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ORIGINAL ARTICLE

A phase III randomised trial on the addition of a contact X-ray brachytherapy boost to standard neoadjuvant chemo-radiotherapy for organ preservation in early rectal adenocarcinoma: 5 year results of the OPERA trial

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Background: The OPERA trial has shown that a contact X-ray brachytherapy 50 kV (CXB) boost with neoadjuvant chemoradiotherapy (NCRT) can increase organ preservation (OP) rate for early rectal adenocarcinoma (ADK) of low-mid rectum. We report the results after 5 years of follow-up.

Patients and methods: OPERA was a multicentre, phase III trial that included operable patients (pts), with cT2-cT3b low-mid rectal ADK, tumours <5 cm, cN0 or cN1 <8 mm. All pts received external beam radiotherapy (EBRT): 45 Gy in 25 fractions with concurrent capecitabine. Pts were randomly assigned (1:1) to receive a boost of EBRT in group A (9 Gy/5 fractions) or a boost with CXB (90 Gy/3 fractions) in group B. The primary end point was OP rate.

Results: Out of 148 patients randomised, 141 were eligible. Between week 14-24, a clinical complete (or near) response was observed in 44 pts in group A (64%) versus 66 in group B (92%); $P < 0.001$. The 3-year OP rate was 59% in group A versus 81% in group B ($P = 0.003$). After update the median follow-up was 61.1 months [56.8-64.5]. The 5-year local regrowth was 39% in group A and 17% in group B ($P = 0.1$). The difference in OP was still highly significant between both groups: A 56% versus B 79% ($P = 0.004$). The difference was more significant if tumours <3 cm, with an OP rate of 93% in group B compared to 54% in group A. Of the 28 local regrowths, 3 occurred after 3 years of follow-up. Rectal bleeding (grade 1-2), which was the most prevalent toxicity during follow-up, disappeared most of the time after three years. Bowel function was not worsened by the CXB boost.

Conclusion: The OPERA trial was the first trial to demonstrate that CXB dose escalation was increasing the OP rate with good bowel function at 3 years. At 5 years, these results are sustained, especially in small early-stage tumours. The occurrence of some local regrowth after 3 years necessitates close surveillance of these pts during the 5-year period.

Key words: organ preservation, rectal cancer, neoadjuvant treatment, contact X-ray brachytherapy, TME surgery, randomised trial

INTRODUCTION

Contact X-ray brachytherapy (CXB) is an endocavitary brachytherapy technique that allows for rapid and safe irradiation with high doses in direct contact with the rectal tumour, while preserving the healthy pelvic organs.[1-5]

Watch-and-Wait (W&W) strategies can preserve organs in rectal cancer patients who achieve a complete clinical response (cCR) after neoadjuvant therapy. To optimise the chances of achieving a cCR, the OPERA trial compared neoadjuvant chemoradiotherapy (NCRT) with dose escalation by CXB or external beam radiotherapy (EBRT).

The results, with a median follow-up of 3 years, showed a significant improvement in organ preservation rates with NCRT and CXB boost, especially for patients with tumours of less than 3 cm, compared to the EBRT boost.

Furthermore, for incomplete response after neoadjuvant treatments or local regrowth, salvage total mesorectal excision (TME) surgery can be performed safely and effectively.[6]

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As the risk of local regrowth is low but persists beyond three years in the W&W strategy,[7] longer follow-up was needed. Here, we report updated results of the OPERA trial, with a median follow-up of 5 years.

METHODS

Study design

OPERA was a multicentre, open-label, phase 3 randomised controlled trial done at 17 cancer centres with radiotherapy departments (ClinicalTrials.gov identifier: NCT02505750). Eligible patients were aged 18 years or older with biopsy proven adenocarcinoma with a cT2, cT3a, or T3b tumour up to 10 cm from anal verge, less than 5 cm in diameter, and less than half the rectal circumference. They also had cN0-cN1 disease (with lymph node <8 mm), no metastases, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and were fully operable. The detailed study design have previously been described.[8]

Patients were randomly assigned (1:1) to receive a boost with EBRT at 9 Gy in five fractions (group A) or a boost with CXB at 90 Gy in three fractions (group B). Stratification by trial centre, tumour classification (cT2 versus cT3a or cT3b), tumour distance from rectum (<6 cm from anal verge versus ≥ 6 cm), and tumour diameter (<3 cm versus ≥ 3 cm) was done.

The trial protocol was approved by an ethics committee and all patients provided written informed consent.

Procedures

The study design is shown in Figure 1.

All patients received chemoradiotherapy CAP45 consisting in external beam radiotherapy on gross tumour volume (GTV) and nodal pelvic fields (mesorectum, presacral, and internal iliac nodal) at a dose of 45 Gy in 25 fractions over 5 weeks and concurrent oral capecitabine (825 mg/m^2 twice a day).

In group A, the external beam radiotherapy boost consisted in 9 Gy in five fractions over 1 week on GTV + 2 cm without any interruption after neoadjuvant CAP45.

In group B, contact X-ray brachytherapy delivered 90 Gy in three fractions over 4 weeks by the Papillon 50 system (Ariane Medical Systems; Alfreton, UK). The timing of contact X-ray brachytherapy dose was stratified by tumour size: for patients with tumour diameter <3 cm, NCRT was initiated 1-2 weeks after the CXB boost was completed. For those with tumour diameter ≥ 3 cm, the CXB boost was initiated 2-3 weeks after NCRT was completed.

For patients with a cCR or near cCR (ncCR), a local excision was proposed, and for patients with partial response a radical proctectomy by TME was recommended.

After treatment completion, clinical, endoscopic and MRI evaluations were performed at week 14, 20 and 24. For patients with cCR or ncCR, W&W strategies was applied: digital rectal examination, endoscopy, and MRI every 3 months for 2 years and every 6 months from 3 years onwards.

Any surgery and local or distant relapse was reported. Toxicity and bowel function were measured at each visit.

Outcomes

The primary outcome was the 3-year organ preservation rate, without non-salvageable pelvic disease and without diversion stoma. We report updated results with a median follow-up of 5 years.

Complete and near complete clinical tumour response rate was a secondary outcome, defined as no visible tumour with a supple rectal wall, and superficial ulceration with smooth edges or firm rectal wall respectively. In a pragmatic *post-hoc* approach cCR and ncCR were pooled since in both situations a watch and wait strategy was performed.

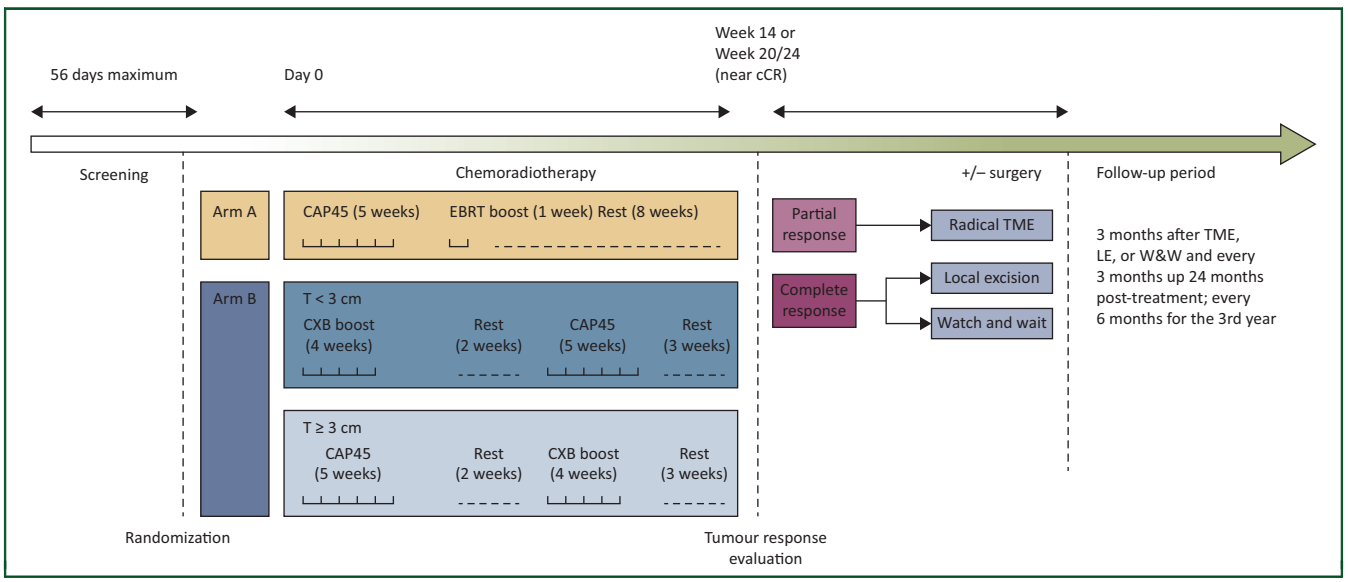

Figure 1. Trial design.
CAP45, capecitabine concurrent with external beam radiotherapy to a dose of 45 Gy; CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy; LE, local excision; TME, total mesorectal excision; W&W, watch and wait.

Overall survival (OS), disease-specific survival (DSS), bowel function assessed with the LARS score,[9] early (in the first year) and late treatment toxicities and quality of life were also secondary outcomes.

OS and DSS were both calculated from time of randomisation. Events for OS included death from any cause, while events for DSS included local regrowth, distant relapse, or death due to cancer.

Adverse events were measured using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and grade $\geq$2 were reported. Surgical toxicity was assessed according to the Clavien-Dindo classification.[10] Quality of life was analysed using the EORTC QLQ-C30 (Quality of life Questionnaire Core-30) and the colorectal cancer module (QLQ-CR29).

For patients undergoing total mesorectal excision, we analysed the rate of anterior resection preserving the sphincter and the tumour regression score on the pathological specimen. Analysis of distant metastases was done *post-hoc*. Local regrowth was a *post-hoc* outcome defined as any recurrence in the pelvis (rectal wall 'local regrowth', mesorectum, or pelvis) occurring after cCR or ncCR. A non-salvageable local regrowth was any regrowth which was not resectable.

Statistical analysis

Kaplan—Meier method was used to estimate time-to event outcomes and a stratified Cox proportional hazards model to estimate HRs with 95% CIs for analysis of the 5-year organ preservation rate. Patients without any events were censored at the date of last follow-up. All analyses were performed in a modified intention-to-treat population, excluding patients who withdrew consent. Statistical methods have been previously reported.[8]

RESULTS

Of the 148 patients randomly assigned between June 14, 2015, and June 26, 2020, 74 were assigned to EBRT boost (group A) and 74 on CXB boost (group B) and 141 patients were evaluable (69 in group A, 72 in group B). Baseline and tumour characteristics are summarised in Table 1, showing no significant difference between the 2 groups. These were mainly T2 lesions (group A: 64% versus group B: 65%), N0 status (group A: 71% versus group B: 76%), of the lower rectum (distance from anal margin $<$6 cm: group A: 77% versus group B: 74%). One hundred twenty-six (90%) of 141 patients received chemoradiotherapy according to protocol [58 (84%) in group A versus 68 (94%) pts in group B]. All patients (69) in group A and 93% of patients in group B (72 pts) received radiation boosts according to the protocol. Twenty-nine (42%) patients in group A had tumours $<$3 cm in diameter and 40 (58%) had tumours diameter $\geq$3 cm, and 32 (44%) and 40 (56%) in group B respectively. No patients were lost to follow-up (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.10.827).

Clinical and MRI responses at week 14 and up to week 24 were previously detailed in the initial article. As a reminder, 112 patients without total mesorectal excision integrated into a W&W strategy: 45 (65%) patients in group A achieved a complete or near complete clinical response, compared with 67 (93%) in group B ($P < 0.0001$). For patients with patients with tumours $<$3 cm in diameter, 23 (79%) of 29 patients in group A and 31 (97%) of 32 patients in group B had a cCR or ncCR ($P = 0.04$). Among patients with tumours $\geq$3 cm in diameter, 22 (55%) of 40 in group A and 36 (90%) of 40 in group B had a cCR or ncCR ($P < 0.001$).

With a median follow-up of 61.1 months [IQR (56.8-64.5)], the 5-year organ preservation rate was 56% [95% CI (49-72)] in group A versus 79% (70-89) in group B [HR 0.4, 95% CI (0.21-0.75); $P = 0.003$; Figure 2]. In patients with tumour diameter $<$3 cm, the organ preservation rate was 54% [95% CI (47-82)] in group A and 93% (85-100) in group B [HR 0.12, 95% CI (0.028-0.55); $P = 0.006$]. In patients with tumour diameter of 3 cm or more, the 5-year organ preservation was 57% [95% CI (44-75)] in group A and 67% (54-83) in group B [HR 0.61, 95% CI (0.29-1.3); $P = 0.17$].

The local regrowth rate at 5 years for patients in W&W strategy (112 patients, Figure 3) was 26% (28 local regrowth), 17% in group B and 39% in group A ($P = 0.1$). Of the 28 local regrowth, 25 (89%) involved the tumour bed (recurrence in the rectal wall) and 3 (11%) involved perirectal lymph nodes. For patients with tumours smaller than 3 cm (Figure 3), the local regrowth rate in group B was 3% versus 44% in group A [95% CI (0.006-0.38), $P = 0.003$]. For tumours with diameters of 3 cm or more (Figure 3), the local regrowth rate was 29% in group A and 31% in group B ($P = 0.9$). There was no significant difference in the rate of local regrowth between cCR or ncCR patients in arm A or arm B (41% versus 31% in group A, $P = 0.3$; 14% versus 19% in group B, $P = 0.7$). Of the 28 local regrowths, 3 occurred after 3 years' follow-up.

For the entire cohort of 141 patients, including patients who underwent TME within 24 weeks after NCRT for a partial/stable/progression clinical response, there were 32 local regrowth: local regrowth rate was 16% [95% CI (7-24)] in group B and 33% [95% CI (19-44)] in group A [95% CI (0.21-0.91), $P = 0.02$, Figure 3].

Management of local regrowth comprised total mesorectal excision in 15 out of 28 (68%) cases, local excision in 7 cases of which 3 required a subsequent total mesorectal excision. Six patients refused a local procedure or opted for supportive care instead. A diversion stoma was performed in one (5%) patient. Four patients who had undergone early TME for initial incomplete response, experienced local recurrence: 3 were treated with local excision followed by TME, while 1 refused surgery and received supportive care instead.

OS was 91% [95% CI (87-96)], without significant difference between group A (91%) and group B (92%, $P = 0.5$, Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.10.827). Twelve deaths were reported (7 in group A and 5 in group B), 9 of them cancer-related.

Five-year DSS for W&W patients (112 patients) in a *post-hoc* analysis was 66% [95% CI (57-76)] and varied between

Table 1. Baseline demographic and clinical characteristics in the modified intention-to-treat population

	Total		Tumours <3 cm in diameter		Tumours ≥3 cm in diameter	
	Group A (n = 69)	Group B (n = 72)	Group A (n = 29)	Group B (n = 32)	Group A (n = 40)	Group B (n = 40)
Age, years	69 (61-74)	70 (60-74)	69 (66-79)	68 (57-71)	69 (61-75)	70 (62-76)
Sex						
Male	45 (65%)	42 (58%)	18 (62%)	18 (56%)	27 (68%)	24 (60%)
Female	24 (35%)	30 (42%)	11 (38%)	14 (44%)	13 (32%)	16 (40%)
ECOG performance status						
0	51 (74%)	55 (76%)	24 (83%)	24 (75%)	27 (68%)	31 (77%)
1	10 (14%)	12 (17%)	3 (10%)	5 (16%)	7 (17%)	7 (17%)
2	0	1 (1%)	0	0	0	1 (3%)
Unknown	8 (12%)	4 (6%)	2 (7%)	3 (9%)	6 (15%)	1 (3%)
Tumour differentiation						
Well	21 (30%)	29 (40%)	7 (24%)	13 (41%)	14 (35%)	16 (40%)
Moderately	34 (49%)	30 (42%)	15 (52%)	15 (47%)	19 (48%)	15 (38%)
Poorly	0	1 (1%)	0	1 (3%)	0	0
Unknown	14 (20%)	12 (17%)	7 (24%)	3 (9%)	7 (17%)	9 (22%)
T status						
cT2	44 (64%)	47 (65%)	24 (83%)	29 (91%)	20 (50%)	18 (45%)
cT3a or T3b	25 (36%)	25 (35%)	5 (17%)	3 (9%)	20 (50%)	22 (55%)
Unknown	0	0	0	0	0	0
Clinical N status						
cN0	49 (71%)	55 (76%)	24 (83%)	26 (81%)	25 (63%)	29 (73%)
cN1	19 (28%)	17 (24%)	4 (14%)	6 (19%)	15 (37%)	11 (27%)
Unknown	1 (1%)	0	1 (3%)	0	0	0
Distance from anal verge						
<6 cm	53 (77%)	53 (74%)	21 (72%)	27 (84%)	32 (80%)	26 (65%)
≥6 cm	16 (23%)	19 (26%)	8 (28%)	5 (16%)	8 (20%)	14 (35%)
Unknown	0	0	0	0	0	0
Tumour diameter						
<3 cm	29 (42%)	32 (44%)	29 (100%)	32 (100%)	0	0
≥3 cm	40 (58%)	40 (56%)	0	0	40 (100%)	40 (100%)
Unknown	0	0	0	0	0	0
Carcinoembryonic antigen (ng/ml)						
<2.5	38 (55%)	33 (46%)	20 (69%)	14 (44%)	18 (45%)	19 (48%)
≥2.5	23 (33%)	31 (43%)	6 (21%)	12 (38%)	17 (43%)	19 (48%)
Unknown	8 (12%)	8 (11%)	3 (10%)	6 (19%)	5 (12%)	2 (5%)

ECOG, Eastern Cooperative Oncology Group.

groups [53% in group A 95% CI (40-71), and 75% in group B (65-86), P = 0.04, Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.10.827]. For the entire cohort (141 patients), 5-year DSS was 60% [46% in group A, 95% CI (34-61), and 73% in group B, 95% CI (63-85), P = 0.003, Supplementary Figure S3, available at

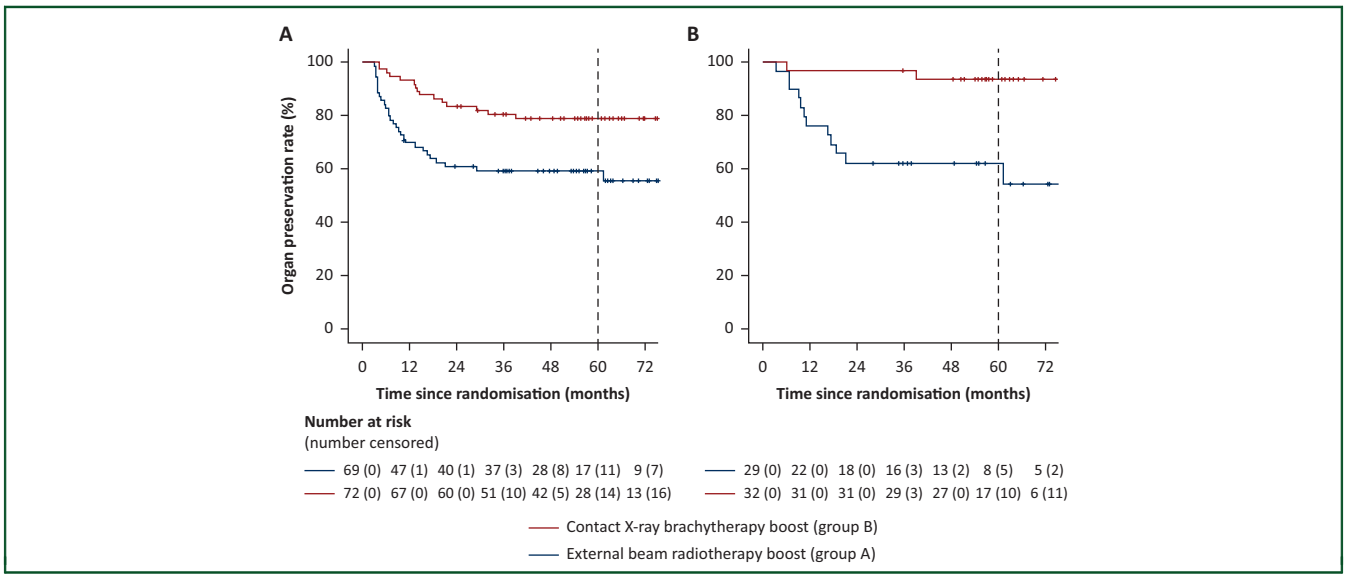

Figure 2. 5-year organ preservation rate. (A) All patients (n = 141). (B) Patients with tumours smaller than 3 cm (n = 61).

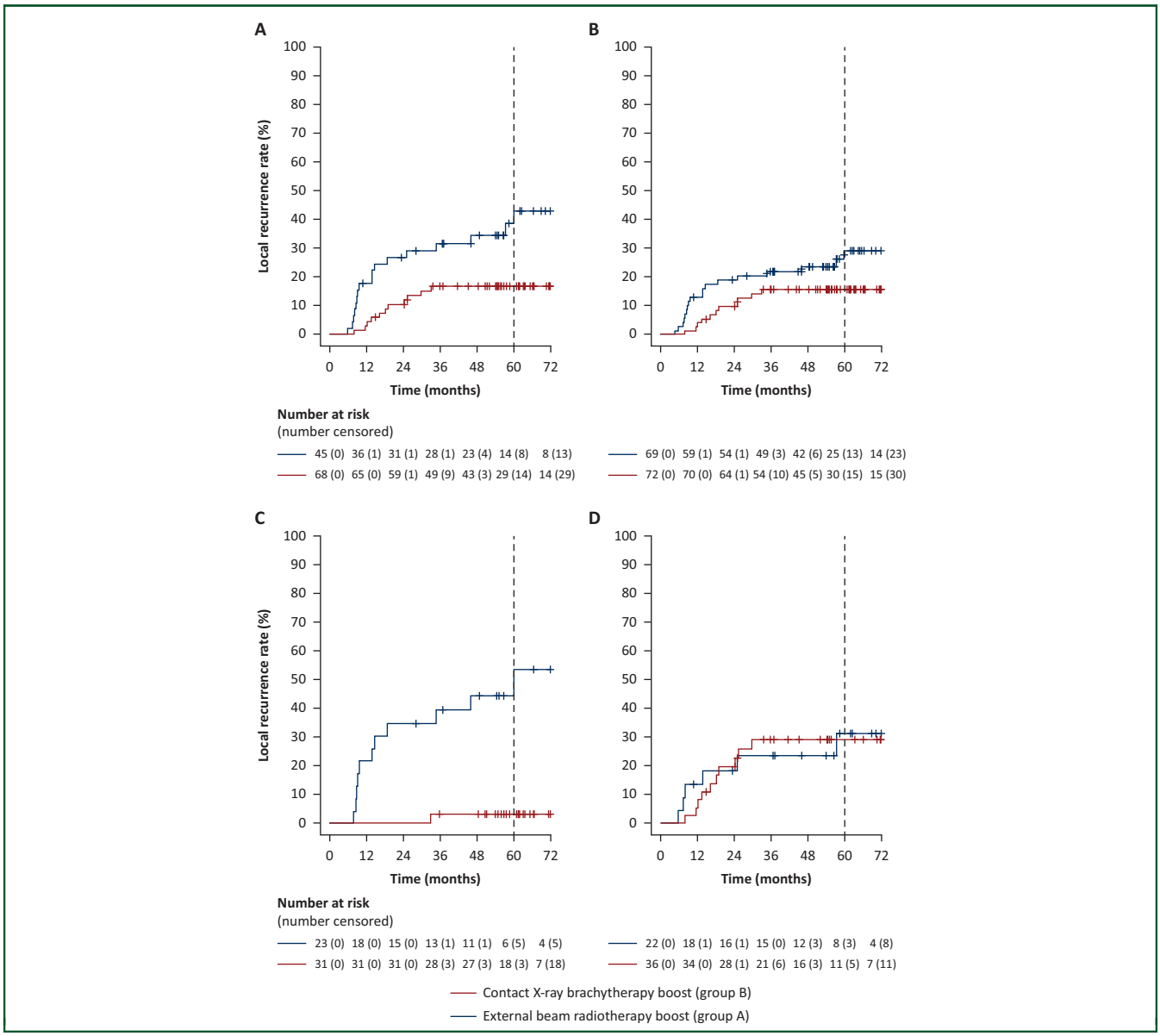

Figure 3. 5-year local recurrence rate. (A) Patients under Watch and Wait strategy ($n = 112$). (B) All patients ($n = 141$). (C) Patients with tumours smaller than 3 cm ($n = 54/112$). (D) Patients with tumours 3 cm or greater ($n = 59/112$).

https://doi.org/10.1016/j.annonc.2024.10.827]. There was no significant difference in the rate of DSS between cCR or ncCR patients in arm A or arm B (56% versus 53% in group A, $P = 0.5$; 78% versus 69% in group B, $P = 0.5$).

Twenty patients developed distant metastasis, located in the liver ($n = 5$), lung ($n = 8$), liver and lung ($n = 1$), bone ($n = 3$), and abdominal lymph node ($n = 3$). The 5-year cumulative rate of distant metastasis was 14% [95% CI (7-19)], with no difference between the two groups (14% in group A and 13% in group B, Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.10.827).

Local excision was performed in 28/141 patients [20 in group A and 8 in group B, 95% CI (0.13-0.63), $P = 0.001$, Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2024.10.827], mainly within 2 years of treatment. Final pathology found no residual cancer (ypT0) in 10 (37%) of 27 patients with no difference between the 2 groups.

Forty-two (42/141) patients underwent TME [27 (39%) of 69 patients in group A and 15 (21%) of 72 patients in group B, IC95% (0.22-0.78), $P = 0.006$], mainly during the first 2 years after treatment (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2024.10.827). Among patients with tumours diameter <3 cm, 10 patients in group A and 2 patients in group B underwent TME ($P = 0.008$); for tumours diameter ≥ 3 cm, 17 in group A and 13 in group B underwent total mesorectal excision ($P = 0.19$).

Among patients who underwent TME, 18 (43%) had an abdomino-perineal excision, 23 (55%) an anterior resection

and one (2%) a Hartmann resection. They were mostly performed laparoscopically [26 (62%)].

Histopathology of TME resection did not differ between group A and group B: with no evidence of invasive malignancy (ypT0-is) in 10 patients (7 in group A, 3 in group B), ypT1−3 in 31 patients (20 in group A, 11 in group B), and ypT4 in one patient in group A. Lymph node involvement was found in 8 patients (ypN1; 3 in group A, 5 in group B). Twenty-three patients (88%) of 26 in group A and 11 (85%) of 13 in group B had an R0 resection. Involved resection margin (R1) was seen in four patients (2 in both groups), and there were no patients with R2 resection margin.

In the *post-hoc* univariate Cox regression analysis of factors that might predict 5-year organ preservation (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.10.827), tumour diameter <3 cm was significantly associated with organ preservation rate improvement ($P = 0.04$), confirmed in multivariate analysis ($P = 0.04$). There were no significant differences (log rank test) for cT stage (2 versus 3a or 3b), age, sex, differentiation (moderately versus well), ECOG performance status (0 versus 1 or 2), cN stage (N0 versus N1), distance from anal verge (<6 cm versus ≥6 cm), carcinoembryogenic antigen (<2.5 ng/ml versus ≥2.5 ng/ml), EBRT technique (three dimensional conformal versus intensity modulated radiotherapy), number of radiotherapy interruption days (no interruption versus 3 consecutive days) and contact position (knee-chest versus lithotomy).

Bowel function was evaluated in 86 patients who had not undergone TME and had at least 1 year of follow-up. The LARS score was 30 or more in 8 (24%) of 34 in group A and 9 (17%) of 52 in group B ($P = 0.5$).

Forty-four CTCAE grade 2-3 early or late adverse events occurred without significative difference ($P = 0.7$) between the 2 groups (Table 2). The most common were proctitis [4 (6%) in group A and 9 (13%) in group B] and radiation dermatitis [6 (9%) in group A and 1 (1%) in group B]. No patients underwent grade 4-5 adverse events. The main late side effect was rectal bleeding (CTCAE grade 1 or 2): 12/69 pts (17%) in group A and 46/12 pts (64%) in group B. All rectal blood spotting occurred within the first 3 years and generally disappeared thereafter. Indeed, only 2 patients in group A and 9 in group B experienced rectal blood spotting after 3 years. Of the 99 patients who did not undergo TME and had at least 1 year of follow-up, rectal bleeding affected 63% (36/57) of the patients in group B and 12% (5/42) in group A ($P < 0.001$). In 6 patients, minor cauterisation was required, resulting in grade 2 toxicity (Table 2).

Postoperative toxicities if local excision or TME were previously published.[6] Clavien-Dindo IIIb complications occurred in with 4/26 (15%) in group A and 2/13 (15%) in group B. In group A reoperation occurred to excise the anastomosis for an anastomotic leak, and for 2 cases because of intrabdominal collections. In group B second surgery was performed because of adhesional bowel obstruction, and in another patient for removal of a cystic ovarian mass. Hospitalization for Clavien-Dindo II complication were reported in one patient in group A (urinary sepsis), and three patients in Arm B (shingles, sepsis, and vaginal perforation).

Quality of life data is not yet mature.

DISCUSSION

The present study provides 5-year results from the phase III OPERA trial. It demonstrated that, in the management of early rectal cancer, increasing the dose of the boost from 9 Gy to 90 Gy (8.8 Gy versus 300 Gy EQ2D, with an α/β of 10 Gy) significantly increased the organ preservation rate (79% versus 56%). The efficacy was particularly high in tumours <3 cm, with a 5-year preservation rate of 93%.

Due to a very sharp dose fall-off, the CXB endocavitary technique can deliver a high dose to the rectal tumour while preserving adjacent organs. Despite the dramatic increase in the dose to the tumour, healthy tissues were well preserved, as bowel function was maintained and the rate of grade ≥2 toxicity did not differ from that in EBRT. Late side effects consisted of grade 1-2 rectal blood spotting, which generally disappeared after 3 years. There were some postoperative toxicities associated with the need for further surgery (TME or local excision), with similar rates of Clavien-Dindo complications between the two treatment arms, as previously published.[6] Quality of life data is not yet mature.

Local control was significantly better with CXB, showing significantly less tumour regrowth than the control arm (16% versus 33%). Local regrowth was a rare event after 3 years, with almost no occurrences in the CXB arm, while it increased steadily in the control arm. Notably, when considering a patient for an organ preservation strategy, local regrowth/relapse/recurrence cannot be regarded as a tumour recurrence, as it is compensated by TME. It can only be considered an event if the tumour is unresectable or if surgery shows a positive (R1) margin.

Several trials have also tested the organ preservation strategy in early low/mid rectal cancers. The W&W2 phase II trial escalated the radiotherapy dose to 62 Gy using external techniques and reported a 61% organ preservation rate at 2 years. The randomised phase III GRECCAR 12 trial escalated chemotherapy by adding four cycles of Folfirinox (fluorouracil, leucovorin, irinotecan, and oxaliplatin) before CAP50, leading to an organ preservation rate of 71.7% at 2 years. These results appear similar to those of the OPERA trial, though they may be numerically lower, and no strict comparison can be made.

The randomised phase II OPRA trial demonstrated a 54% TME-free survival rate at 5 years with a dose of 56 Gy (2.24 Gy per fraction) and concurrent 5-fluorouracil (5-FU), followed by consolidation chemotherapy with 5-FU and oxaliplatin. However, this study included a higher proportion of T4 (11%), T3 (76%), and N+ (72%) patients, making comparisons with the OPERA trial challenging.

Table 2. Early and late adverse events

	Group A ($n = 69$)				Group B ($n = 72$)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Blood disorders	0	0	0	0	1 (1%)	2 (3%)	0	0
Neutropenia	0	0	0	0	0	1 (1%)	0	0
Lymphopenia	0	0	0	0	0	1 (1%)	0	0
Venous thromboembolism	0	0	0	0	1 (1%)	0	0	0
Gastrointestinal	3 (4%)	1 (1%)	0	0	9 (13%)	4 (6%)	0	0
Proctitis	3 (4%)	1 (1%)	0	0	7 (10%)	2 (3%)	0	0
Diarrhoea	0	0	0	0	2 (3%)	2 (3%)	0	0
General disorders and administration site conditions	0	1 (1%)	0	0	4 (6%)	0	0	0
Asthenia	0	0	0	0	2 (3%)	0	0	0
Coronary artery spasms	0	1 (1%)	0	0	0	0	0	0
Anorexia	0	0	0	0	1 (1%)	0	0	0
Erectile dysfunction	0	0	0	0	1 (1%)	0	0	0
Renal and urinary disorders	2 (3%)	3 (4%)	0	0	1 (1%)	0	0	0
Urinary infection	0	2 (3%)	0	0	0	0	0	0
Dysuria	2 (3%)	1 (1%)	0	0	1 (1%)	0	0	0
Skin disorders	6 (9%)	0	0	0	1 (1%)	0	0	0
Radiation dermatitis	6 (9%)	0	0	0	1 (1%)	0	0	0
Other	4 (6%)	0	0	0	7 (10%)	0	0	0
Rectal bleeding	1 (1%)	0	0	0	5 (7%)	0	0	0
Chest pain	0	0	0	0	2 (3%)	0	0	0
Oral candidiasis	0	0	0	0	0	0	0	0
Palmar-plantar erythrodysesthesia	0	0	0	0	0	0	0	0

The highest-grade adverse event for each patient is reported.

The local recurrence rate in the OPERA trial compared favourably with those of the international Watch-and-Wait database (17% versus 25% at 2 years in the Watch-and-Wait database).[11]

Numerous ongoing and future trials are investigating new strategies for organ preservation in early rectal cancer. Some are escalating the chemotherapy regimen: the US JANUS phase 2 randomised trial (NCT05610163) is comparing consolidation chemotherapy with FOLFOX/CAPOX versus FOLFIRINOX after long-course chemoradiotherapy. The South American CCHOWW randomised trial (NCT05000697) is conducting a similar comparison, evaluating capecitabine versus FOLFOX/XELOX for consolidation. The ACO/ARO/AIO 18.1 phase III trial (NCT04246684) is comparing long-course chemoradiotherapy with short-course radiotherapy followed by consolidation chemotherapy (FOLFOX or CAPOX).

Other trials are testing the effect of external radiotherapy dose escalation on organ preservation rates: the British APHRODITE trial (ISRCTN16158514) and the Danish WW3 trial (NCT04095299) are comparing a total dose of 50.4 Gy (1.8 Gy per session) with 62 Gy using a simultaneous integrated boost.

Additionally, some trials are escalating the radiation dose with an endorectal boost, similar to the OPERA trial. The MORPHEUS trial (NCT03051464) is a Canadian study that uses iridium high-dose rate endocavitary brachytherapy.

Finally, the STAR-TREC trial (NCT02945566) is randomizing the optimal strategy to use local excision: TME alone versus short course radiotherapy (25 Gy/5) versus long course radiotherapy (CAP50) and then local excision. The OPAXX trial (NCT05772923) is also exploring the best approach for local excision by including patients who achieve a near-complete response after any prior radiotherapy regimen, randomizing between immediate CXB boost and extending the waiting period.

Notably, the organ preservation rate was not improved by the CXB boost in tumours $\geq$3 cm in the OPERA trial. Our results also did not suggest any improvement with increased statistical power. Additional treatments, such as chemotherapy, might be needed to enhance tumour response. One explanation could be that the thickness of large tumours is not entirely irradiated due to the sharp dose fall-off. However, because tumour thickness decreases rapidly from one session to another, the entire thickness may ultimately be irradiated. Large tumours may also exhibit additional radioresistance factors due to genetic mutations. Slipsager et al. recently reviewed predictive biomarkers of radioresistance in rectal cancer and identified factors such as the overexpression of HMGCS2, a protein involved in ketogenesis, and COASY, a protein involved in the PI3 kinase pathway.[12] If these factors are overexpressed, further treatment escalation could be proposed to enable organ preservation or immediate TME in early rectal cancer, thereby avoiding unnecessary neoadjuvant treatment.

To enable organ preservation for more advanced tumours, we may need not only radiation dose escalation but also chemotherapy escalation. To test this hypothesis in intermediate low/mid rectal cancers, the phase III TRESOR trial is currently underway and open for inclusion. This trial is administering neoadjuvant chemotherapy with FOLFIRINOX, external beam radiotherapy, and concomitant chemotherapy (CAP50), with or without a CXB boost. A feasibility study including 14 patients has already demonstrated promising results, with no grade 4-5 toxicities and

an 85% organ preservation rate at a mean follow-up of 17.8 months.[13]

Considering the risk of distant metastases, using propensity scores, we also previously observed no significant difference in cancer-specific survival between the OPERA trial and similar patients from the phase III ACCORD12 trial[14] which has tested the addition of oxaliplatin to neoadjuvant CAP50 and proctectomy.[15] Consequently, regarding the metastatic risk, not performing TME in patients treated with organ preservation after CXB seems safe.

We will provide an update of the OPERA trial at 10 years, considering data from the Lyon R96-02 phase III trial,[2] which showed a colostomy-free survival rate of 83% at 10 years for patients with an initial complete clinical response in T2-T3 lower rectal tumours treated with a combination of CXB boost and EBRT.

Watch-and-wait strategy is a hot topic, with several promising therapeutic strategies being explored. The 5-year results of the OPERA trial are encouraging and position the CXB boost as one of the treatment options of choice for achieving organ preservation in tumours <3 cm. Thus contact X-ray brachytherapy boost has been included in the therapeutic options in the French recommendations for the management of rectal tumours under 3 cm diameter.[16]

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DISCLOSURE

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