach, however the decision to manage using a WW approach or perform local excision or TME surgery should be made by the local multidisciplinary team (MDT) after 14 weeks or finally at the 24-week assessment. Patients who develop local regrowth later after achieving cCR were offered surgery with TME surgery based on local MDT discussions and recommendations.

In addition to routine biochemical and clinical evaluation, all potentially eligible patients had evaluation of the Eastern Cooperative Oncology Group (ECOG) performance status (PS). At baseline, all patients underwent colonoscopy or flexible endoscopy and biopsy for histological confirmation of the diagnosis. Magnetic Resonance Imaging (MRI) staging of local disease was mandatory with optional endorectal ultrasound (EUS). Computed tomography of the chest, abdomen, and pelvis (CTCAP) was mandatory to exclude metastatic disease. Randomisation of eligible patients was mandated within 6 weeks following completion of these investigations.

Inclusion and exclusion criteria

Patients aged ≥18 years, ECOG PS 0–1, with histologically confirmed cT2-3a-b (<5 cm), tumour <50% of rectal circumference, cN0-1 (lymph node <0.8 cm) M0 rectal adenocarcinoma, accessible to digital rectal examination (DRE) and CXB applicators, who were fit for surgery but wanted to avoid TME and a stoma, if possible, were potentially eligible for randomisation.

Patients with staging cT1, cT≥3c, cN1 (lymph node >0.8 cm), cN2, and M ≥ 1 were excluded. Patients with adverse prognostic features on imaging or biopsy, for example, extramural vascular invasion (EMVI), or poorly differentiated tumours were excluded. Other exclusion criteria included ECOG PS ≥2, clinically significant cardiac or kidney disease preventing chemotherapy or surgery, previous pelvic irradiation, cancer within the past 5 years (except skin basal cell or cervical cancer in situ), pregnancy, and patients who were not suitable for chemotherapy or surgery for any other reasons.

We report the surgical outcomes at 38.2 months follow-up. Specifically, type of surgery (TME and LE), safety and histology from the surgical specimens.

Radiation therapy

EBCRT was delivered with photon energies ≥6 MV using a linear accelerator. Either 3D conformal or IMRT were acceptable techniques. EBCRT was delivered once daily (Monday–Friday) for 5 weeks to a planned target volume (primary in the rectum and regional pelvic lymph nodes) at a dose of 45 Gy in 25 fractions over 5 weeks with concurrent chemotherapy using oral capecitabine 825 mg/m^2/day. Dose modification was allowed depending on severity of toxicity.

In Arm A, the boost dose of 9 Gy to primary in the rectum was given using EBRT alone (3D conformal or IMRT) without any delay following EBCRT. The cone-down boost used the initial GTV with a 2 cm margin. The boost was given without concurrent chemotherapy (Figure 1).

In Arm B, the CXB boost was given depending on the original tumour size. CXB was given before EBCRT, if the tumour was <3 cm in greatest diameter or after EBCRT if tumour ≥3 cm. This was to reduce the tumour size down to <3 cm before CXB. In both Arms CXB was delivered using a Papillon 50© machine (Ariane

Medical Systems Ltd, Alfreton, UK). The applied dose was 30 Gy per fraction with the biologically equivalent dose (EQD^2) of 100, which is very high and applied three times at 2-week intervals (Figure 1).

Surgery

If there was persistence of abnormality at 24 weeks either on imaging, DRE or endoscopy, surgery was offered. TME or local excision (LE) surgery was recommended following a partial response. For TME surgery, surgical technique (anterior resection, abdominoperineal resection [APR], intersphincteric dissection, or Hartmann's procedure) was left to the discretion of the local team. In cases of cCR or ncCR the decision to manage using a WW approach or perform local excision (LE) was made by the local MDT. TME was recommended if high-risk features were identified in the postoperative histology of the LE specimen such as incomplete (R1) (resection margin <1 mm) or ≥ T2 histology, but the final decision was left to the local colorectal MDT. Surgical morbidity and mortality were prospectively recorded and collated at the department of research and clinical innovation of Centre Antoine Lacassagne.

Statistical analysis

All the analyses were performed on an intention-to-treat basis. Qualitative variables are presented as absolute frequency, relative frequency, and percentage of missing data. Quantitative variables are presented as median, range and percentage of missing data. Survival estimates are presented as Kaplan–Meier curves, with survival rates and corresponding 95% confidence intervals. All analyses were performed using the R.3.6.1 software.

Trial oversight and ethical approval

The trial was sponsored by Centre Antoine Lacassagne and designed under the auspices of the French INCA (Institute National du Cancer) with the participation of 17 institutions from France, UK, and Switzerland. An independent data monitoring committee (IDMC) was established to review the trial data after inclusion of the first 80 patients. IDMC include a colorectal surgeon (UK), two clinical oncologists (France and Norway) and one methodologist (France). A safety rule was set up to stop the trial if any progressive nonsalvageable local pelvic recurrence was seen in more than 10% of patients. A central review of MRIs was established to help local radiologists when necessary. A quality control programme was set up to assess the performance of the Papillon 50 TM systems and the EBRT technique. The department of research and clinical innovation of Centre Antoine Lacassagne collected and analysed the data. This study was supported by a grant from the French Ministry of Health (PHRC-K 2015-128), and charity grants were received by Centre Antoine Lacassagne and Clatterbridge Cancer Centre (Liverpool, UK). However, the funders were not involved in the study design, data collection, data analysis, interpretation or writing of the manuscript.

The trial protocol was approved by an independent ethics committee in France (Nice 06) and in the UK by the Health Research Authority (IRAS project ID: 210067). All patients signed written consent forms after receiving the full verbal and written information. The trial was conducted according to the latest version of the Declaration of Helsinki, Good Clinical Practice guidelines, relevant French, UK, and European laws and directives.

RESULTS

From July 2015 to June 2020, 148 patients were randomised of whom 141 were evaluable. Seven of these patients were excluded from analysis because they withdrew their consent (Figure 2). Median follow-up was 38.2 months (IQR 34.2–42.5). The staging and demographic characteristics of included patients are shown in Table 1.

Surgery was performed in 66 patients. Local excision was carried out in 27 patients (20% of all patients, 95% CI: 13%-26%) and TME surgery was performed in 39 patients (29% of all patients, 95% CI: 21%–36%). A total of 26 patients in Arm A underwent TME surgery (39% of patients in Arm A, 95% CI: 26%–50%) and 13 patients in Arm B (19% of patients in Arm B, 95% CI: 9%–28%). In the subgroup of patients who had tumours of less than 3 cm only 9/29 (33%, 95% CI: 13%–18%) in Arm A and 1/32 (3%, 95% CI: 0%–9%) in Arm B underwent TME surgery. Given the very small number of patients who underwent TME surgery in this subgroup further analysis was not undertaken.

22/39 who underwent TME surgery had anterior resection (56%, 95% CI: 40%–72%), and the remaining 17/39 patients had abdominoperineal excision of the rectum (APER) (44%, 95% CI: 28%–60%). 10/26 (39%, 95% CI: 20%–59%) in Arm A and 7/13 (54%, 95%CI 25%–81%) in Arm B. For the whole group, the number of patients who needed APER was 17/141 (13%, 95% CI: 8%–20%). 10/69 (14%, 95%CI 7%–25%) in Arm A and 7/72 (10%, 95% CI: 4%–19%) in Arm B (Table 2).

Laparoscopic surgery was attempted in 28/39 patients (72%, 95% CI: 55%–85%) with 20/26 in Arm A (77%, 95% CI: 56%–91%) and 8/13 in Arm B (62%, 95% CI: 21%–86%). 7/28 patients were converted from a laparoscopic to an open surgical approach (25%, 95% CI: 11%–45%). The conversion rate was (25%, 95% CI: 9%–49%) in Arm A and (25%, 95% CI: 3%–65%) in Arm B (Table 2).

Whilst the TME rate was statistically lower in Arm B (HR 0.38. 95% CI: 0.19–0.74, $p = 0.00419$), there was no statistically significant difference in the type of TME surgery that was performed. Further details about the patients who had local excision will be published separately.

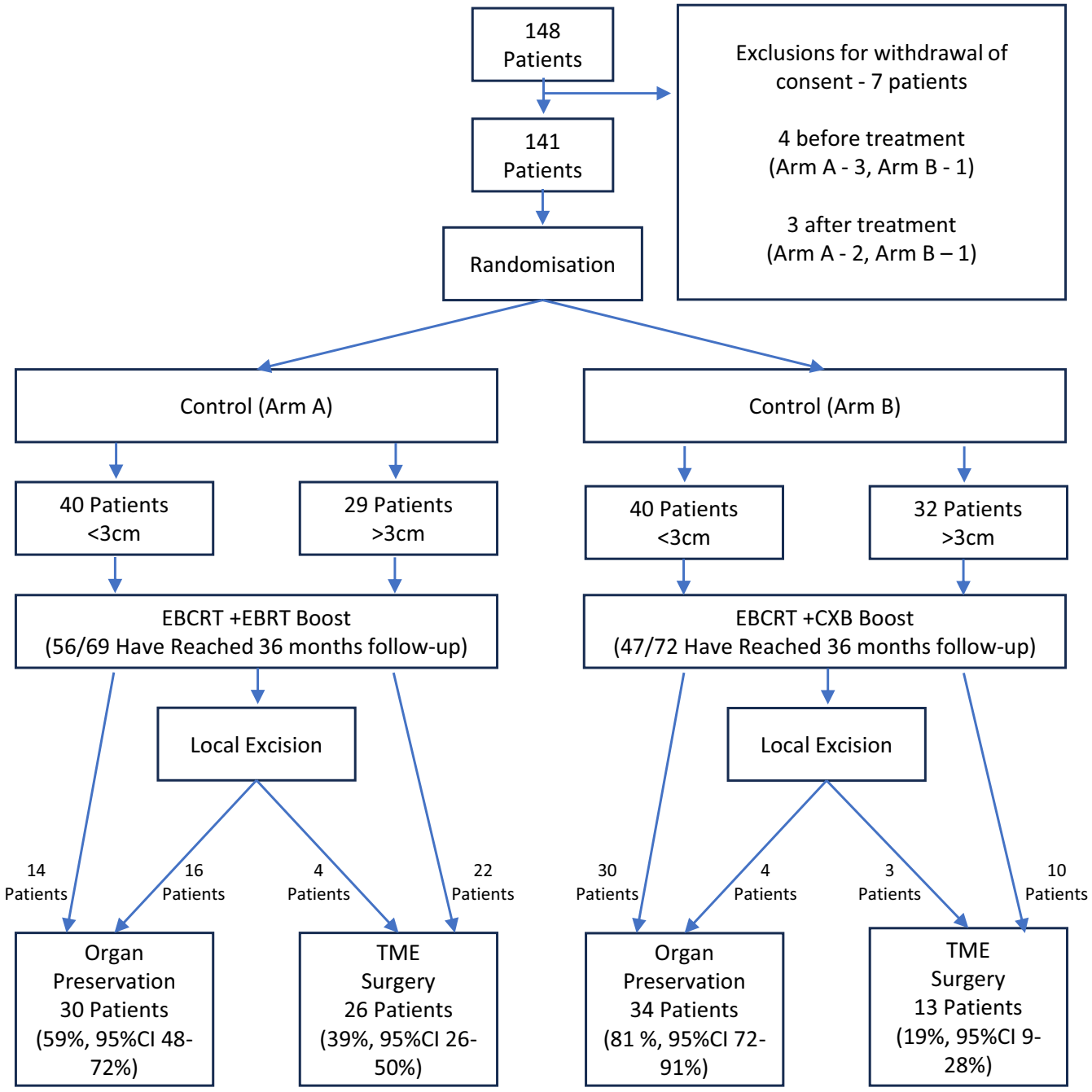

FIGURE 2 Patient flow diagram.

Timing of surgery

After the first assessment at 14 weeks 10patients had TME and 22 patients had TME surgery at 24 weeks. A total of 15 patients had highly suspicious residual disease and four patients had ncCR (Table 2). A further seven had TME after 24 weeks for local re-growths. Local excision was carried out at 14 weeks in 20 patients and a further seven at 24 weeks. No local excision was carried out after 24 weeks. No difference in the timing of surgery was seen between the two arms.

Oncological outcomes and pathology following TME surgery

A total of 4/20 patients (20%, 95% CI: 6%–44%) in Arm A and 3/7 patients (43%, 95% CI: 10%–82%) in Arm B underwent TME surgery following local excision (Figure 2). Full details of the pathological stage of patients following TME surgery are shown in Table 3. Out of 39 patients who had TME surgery, there was tumour perforation during surgery in two patients (5%, 95% CI: 1%–17%), one in each arm. There was no evidence of residual tumour (ypT0) in 9/39 (23%,

TABLE 1 Demographic and patient clinical characteristics at baseline.

Variable	Total ($n=141$)	Arm A ($n=69$) EBRT boost	Arm B ($n=72$) CXB boost	p-value
Age – years				
Median [range]	69 [40–92]	69 [40–86]	70 [46–92]	>0.05
Sex (%)				
Male	87 (61.7)	45 (65.2)	42 (58.3)	>0.05
WHO performance status (%)				>0.05
0	106 (75.2)	51 (73.9)	55 (76.4)	
1	22 (15.6)	10 (14.5)	12 (16.7)	
2	1 (0.7)	0 (0)	1 (1.4)	
Unknown	12 (18.4)	8 (11.6)	12 (16.7)	
Tumour grade (%)				>0.05
Well	50 (35.5)	21 (30.4)	29 (40.3)	
Moderately	64 (45.4)	34 (49.3)	30 (41.7)	
Poorly	1 (0.7)	0 (0)	1 (1.4)	
Unknown	26 (18.4)	14 (20.3)	12 (16.7)	
Clinical T status (%)				>0.05
cT2	91 (64.5)	44 (63.8)	47 (65.3)	
CT3a-b	50 (35.5)	25 (36.2)	25 (34.7)	
Clinical N status (%)				>0.05
cN0	104 (73.8)	49 (71)	55 (76.4)	
CN1	34 (24.1)	18 (26.1)	16 (22.2)	
Unknown	2 (2.1)	2 (2.9)	1 (1.4)	
Distance from the anal verge (%)				>0.05
<6 cm	106 (75.2)	53 (76.8)	53 (73.6)	
≥6 cm	35 (24.8)	16 (23.2)	19 (26.4)	
Tumour diameter (%)				>0.05
<3 cm	61 (43.3)	29 (42)	32 (44.4)	
≥3 cm	80 (56.7)	40 (58)	40 (56.6)	

TABLE 2 Details of TME surgery.

Variable	Total ($n=39$)	Arm A ($n=26$) EBRT boost	Arm B ($n=13$) CXB boost	p-value
Type of approach (%)				>0.05
Laparoscopic	28 (71.8)	20 (76.9)	8 (61.5)	
Laparoscopic converted to open	7 (25)	5 (25)	2 (25)	
Open	11(22.2)	6 (23.1)	5 (38.5)	
Surgery type (%)				>0.05
APER	17 (43.59)	10 (38.5)	7 (53.8)	
Anterior resection	22 (56.41)	16 (61.5)	6 (46.2)	
Gross complete (%)	38	24 (100)	14 (100)	>0.05
Unknown	1 (2.6)	1 (3.8)	0 (0)	
Tumour perforation during surgery (%)	2 (5.41)	1 (3.8)	1 (7.7)	>0.05

Abbreviation: APER, abdominoperineal excision of the rectum; TME, total mesorectal excision.

95% CI: 11%–39%) for the whole cohort and 6/26 (23%, 95% CI: 9%–44%) in Arm A and 3/13 (23%, 95% CI: 5%–54%) in Arm B. The majority of patients were ypN0 30/39 (77%, 95% CI: 61%–89%) with 22/26 (85%, 95% CI: 65%–96%) in Arm A and 8/13 (62%, 95% CI: 32%–86%) in Arm B. More importantly, R0 resection was achieved in 34/39 patients (87%, 95%CI 73%–96%) and 23/26 (92%, 95% CI:

TABLE 3 Pathology following TME surgery.

Variable	Total ($n=39$)	Arm A ($n=26$) EBRT boost	Arm B ($n=13$) CXB boost	p-value
ypT (%)				>0.05
T0	7 (17.9)	4 (15.4)	3 (23.1)	
Tis	2 (5.1)	2 (7.7)	0 (0)	
T1	5 (12.8)	3 (11.5)	2 (15.4)	
T2	18 (46.2)	12 (46.2)	6 (46.2)	
T3	6 (15.4)	4 (15.4)	2 (15.4)	
T4	1 (2.6)	1 (3.8)	0 (0)	
ypN (%)				>0.05
N0	30 (78.9)	22 (88)	8 (61.5)	
N1	8 (21.1)	3 (12)	5 (38.5)	
Unknown	1 (2.6)	1 (3.8)	0 (0)	
Surgical margin (CRM) (%)				>0.05
R0	34 (89.5)	23 (92)	11 (84.6)	
R1	4 (10.5)	2 (8)	2 (15.4)	
Unknown	1 (2.6)	1 (3.8)	0 (0)	

Abbreviation: CRM, circumferential resection margin; TME, total mesorectal excision.

TABLE 4 Pathology following local excision.

Variable	Total ($n=27$)	Arm A ($n=20$) EBRT boost	Arm B ($n=7$) CXB boost	p-value
ypT (%)				>0.05
T0	10 (37)	8 (40)	2 (28.6)	
Tis	2 (7.4)	1 (5)	1 (14.3)	
T1	5 (18.5)	4 (20)	1 (14.3)	
T2	8 (29.6)	5 (25)	3 (42.9)	
T3	2 (7.4)	2 (10)	0 (0)	
Unknown	0 (0)	0 (0)	0 (0)	
Surgical margin (%)				>0.05
R0	17 (81)	15 (88.2)	2 (50)	
R1	4 (19)	2 (11.8)	2 (50)	
Unknown	6 (22.2)	3 (15)	3 (42.9)	

Abbreviation: CXB, contact X-ray brachytherapy EBRT; external beam radiotherapy.

70%–98%) in Arm A with 11/13 (85%, 95% CI: 56%–98%) in Arm B. There were no statistically significant differences in pathological outcomes between the two arms. Whilst details about the patients who had local excision will be published separately, the post-excision histology is reported in Table 4.

No patients had pelvic recurrence following TME surgery. The rate of metastasis was 9% (95% CI: 1%–15%) in Arm A and 8% (95% CI: 2%–16%) in Arm B.

Complications following TME surgery

There was no death associated with either local excision or TME surgery. Median hospital stay was 9 days (range: 1–37). It was 8 days (range: 1–37) for patients in Arm A and 10 days (range: 6–24) for those in Arm B.

Hospital readmission with second surgery occurred in seven patients in total. In one case this was for a reversal of ileostomy. Clavien-Dindo IIIb complications occurred in 6/39 (15%, 95% CI: 6%–31%) patients with 4/26 (15%, 95% CI: 4%–35%) in Arm A and 2/13 (15%, 95% CI: 2%–45%) in Arm B. In Arm A reoperation occurred because of an R1 resection to excise the anastomosis and reanastomose the bowel, for an anastomotic leak, and for two cases of intrabdominal collections. In Arm B reoperation occurred for adhesional bowel obstruction, and in another patient for removal of a cystic ovarian mass. Readmission for Clavien-Dindo II complication were reported in one patient in Arm A (urinary sepsis), and three patients in Arm B (shingles, sepsis of unknown

aetiology, and a conservatively managed iatrogenic vaginal perforation).

DISCUSSION

The OPERA trial has reported a cCR or ncCR response rate following dose-escalation with CXB boost in 97% of patients with tumour <3 cm, compared to 63% of patients treated with EBRT boost alone [18]. For the whole group cCR of 68% following CXB boost compares favourably with internationally reported WW series [5, 6, 10, 11]. If a cCR is achieved, we found it to be more durable following CXB boost with fewer patients experiencing local regrowth compared to patients treated with EBRT boost [18]. Similarly, the local regrowth rate compares favourably with reported WW series [5, 6, 10, 11]. The high cCR rate and low local regrowth rate has resulted in an excellent organ preservation rate in the OPERA trial following CXB boost 81% (95% CI: 72%–91%) for all cT2-3 tumours at 3 years.

The concern is whether organ preservation is at the expense of compromised surgical outcomes, and if surgical outcomes are compromised is this compounded by dose escalation? Specifically, is surgery more technically challenging resulting in higher complication rates and compromised oncological outcomes? Do extended neoadjuvant regimens and WW follow-up result in uncontrolled progression of tumour regrowth, requiring more extensive surgery, and are patients more likely to develop metastatic disease which may render surgical salvage inappropriate?

This study supports existing literature that suggests that when a cCR was not achieved or when local regrowth occurred, this can be detected in a timely fashion and successful salvage TME surgery can be performed. No patients required beyond-TME or exenterative surgery. Whilst this study was not powered to detect a difference in surgical outcomes between patients treated with a CXB or EBRT boost, no differences in outcomes were observed. Not only was the ratio of patients treated with APER compared to anterior resection comparable in both groups, the rate of TME surgery with sphincter preservation (anterior resection) (56%, 95% CI: 40%–72%), was comparable to reported WW series [20–23], and the 43.5% reported in a systematic review of the WW literature [6]. The rate of TME surgery with sphincter preservation must be interpreted in the context of the height of the tumours from the anal verge at initial presentation with 75% (95% CI: 87%–82%) <6 cm from the anal verge suggesting that the rate of TME surgery with sphincter preservation was not adversely affected by dose escalation.

No pelvic recurrence was detected; however, a median follow-up of 38.2 months and the sample size are probably inadequate to observe this. The R0 resection rate, however, has been shown to be associated with pelvic recurrence [24]. No difference was observed in the R0 resection rate between groups and the overall R0 resection rate (87%, 95% CI: 73%–96%) was comparable to series of TME surgery reported in WW cohorts [4, 6, 20–23, 25–27], the international watch and wait database (88%) [5], and a systematic review of the WW literature (93%) [6]. Moreover, the R0 resection rate in this study was comparable to other clinical trials for TME surgery such as the MERCURY study (86%) in which neoadjuvant EBCRT was given primarily for threatened or compromised circumferential resection margin [24], and the UK National Bowel Cancer Audit (93%) [28]. Regrettably the TME grade was not formally recorded including the incidence of breached TME plane. The rate of metastasis was 9% (95% CI: 1%–15%) in Arm A and 8% (95% CI: 2%–16%) in Arm B, this is congruent with the incidence of metastatic disease in previously reported surgically managed cohorts [4, 5].

Many surgeons are concerned that dose escalation regimens may make TME more technically challenging. There is limited evidence of this in our cohort. Laparoscopic surgery was attempted in 28/39 patients (72%, 95% CI: 55%–85%) with no difference between CXB and EBRT boost groups. This is comparable to registry data such as NBOCA for all colorectal surgery [28]. Whilst the conversion rate in our study 7/28 (25%, 95%11%–45%) was slightly higher [28], this may not be the case for low rectal resections. Finally, the complications associated with TME surgery in the OPERA trial, including the anastomotic leak rate, were consistent or compared favourably with the reported literature.

The primary outcome of the OPERA trial was to investigate the impact of CXB boost on the rate on organ preservation and it was not designed or powered to evaluate surgical outcomes. We must consider whether rare and heterogeneous events such as complications resulting from TME surgery following organ preservation strategies could ever be captured adequately by a randomised controlled trial, and whether registry-based studies may be a more effective tool, albeit with the risk of confounding, for understanding and quantifying these risks.

A further difficulty in drawing firm conclusions about the safety and efficacy of TME surgery following dose escalation is that OPERA did not compare our treatment arms with TME surgery which is the standard of care for fit patients. It has historically been difficult to recruit to trials randomising patients between highly invasive and much less invasive therapies when oncological outcomes may be equivalent. Increasingly, there has also been a shift in attitude toward supporting patients who are unable or unwilling to accept permanent stoma and the risks of surgery. National governing authorities now recommend shared decision making with patients [29]. Consequently, more recent organ preservation trials such as STAR TREC, after the phase II feasibility data highlighted difficulty in recruitment, have modified standard of care arms to incorporate patients' preference instead of TME surgery, for their standard of care randomised arm. This pragmatic decision reflects changing public opinion that would make a randomised organ preservation trial untenable, if TME surgery was the standard of care, and if equipoise between interventions was assumed [25].

CONCLUSION

Data from the OPERA study does not suggest that the safety and efficacy of TME surgery is compromised following dose escalation. This supports previously published data that advocates the use of CXB boost as an adjunct to EBCRT in order to increase the cCR rate and durability to achieve organ preservation.

AUTHOR CONTRIBUTIONS

Christopher Rao: Conceptualization; investigation; writing – review and editing. **Nicolas Barbet:** Conceptualization; investigation; supervision; resources. **Brice Thamphya:** Conceptualization; methodology; data curation; project administration; software; formal analysis. **Tangy Pace-Loscos:** Methodology; data curation; formal analysis; software. **Nicolas Magné:** Investigation. **Isabelle Martel-Lafay:** Investigation. **Laurent Mineur:** Conceptualization; investigation. **Melanie Deberne:** Investigation. **Thomas Zilli:** Investigation. **A. Dhadda:** Conceptualization; methodology; investigation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Centre Antoine-Lacassagne, Nice, France. The data that support the findings of this study are openly available in [Centre Antoine-Lacassagne, Nice, Fr] at [www.centreantoinelacassgne.org].

ETHICS STATEMENT

The trial protocol was approved by an independent ethics committee in France (Nice 06) and in the UK by the Health Research Authority (IRAS project ID: 210067).

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