Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial

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Summary

Background Organ preservation after reaching clinical complete response on neoadjuvant therapy is gaining interest for rectal cancers, although the role of radiation dose escalation is still not known. We aimed to determine whether a contact x-ray brachytherapy boost, following or preceding neoadjuvant chemoradiotherapy, increases the probability of 3-year organ preservation for patients with early rectal cancers.

Methods OPERA was a multicentre, open-label, phase 3 randomised controlled trial done at 17 cancer centres that included operable patients, aged 18 years or older, with cT2, cT3a, or cT3b adenocarcinoma of low-mid rectum, tumours of less than 5 cm in diameter, and cN0 or cN1 smaller than 8 mm. All patients received neoadjuvant chemoradiotherapy and 45 Gy external beam radiotherapy in 25 fractions over 5 weeks with concurrent oral capecitabine (825 mg/m² twice a day). Patients were randomly assigned (1:1) to receive a boost of external beam radiotherapy at 9 Gy in five fractions (group A) or a boost with contact x-ray brachytherapy (90 Gy in three fractions; group B). Randomisation was done centrally using an independent web-based system and stratified by trial centre, tumour classification (cT2 *vs* cT3a or cT3b), tumour distance from rectum (<6 cm from anal verge *vs* ≥6 cm), and tumour diameter (<3 cm *vs* ≥3 cm). Treatment in group B was stratified by tumour diameter, with the contact x-ray brachytherapy boost given before neoadjuvant chemoradiotherapy in patients with tumours smaller than 3 cm. The primary outcome was organ preservation at 3 years, analysed in the modified intention-to-treat population. This study was registered with ClinicalTrials.gov, NCT02505750, and is ongoing.

Findings Between June 14, 2015, and June 26, 2020, 148 patients were assessed for eligibility and were randomly assigned to group A (n=74) or group B (n=74). Seven patients withdrew their consent (five in group A and two in group B). 141 patients were included in the primary efficacy analysis, including 69 assigned to group A (29 with tumours <3 cm in diameter and 40 with tumours ≥3 cm) and 72 assigned to group B (32 with tumours <3 cm and 40 with tumours ≥3 cm). After a median follow-up of 38·2 months (IQR 34·2–42·5), the 3-year organ preservation rate was 59% (95% CI 48–72) in group A versus 81% (72–91) in group B (hazard ratio [HR] 0·36, 95% CI 0·19–0·70; p=0·0026). For patients with tumours less than 3 cm in diameter, 3-year organ preservation rates were 63% (95% CI 47–84) in group A versus 97% (91–100) in group B (HR 0·07, 95% CI 0·01–0·57; p=0·012). For patients with tumours of 3 cm or larger, 3-year organ preservation rates were 55% (95% CI 41–74) in group A versus 68% (54–85) in group B (HR 0·54, 95% CI 0·26–1·10; p=0·11). 21 (30%) patients in group A and 30 (42%) in group B had an early grade 2–3 adverse event (p=1·0). The most common early grade 2–3 adverse events were proctitis (four [6%] in group A, nine [13%] in group B) and radiation dermatitis (seven [10%] in group A, two [3%] in group B). The main late side-effect was grade 1–2 rectal bleeding due to telangiectasia, which was more frequent in group B (37 [63%] of 59) than in group A (five [12%] of 43; p<0·0001) and subsided after 3 years.

Interpretation Neoadjuvant chemoradiotherapy with a contact x-ray brachytherapy boost significantly improved the 3-year organ preservation rate, particularly for patients with tumours smaller than 3 cm who were treated with contact x-ray brachytherapy first, compared with neoadjuvant chemoradiotherapy with a boost via external beam radiotherapy. This approach could be discussed and offered to operable patients with early cT2–cT3 disease who are keen to avoid surgery and seek organ preservation.

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Research in context

Evidence before study

In most recent series of patients with early or mostly locally advanced rectal cancer with neoadjuvant regimens, the 3-year rate of organ preservation is usually between 30 and 60%, depending on the tumour stage and duration of interval after radiotherapy. No robust prospective trial has ever demonstrated that increasing the radiation dose was able to increase the organ preservation rate without excessive toxicity and maintenance of a good bowel function. Organ preservation remains in most institutions an opportunistic strategy with a significant risk of local failure above 20%, possibly detrimental to overall survival. Salvage radical surgery after such high radiation doses might be associated with an excessive rate of severe toxicity which needs to be explored.

Added value of this study

This is the first randomised controlled trial to show that neoadjuvant chemoradiotherapy with a radiation dose escalation using intracavitary contact x-ray brachytherapy (boost dose of 90 Gy in three fractions) significantly increases the 3-year organ preservation rate compared with a boost via external beam radiotherapy, without excessive toxicity and with good bowel function. In a stratified subgroup of tumours of less than 3 cm in diameter, for whom using contact x-ray brachytherapy was given first before chemoradiotherapy, organ preservation might be expected in around 90% of cases.

Implications of all the available evidence

The findings of this trial suggest that in selected, well informed patients with cT2–cT3a/b tumours in the distal-middle rectum, and of less than 5 cm in diameter with negative nodes (cN0) or cN1 with lymph nodes less than 8 cm in diameter, a treatment approach to achieve organ preservation using neoadjuvant chemoradiotherapy and a contact x-ray brachytherapy boost should be discussed as a valid option within the multidisciplinary team. Greater availability of contact x-ray brachytherapy machines and training of radiation oncologists in their use is mandatory to be able to adopt and expand this approach.

Introduction

The standard of care for rectal cT2–cT3 adenocarcinoma is radical proctectomy by total mesorectal excision,[1–3] sometimes preceded by neoadjuvant chemoradiotherapy,[4] external beam radiotherapy, or total neoadjuvant treatment. To enhance quality of life, interest in organ preservation is growing, with a watch and wait approach after neoadjuvant chemoradiotherapy in cases of clinical complete response (cCR) to neoadjuvant treatment.[5–8] An alternative for organ preservation uses contact x-ray brachytherapy, delivering a higher radiation dose through an endocavitary approach.[9] The Lyon R 96-02 randomised controlled trial[10,11] in cT2–cT3 disease showed that external beam radiotherapy with a contact x-ray brachytherapy boost increased the rate of cCR and of sphincter-saving surgery, with some patients achieving long term-organ preservation. Published data show that neoadjuvant chemoradiotherapy with a contact x-ray brachytherapy boost for early cT2–cT3 disease can result in a cCR rate of up to 80%,[13–15] especially for tumours of 3 cm in diameter or smaller when treated first with contact x-ray brachytherapy.[16] We therefore aimed to test the hypothesis that adding a contact x-ray brachytherapy boost to neoadjuvant chemoradiotherapy regimens would increase the proportion of patients achieving organ preservation.

Methods

Study design and participants

OPERA was a multicentre, open-label, phase 3 randomised controlled trial done at 17 cancer centres with radiotherapy departments. Eight of these centres were using contact x-ray brachytherapy (four in the UK, three in France, and one in Switzerland; appendix pp 51–55). 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 ECOG performance status of 0 or 1 and were fully operable. Patients with cT1, cT3c, or cN2 disease, extramural vascular invasion, poorly differentiated tumour, previous pelvic irradiation, or co-morbidity preventing chemotherapy administration were excluded. All patients provided written informed consent.

This trial was sponsored by Centre Antoine Lacassagne. An independent data monitoring committee reviewed trial data (appendix p 46). A central review of MRI was established for equivocal MRI interpretation. The Lacassagne research department collected and analysed the data. The trial protocol was approved by an ethics committee (Comité de Protection des Personnes Sud Méditerranée V; appendix pp 56–57).

Randomisation and masking

Patients were randomly assigned (1:1) to receive a boost with external beam radiotherapy at 9 Gy in five fractions (group A) or a boost with contact x-ray brachytherapy at 90 Gy in three fractions (group B). Randomisation was done centrally using an independent web-based system (CS Online 7.5.501) and stratified by trial centre, tumour classification (cT2 *vs* cT3a or cT3b), tumour distance from rectum (<6 cm from anal verge *vs* ≥6 cm), and tumour diameter (<3 cm *vs* ≥3 cm). We used the Pocock and Simon method of minimisation by comparing each new patient to the previously randomly assigned patients on the basis of three strata: tumour size, tumour diameter by MRI, and distance from anal verge. We used

See Online for appendix

CS Online version 7.5.501 to automatically allocate the treatment scheme that was the least allocated on the basis of these parameters. Investigators and patients were not masked to randomisation allocation.

Procedures

At baseline all the patients received digital rectal examination, colonoscopy, MRI with or without endorectal ultrasound, and CT of the chest, abdomen, and pelvis. Before randomisation and stratification, tumour size was measured using digital rectal examination, endoscopy, and MRI. The study design is shown in figure 1.

All patients received external beam radiotherapy using CT scan planning; the clinical target volume included gross visible tumour, mesorectum, presacral, and internal iliac nodal structures. The S2 or S3 interspace was the clinical target volume upper limit. Radiotherapy was delivered either as 3D conformal radiotherapy or intensity modulated radiotherapy with photon beam of 6 mV or more and image guidance at a dose of 45 Gy in 25 fractions over 5 weeks. Concurrent chemotherapy was given to all patients and consisted of oral capecitabine (825 mg/m² twice a day) over 5 weeks from the first day patients received their radiotherapy. In group A, the external beam radiotherapy boost was given using 3D conformal or intensity modulated radiotherapy without any interruption after neoadjuvant chemoradiotherapy. The target was the initial gross tumour volume with a margin of 2 cm. The dose was 9 Gy in five fractions over 1 week.

In group B, contact x-ray brachytherapy was delivered by the Papillon 50 system (Ariane Medical Systems; Alfreton, UK). Delivery of contact x-ray brachytherapy boost differed for those with tumours of less than 3 cm diameter and those with tumours of 3 cm or greater diameter. The timing of contact x-ray brachytherapy dose was stratified by tumour size: contact x-ray brachytherapy boost was given before neoadjuvant chemoradiotherapy in patients with tumours less than 3 cm in diameter or after neoadjuvant chemoradiotherapy for patients with tumours 3 cm in diameter or more. This difference in approach was adopted on the basis of 50 years of experience with contact x-ray brachytherapy in France, where 80% of patients with early tumours of less than 3 cm in diameter achieved cCR and long-term local control with moderate toxicity and acceptable bowel function when contact x-ray brachytherapy is given first.[9,13] For tumours less than 3 cm in diameter, giving contact x-ray brachytherapy allows tumour targeting under the naked eye. It is more difficult to accurately target the tumour after delivery of chemoradiation first if a near cCR is achieved and there is an inflammatory mucosal reaction and some underlying fibrosis.

The dose was prescribed and reported at the surface of the rectal applicator. The dose was 30 Gy per fraction. Total dose was 90 Gy in three fractions over 4 weeks. For patients with tumours of less than 3 cm diameter in group B, neoadjuvant chemoradiotherapy was initiated 1–2 weeks after the contact x-ray brachytherapy boost was completed. For those with tumours of 3 cm or larger in diameter, the contact x-ray brachytherapy boost was initiated 2–3 weeks after neoadjuvant chemoradiotherapy was completed. A quality control was set up to ensure good protocol compliance for radiotherapy techniques according to radiotherapy guidelines (appendix pp 75–84).

Radical proctectomy by total mesorectal excision was recommended for patients who had a partial response to

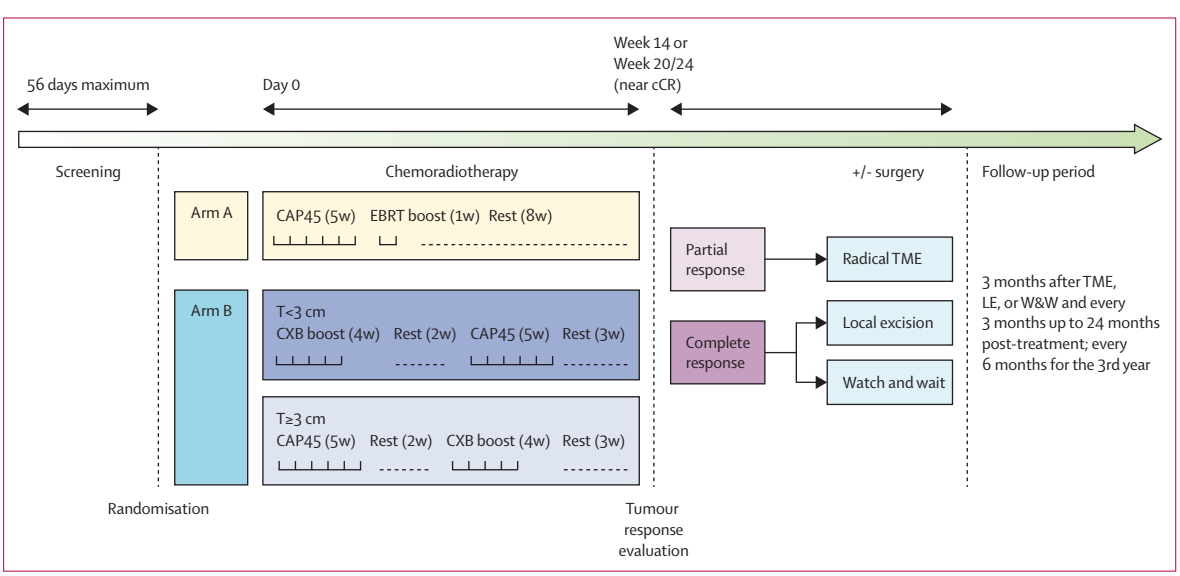

Figure 1: **Trial design**

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.

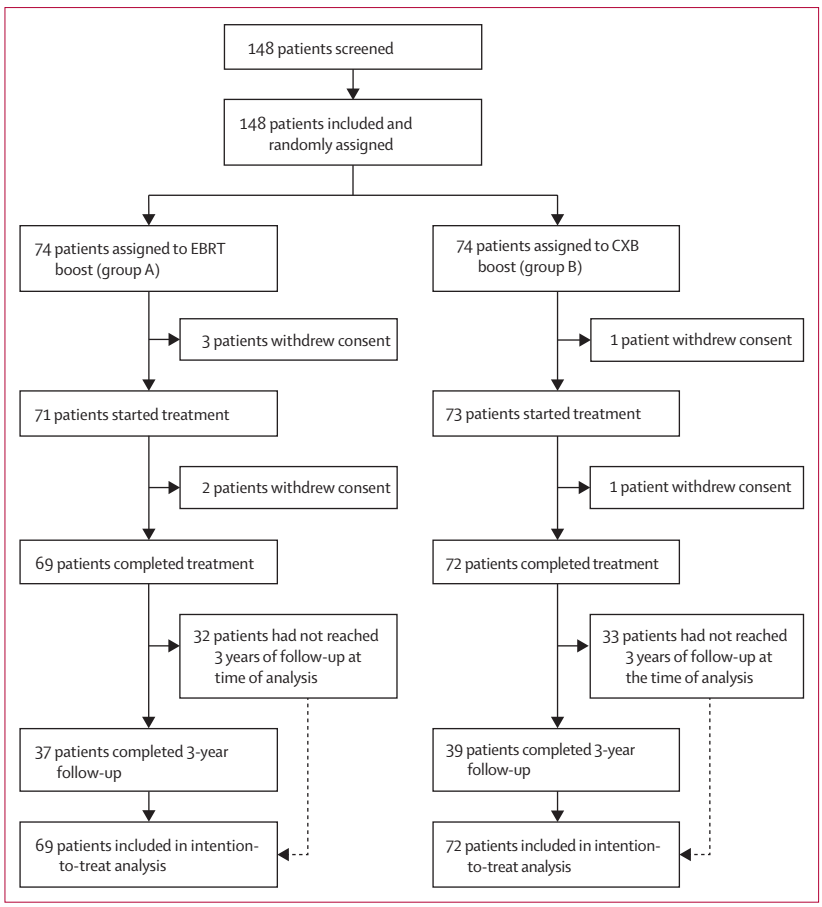

***Figure 2*: Study profile**
CXB=contact x-ray brachytherapy. EBRT=external beam radiotherapy.

study treatment. For patients with a cCR or near cCR (ncCR), a local excision was possible with optional radical proctectomy in case of poor pathological findings. Diversion stoma was possible for palliation. Adjuvant chemotherapy was not recommended and left to institution decision.

During contact x-ray brachytherapy, at each session, the radiation oncologist performed a digital rectal examination and rigid rectoscopy to assess tumour response and treatment tolerance. On week 14, after all treatments were completed, a tumour response was evaluated using digital rectal examination, rigid recto-scopy, or flexible recto-sigmoidoscopy and MRI. The same examinations done on week 20 or 24, depending on the results of the previous clinical assessment. At this time (week 24), patients' overall best responses were determined. If patients reached cCR or ncCR, they were followed with 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. Data were collected by research technicians and monitored by monitoring assistants in each participating cancer centre. Data were collected using electronic case report forms and sent immediately to the data manager in Centre Antoine Lacassagne. Data were exported to the statistician at database lock.

Outcomes

The primary outcome was the 3-year organ preservation rate, without non-salvageable pelvic disease and without diversion stoma. Clinical tumour response evaluated according to RECIST 1.1[17] was a secondary outcome. cCR was defined as no visible tumour with a supple rectal wall. A ncCR was reported in case of superficial ulceration with smooth edges or firm rectal wall. In a pragmatic post-hoc approach cCR and ncCR were pooled together because in both situations a watch and wait strategy was chosen. In case of visible, palpable hard tumour or deep ulceration with irregular edges a partial response (PR) or stable disease (SD) was reported. Response as assessed by MRI was classified using the TRG 1–2 (good) versus TRG 3–5 (poor) scoring.[18] In case of an equivocal response at week 14 a new evaluation was performed at week 20 by digital rectal examination and DRE and endoscopy. If the evaluation remained uncertain a third assessment was performed at week 24 with digital rectal examination, endoscopy, and a second MRI.

Overall survival and disease-free survival, both calculated from time of randomisation, were also secondary outcomes, as was bowel function assessed with the LARS score[19] for patients without radical proctectomy (with a complementary assessment for radiation-induced rectal bleeding; appendix p 28).

Early and late treatment toxicities were also secondary endpoints. Adverse events were measured using the Common Terminology Criteria for Adverse Events version 4.03. All grade 2 and higher adverse events from random assignment until the end of the study were reported. Early toxicity was defined as event occurring during the first year after treatment initiation. Surgical toxicity was assessed according to the Clavien-Dindo classification.[20] Quality of life, another secondary endpoint, 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 considering ypT0 as as a favourable score.

Analysis of distant metastases was done post-hoc. Local recurrence was a post-hoc outcome defined as any recurrence in the pelvis occurring after cCR or ncCR. It could be located in the rectal wall ("local regrowth"), in the mesorectum, or in the pelvis. A non-salvageable local recurrence was any recurrence which was not resectable. We had not defined events for disease-free survival in our original protocol, thus we defined disease-free survival post-hoc in accordance with Garcia Aguilar and

	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%)
Moderate	34 (49%)	30 (42%)	15 (52%)	15 (47%)	19 (48%)	15 (38%)
Poor	0	1 (1%)	0	1 (3%)	0	0
Unknown	14 (20%)	12 (17%)	7 (24%)	3 (9%)	7 (17%)	9 (22%)
T status						
T2	44 (64%)	47 (65%)	24 (83%)	29 (91%)	20 (50%)	18 (45%)
T3a or T3b	25 (36%)	25 (35%)	5 (17%)	3 (9%)	20 (50%)	22 (55%)
Unknown	0	0	0	0	0	0
N status						
N0	49 (71%)	55 (76%)	24 (83%)	26 (81%)	25 (63%)	29 (73%)
N1	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%)

Data are median (IQR) or n (%).

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

colleagues,[8] as follows: local recurrence in the rectal wall (local regrowth) or in the mesorectum was not considered as an event if it was salvaged by a total mesorectal excision with R0–R1 resection; only death, distant metastasis and locally persisting tumour were taken as an event. In a post-hoc analysis, survival with organ preservation (total mesorectal excision-free survival) was evaluated, with only death, total mesorectal excision, or diversion stoma as events.

Statistical analysis

For sample size calculations, we anticipated a 3-year organ preservation rate of 20%[5] in group A and 40%[10] in group B, with a hazard ratio (HR) of 0·56. With a two-sided alpha of 5% and beta of 7·5% (power 92·5%), the sample size was calculated as a minimum of 214 evaluable patients. Assuming 10% of patients would be lost to follow-up, 138 events and 236 patients were required.

The independent data monitoring committee for the trial performed a first review of data after inclusion of 80 patients (May, 2019) and recommended to continue the trial and convene a new meeting of the independent data monitoring committee when 140 patients were enrolled (appendix pp 47–48). A second review was done in June, 2020, after 146 patients had been randomly assigned. The recommendation was to stop recruitment to the trial to publish an interim report and wait until 3 years to publish results of the trial as planned in the

protocol (appendix pp 49–50). We report the 3-year results of the trial here.

We used the Kaplan-Meier method to estimate time-to-event outcomes and a stratified Cox proportional hazards model to estimate HRs with 95% CIs for analysis of the 3-year organ preservation rate. All time-to-event outcomes were calculated from date of randomisation. 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. A two-sided p-value of 0·05 or less was considered significant (appendix p 35). All analyses were done using the R version 3.6.1.

Post-hoc analyses were conducted to find predictive factors for organ preservation at 3 years. Factors were analysed in a univariate Cox regression analysis. All variables with a p value of less than 0·1 were used in a multivariate analysis. A stepwise algorithm was used to choose the optimal multivariate model using the Akaike information criterion.

This study was registered with ClinicalTrials.gov, NCT02505750.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 14, 2015, and June 26, 2020, 148 patients were included and randomly assigned to either external beam radiotherapy boost (group A; n=74) or contact x-ray brachytherapy boost (group B; n=74; appendix p 1). Seven patients were subsequently excluded because they withdrew consent (figure 2). Four patients withdrew consent before treatment started (three in group A and one in group B) and three withdrew after starting treatment (two in group A and one in group B). Therefore, 141 (95%) of 148 patients were evaluable (69 in group A, 72 in group B). Baseline characteristics for the study population are shown in table 1. The median age was 69 years (IQR 60–74), 87 (62%) of 141 patients were men, 91 (65%) had cT2 disease, and 106 (75%) patients' tumours were located in the distal end of the rectum (<6 cm from the anal verge; table 1). 29 patients in group A had tumours of less than 3 cm in diameter, as did 32 in group B; 40 patients in group A had tumours of 3 cm or larger in diameter, as did 40 in group B. 93 (66%) patients were from France, 44 (31%) from the UK, and four (3%) from Switzerland. Seven patients (three in group A and four in group B) had a deviation from inclusion criteria (appendix p 29). 126 (90%) of 141 patients received chemoradiotherapy according to protocol (58 [84%] in group A *vs* 68 [94%] in group B). Chemotherapy dose reduction was needed in 28 (20%) patients (11 [16%] in group A *vs* 17 [24%] in group B). Seven patients—five in group A and two in group B—had interruption of chemoradiotherapy for more than 3 days. There was no definitive interruption of chemoradiotherapy in any patient. 69 (100%) of 69 patients in group A and 67 (93%) of 72 patients in group B received radiation boosts according to protocol (appendix pp 30, 31). Adjuvant chemotherapy was given to six patients after surgery at the discretion of the clinician in charge (three in group A and three in group B). No patients were lost to follow-up.

At the data cutoff of March 15, 2022, and after a median follow-up of 38·2 months (IQR 34·2–42·5), with a minimum follow-up of 2 years for every patient, the 3-year organ preservation rate was 59% (95% CI 48–72) in group A versus 81% (72–91) in group B (HR 0·36, 95% CI 0·19–0·70; p=0·0026; figure 3). In patients with tumour diameter of less than 3 cm, the organ preservation

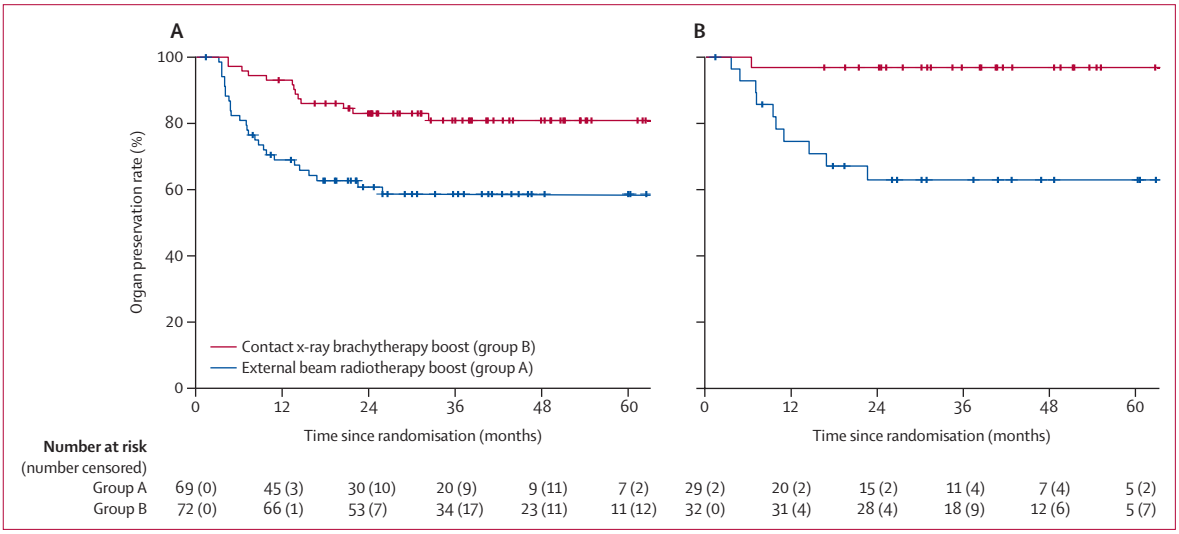

Figure 3: **3-year organ preservation rate**
(A) All patients (n=141). (B) Patients with tumours smaller than 3 cm (n=61).

	Total			Tumours <3 cm in diameter			Tumours ≥3 cm in diameter		
	Group A (n=69)	Group B (n=72)	p value	Group A (n=29)	Group B (n=32)	p value	Group A (n=40)	Group B (n=40)	p value
Week 14									
MRI tumour regression grade			0·74			0·087			0·013
1	31 (45%)	38 (53%)	..	14 (48%)	24 (75%)	..	17 (43%)	14 (35%)	..
2	12 (17%)	18 (25%)	..	8 (28%)	3 (9%)	..	4 (10%)	15 (37%)	..
3 or 4	5 (7%)	4 (6%)	..	1 (3%)	3 (9%)	..	4 (10%)	1 (3%)	..
Unknown	21 (30%)	12 (17%)	..	6 (21%)	2 (6%)	..	15 (37%)	10 (25%)	..
MRI tumour regression grade (post-hoc analysis)			0·51			0·62			0·17
1 or 2	43 (62%)	56 (78%)	..	22 (76%)	27 (84%)	..	21 (53%)	29 (72%)	..
3 or 4	5 (7%)	4 (6%)	..	1 (3%)	3 (9%)	..	4 (10%)	1 (3%)	..
Unknown	21 (30%)	12 (17%)	..	6 (21%)	2 (6%)	..	15 (37%)	10 (25%)	..
Response			<0·0001			0·078			0·0030
Clinical complete response	27 (39%)	34 (47%)	..	16 (55%)	20 (63%)	..	11 (28%)	14 (35%)	..
Near-clinical complete response	13 (19%)	24 (33%)	..	5 (17%)	10 (31%)	..	8 (20%)	14 (35%)	..
Partial response	24 (35%)	5 (7%)	..	6 (21%)	1 (3%)	..	18 (45%)	4 (10%)	..
Stable disease	0	3 (4%)	..	0	1 (3%)	..	0	2 (5%)	..
Progressive disease	1 (1%)	0	..	0	0	..	1 (2%)	0	..
Unknown	4 (6%)	6 (8%)	..	2 (7%)	0	..	2 (5%)	6 (15%)	..
Response (post-hoc analysis)			0·0006			0·13			0·0085
Complete response (clinical or near-clinical)	40 (58%)	58 (81%)	..	21 (72%)	30 (94%)	..	19 (48%)	28 (70%)	..
Partial response, stable disease, or progressive disease	25 (36%)	8 (11%)	..	6 (21%)	2 (6%)	..	19 (48%)	6 (15%)	..
Unknown	5 (7%)	6 (8%)	..	2 (7%)	0	..	2 (5%)	6 (15%)	..
Week 14–24									
MRI tumour regression grade			0·65			0·034			0·051
1	35 (51%)	46 (64%)	..	16 (55%)	26 (81%)	..	19 (48%)	20 (50%)	..
2	13 (19%)	17 (24%)	..	8 (28%)	3 (9%)	..	5 (13%)	14 (35%)	..
3 or 4	5 (7%)	3 (4%)	..	0	2 (6%)	..	5 (13%)	1 (2%)	..
Unknown*	16 (23%)	6 (8%)	..	5 (17%)	1 (3%)	..	11 (28%)	5 (13%)	..
MRI tumour regression grade (post-hoc analysis)			0·46			0·50			0·083
1 or 2	48 (70%)	63 (88%)	..	24 (83%)	29 (91%)	..	24 (60%)	34 (85%)	..
3 or 4	5 (7%)	3 (4%)	..	0 (0%)	2 (6%)	..	5 (13%)	1 (2%)	..
Unknown	16 (23%)	6 (8%)	..	5 (17%)	1 (3%)	..	11 (28%)	5 (13%)	..
Response			<0·0001			0·044			0·0006
Clinical complete response	32 (46%)	49 (68%)	..	19 (66%)	26 (81%)	..	13 (33%)	23 (58%)	..
Near-clinical complete response	12 (17%)	17 (24%)	..	3 (10%)	5 (16%)	..	9 (22%)	12 (30%)	..
Partial response	21 (30%)	2 (3%)	..	5 (17%)	0	..	16 (40%)	2 (5%)	..
Stable disease	0	2 (3%)	..	0	1 (3%)	..	0	1 (2%)	..
Progressive disease	2 (3%)	0	..	1 (3%)	0	..	1 (3%)	0	..
Unknown	2 (3%)	2 (3%)	..	1 (3%)	0	..	1 (3%)	2 (5%)	..
Response (post-hoc analysis)			<0·0001			0·043			0·0005
Complete response (clinical or near-clinical)	44 (64%)	66 (92%)	..	22 (76%)	31 (97%)	..	22 (55%)	35 (88%)	..
Partial response, stable disease, or progressive disease	23 (33%)	4 (6%)	..	6 (21%)	1 (3%)	..	17 (43%)	3 (7%)	..
Unknown	3 (4%)	2 (3%)	..	1 (3%)	0	..	1 (2%)	2 (5%)	..

Data are n (%). Tumour regression grades are as follows: 1 is no evidence of abnormality, 2 is no residual tumour replaced by fibrosis, 3 is more than 50% fibrosis and visible tumour, and 4–5 is obvious persisting cancer. In case of equivocal response on week 14 a new MRI evaluation was performed on week 24. p values were calculated using Fisher's exact test and by excluding the Unknown category, except Response (post-hoc analysis) for group A versus group B, which was calculated by χ^2 test . *Seven (32%) of the 22 patients received total mesorectal excision, so MRI was not performed.

Table 2: **MRI scoring and responses**

rate was 63% (95% CI 47–84) in group A and 97% (91–100) in group B (HR 0·07, 95% CI 0·01–0·57; p=0·012). In patients with tumour diameter of 3 cm or more, the 3-year organ preservation was 55% (95% CI 41–74) in group A and 68% (54–85) in group B (HR 0·54, 95% CI 0·26–1·10; p=0·11; appendix pp 11–13).

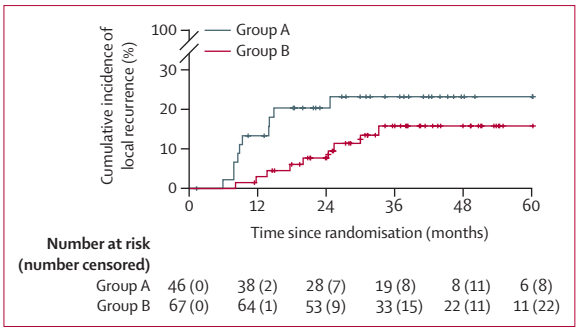

Figure 4: **Cumulative incidence of local recurrence**

At week 14, tumour response was evaluated with endoscopy in 131 patients and with MRI in 108 patients (table 2). 27 (39%) of 69 patients in group A and 34 (47%) of 72 patients in group B had a cCR. 40 patients (58%) in group A and 58 (81%) in group B had a cCR or ncCR (p=0·0006). 21 (72%) of 29 patients with tumours of less than 3 cm in group A and 30 (94%) of 32 with tumours of less than 3 cm in group B had a cCR or ncCR (p=0·13). 19 (48%) of 40 patients with tumours of 3 cm or larger in group A and 28 (70%) of 40 patients with tumours of 3 cm or larger in group B had a cCR or ncCR (p=0·0085). MRIs were scored tumour regression grade 1–2 in 43 (62%) of 69 patients in group A and 56 (78%) of 72 patients in group B (p=0·51). Between week 14 and week 24, 137 patients had a tumour response assessment, of whom 119 were assessed by MRI. 10 patients in group A underwent total mesorectal excision before week 24. Between week 14 and 24, 32 (46%) of 69 patients in group A and 49 (68%) of 72 patients in group B had a cCR. 44 patients (64%) in group A and 66 patients (92%) in group B had a cCR or ncCR (p<0·0001). Among patients with tumours less than 3 cm in diameter, 22 (76%) of 29 patients in group A and 31 (97%) of 32 patients in group B had a cCR or ncCR (p=0·043). Among patients with tumours of 3 cm or larger in diameter, 22 (55%) of 40 in group A and 35 (88%) of 40 in group B had a cCR or ncCR (p=0·0005). MRIs were scored tumour regression grade 1–2 in 48 (70%) of 69 patients in group A and 63 (88%) of 72 patients in group B (p=0·46).

Local excision was performed in 27 patients (20 in group A and seven in group B; appendix p 39), mainly during the first 24 weeks of assessment after treatment (appendix pp 2–4). Final pathology found no residual cancer (ypT0) in ten (37%) of 27 patients with no difference between group A (eight [40%] of 20) and group B (two [29%] of seven; appendix p 32).

Among 113 patients without total mesorectal excision after a partial response, local recurrence was observed in 19 (17%; figure 4; appendix p 40). Recurrence occurred in the tumour bed (regrowth in the rectal wall) in 18 (95%) of these patients and in a perirectal node (close to the primary) in one (5%). Ten (53%) local recurrences occurred in group A, mainly during the first year, and nine (47%) in group B, between years 1 and 3 (appendix pp 5–7). The 3-year cumulative incidence of local recurrence was 23% (95% CI 9–35) in group A and 15% (6–25) in group B (p=0·59). It was 27% (6–44) among patients with tumours of less than 3 cm in group A and 5% (0–13) among those with similarly sized tumours in group B (p=0·051). Among patients with tumours of 3 cm or larger, 3-year cumulative incidence of local recurrence was 20% (0–36) in group A and 26% (8–40) in group B (p=0·76). Management of these local recurrences entailed total mesorectal excision in 13 (68%) of 19 patients (residual cancer in all), local excision in three (16%; two with a subsequent total mesorectal excision) and one (5%; ypT2 R0) with surveillance and local control 2 years later. A diversion stoma was performed in one (5%) patient. Supportive care without stoma was proposed in four (21%) patients who refused surgery for their recurrences. There was no non-salvageable local recurrence and no local recurrences among patients who had total mesorectal excision.

Bowel function was assessed in 86 patients without total mesorectal excision and with 1 year of follow-up. The LARS score was 30 or more in seven (21%) of 34 in group A and nine (17%) of 52 in group B (p=0·55; appendix p 36).

Total mesorectal excision was done in 39 patients (26 [38%] of 69 patients in group A and 13 [18%] of 72 patients in group B; p=0·0042; appendix p 41), mainly during the first 2 years after treatment (appendix pp 8–9). Among patients with tumours of less than 3 cm, nine patients in group A and one patient in group B underwent total mesorectal excision; among patients with tumours of 3 cm or larger, 17 in group A and 12 in group B underwent total mesorectal excision (appendix p 10). 17 (44%) patients who underwent total mesorectal excision had an abdomino-perineal excision and 22 (56%) had anterior resection. The number of patients receiving anterior resection preserving the sphincter did not significantly differ between group A (16 [61%] of 26) and group B (six [46%] of 13). 28 (72%) total mesorectal excision procedures were done laparoscopically. Histopathology of the operative specimen did not significantly differ between group A and group B (p=0·91), with no evidence of invasive malignancy (ypT0-is) in nine patients (six in group A, three in group B), ypT1–3 in 29 patients (19 in group A, ten in group B), and ypT4 in one patient in group A. Positive lymph nodes were found to be involved in eight patients (ypN1; three in group A, five in group B). 23 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 (two in group A, two in group B; appendix pp 33–35), and there were no patients with R2 resection margin.

51 patients (36%) reported a grade 2–3 early adverse event while receiving neoadjuvant chemoradiotherapy

	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	4 (6%)	0	0	0	10 (14%)	5 (7%)	0	0
Proctitis	4 (6%)	0	0	0	7 (10%)	2 (3%)	0	0
Diarrhoea	0	0	0	0	3 (4%)	3 (4%)	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 spams	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	4 (6%)	0	0	0
Urinary infection	0	2 (3%)	0	0	0	0	0	0
Dysuria	2 (3%)	1 (1%)	0	0	4 (6%)	0	0	0
Skin disorders	7 (10%)	0	0	0	2 (3%)	0	0	0
Radiation dermatitis	7 (10%)	0	0	0	2 (3%)	0	0	0
Other	4 (6%)	0	0	0	2 (3%)	0	0	0
Rectal bleeding	2 (3%)	0	0	0	0	0	0	0
Chest pain	0	0	0	0	2 (3%)	0	0	0
Oral candidiasis	1 (1%)	0	0	0	0	0	0	0
Palmar-plantar erythrodysesthesia	1 (1%)	0	0	0	0	0	0	0

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

Table 3: **Adverse events**

(table 3). The most common adverse events were proctitis (four [6%] in group A, nine [13%] in group B) due to external beam radiotherapy and radiation dermatitis (seven [10%] in group A, two [3%] in group B). A grade 2–3 early adverse event occurred in 21 patients (30%) in group A and 30 (42%) in group B (p=1·0). A grade 3 adverse event occurred in six patients (4%) in group A and seven (5%) in group B (table 3). No patients had early grade 4–5 adverse events.

There were no deaths due to total mesorectal excision surgery within the first 30 days; median hospital stay was 9 days (IQR 6–14) and seven patients had second operations (five in group A, two in group B; appendix p 20). The median hospital stay for local excision was 2 days (IQR 1–3). No major serious surgical complications were observed following local excision.

No late adverse event of grade 3 or higher occurred. The most common late side-effect was mild rectal bleeding (grade 1–2), which was analysed in the 102 patients who did not undergo total mesorectal excision. Mild rectal bleeding was more frequent in group B (37 [63%] of 59) than in group A (five [12%] of 43; p<0·0001). Argon coagulation was needed to control bleeding in six patients (one in group A, five in group B; appendix p 36). Rectal bleeding was due to telangiectasia, which on average appeared 6 months after treatment, increased in incidence between 1 year and 2 years, and subsided after 3 years (appendix p 14).

Distant metastasis was seen in 12 patients and was located in the liver (n=4), lung (n=4), liver and lung (n=2), bone (n=1), and abdominal lymph node (n=1; appendix p 42). The 3-year incidence of distant metastases was 9% (95% CI 4–13), with no difference between the two groups (appendix pp 15–16).

Death occurred in four patients (two in group A, two in group B). Three of these deaths were cancer-related. 3-year overall survival was 98% (95% CI 96–100) and did not differ between the two groups (group A 98% [95% CI 95–100], group B 98% [92–100]). 3-year disease-free survival in a post-hoc analysis was 83% (95% CI 76–90) and also did not differ between groups (group A 83% [95% CI 72–96], group B 82% [72–93]; appendix pp 19–20). In a post-hoc analysis, 3-year survival with organ preservation (total mesorectal excision-stoma free) was 69% (95% CI 61–77) and significantly differed between groups (57% [95% CI 46–71] for group A and 79% [70–90] for group B; p=0·0026; 63% [47–84] for patients with tumours <3 cm in group A and 97% [91–100] for group B; p=0·012; 53% [39–72] for patients with tumours ≥3 cm in group A and 65% [51–83] for group B; p=0·11; appendix pp 17–18).

In the post-hoc univariate Cox regression analysis of factors that might predict 3-year organ preservation

(appendix pp 89–90), there were no significant differences (log rank test) for cT stage (2 *vs* 3a or 3b), age, sex, differentiation (moderately *vs* well), ECOG performance status (0 *vs* 1 or 2), cN class (N0 *vs* N1), distance from anal verge (<6 cm *vs* ≥6 cm), carcinoembryogenic antigen (<2·5 ng/mL *vs* ≥2·5 ng/mL), EBRT technique (three-dimensional conformal *vs* intensity modulated radiotherapy), and contact position (knee-chest *vs* lithotomy). Patients with tumour diameter greater than 3 cm were more likely than those with tumours <3 cm to undergo a total mesorectal excision (HR 2·3, 95% CI 1·1–4·6; p=0·021), as were patients with more than 3 consecutive days of interruption compared with patients with no interruption (HR 2·9, 1·0–7·8; p=0·055). These two variables were included in a multivariate model, in which they were both still significant (tumour diameter HR 2·3, 95% CI 1·1–4·6; p=0·021; treatment interruption 3·2, 1·1–9·4; p=0·027).

Discussion

The standard of care for patients with cT2–cT3 rectal adenocarcinoma who are fit but who refuse surgery is to offer them chemoradiotherapy, with the hope of reaching cCR, and to adopt a watch and wait policy in those who have a cCR. In Habr-Gama and colleagues' experience,[5] external beam dose escalation from 45 Gy to 54 Gy and addition of neoadjuvant chemotherapy, increased the cCR rate from 24% to 49%, but local recurrence rates were still high, in about a third of patients needing surgery. Therefore, the organ preservation rate for the whole group of patients remained low at 34%.

In the OPERA trial we found that in combination with chemoradiotherapy, when compared to a boost with external beam radiotherapy, a contact x-ray brachytherapy boost significantly increased the cCR rate and the 3-year organ preservation rate for early cT2–cT3 rectal adenocarcinomas. This is the first randomised controlled trial to show that dose escalation can result in increased organ preservation. The organ preservation rate was more than 90% for tumours less than 3 cm diameter using contact x-ray brachytherapy as initial treatment. This benefit was achieved without increased toxicity and with good rectal function in most cases. The organ preservation rate was much the same for tumours located in the distal or middle rectum. These results concur with published data on contact x-ray brachytherapy in Europe.[13–15] Data from this trial also show that patients who wish to avoid surgery with a watch and wait approach but present local regrowth at a later date can be offered delayed surgery as a salvage procedure without compromising their chance of cure and with no undue surgical toxicity.

This trial had many limitations. First, follow-up was only 3 years, but we intend to publish results after longer follow-up at 5 years and 10 years. 3-year follow-up is usually reported when organ preservation is the outcome, because most recurrences (local regrowth, local recurrence) occur during the first 2 years. Second, the study was halted early on the recommendation of the independent data monitoring committee, with fewer patients than originally planned. We did not find a difference between external beam radiotherapy boost and contact x-ray brachytherapy boost in patients with tumours of 3 cm or larger, which may be a result of the underpowering of the study. A phase 3 trial (TRESOR) will be initiated in France in 2023 for patients with T3 tumours larger than 3·5 cm in diameter to test the combination of contact x-ray brachytherapy and total neoadjuvant treatment using FOLFIRINOX and capecitabine combined with external beam radiotherapy at a dose of 50 Gy, with organ preservation as the primary outcome. In the Netherlands, the OPAXX trial will also test the role of contact x-ray brachytherapy in advanced T3 disease. Third, rigid rectoscopy was regularly performed by the radiation oncologist for response assessment in group B (not blinded), particularly for patients with tumours of less than 3 cm in diameter. This could have affected the overall response assessment, because these assessments were not made regularly in group A. However, this rigid rectoscopy could be seen as a benefit of contact x-ray brachytherapy. Its use as part of a watch and wait strategy could provide accurate, easy, and frequent assessments of tumour size and response. In most cases, even in group A, response assessments were done by experienced oncologists using either flexible or rigid rectoscopy, but, even in experienced hands and eyes, assessment of tumour response can remain uncertain and must be adapted to the dynamic, time-related nature of this process. This is especially true for ncCR, whose definition remains without consensus.

Fourth, the stratification on the basis of tumour diameter introduced some heterogeneity, with better results seen in smaller tumours. Fifth, we do not at present have detailed data from MRI analyses, local excisions, and quality-of-life results; these will be published at a later date. Finally, the main limitation of a boost with contact x-ray brachytherapy in terms of changing practice is the ability to offer contact x-ray brachytherapy in only a small number of institutions around Europe. This could be improved by training more radiation oncologists interested in this approach; we also need greater collaboration with industry to make the technology more user friendly and to speed up the production of new affordable machines.

It is well established that high radiation dose and tumour volume are crucial to achieve sterilisation of rectal adenocarcinoma.[21–23] The Danish Veile group used dose escalation with a higher external beam radiotherapy dose of 60 Gy and an additional 5 Gy high dose rate brachytherapy boost. Although the initial cCR rate improved to 68%, the local regrowth rate was still high at 25% at 2 years and the organ preservation rate was just over 50%.[22] They produced a dose response model to investigate this and found that a radiation dose (equivalent

dose in 2 Gy fractions) of above 92 Gy is necessary to achieve local control in more than 50% of patients with a T3 rectal adenocarcinoma.[22] It is not possible to deliver such a high dose of radiation using available external beam technologies.

Over the past 40 years, in centres using contact x-ray brachytherapy, we found that in combination with chemoradiotherapy, contact x-ray brachytherapy boost significantly increased the clinical response rate (cCR and ncCR) for early cT2–cT3 rectal adenocarcinomas to more than 70%.[9,10,14,15] The reason for this increased response can be explained by the ability of contact x-ray brachytherapy to deliver a very high dose of radiation beyond 92 Gy (equivalent dose in 2 Gy fractions).[23] Owing to its low energy of 50 kVp, the penetration of contact x-ray brachytherapy radiation dose is limited and a very high dose of radiation (90 Gy) can be delivered directly to the tumour with very little damage to the normal surrounding tissues. The biological equivalent dose in 2 Gy fractions of this type of radiation is estimated to be around 300 Gy using contact x-ray brachytherapy technology. This dose is much higher than the external beam radiotherapy dose usually used for rectal cancer (45–60 Gy).

Dose escalation with an endoluminal, high dose rate approach remains a promising way to deliver a high radiation dose above 92 Gy without undue toxicity.[24] Other approaches that can be used for organ preservation include local excision,[25] neoadjuvant chemotherapy (often with total neoadjuvant treatment),[26–27] and external beam radiotherapy dose escalation.[8,28–31] There are some ongoing trials testing local excision or total neoadjuvant treatment, and future studies could explore the relevance of combining contact x-ray brachytherapy with these approaches to increase the chance of organ preservation. Tumour response assessment remains challenging and requires methods to accurately predict tumour sterilisation. The distinction between cCR and ncCR remains uncertain even in experienced centres. At present, there are no reliable markers or methods to predict radiation response and exploration of ways to predict tumour sterilisation after radiation should be encouraged. The risk of toxicity should be explained to the patient alongside possible benefit to facilitate balance in decision making for their rectal cancer management. The data provided by OPERA will possibly help consenting patients make a decision. Because the OPERA trial only included patients with a ECOG performance status of 0–1 who were fit for surgery, we must avoid the risk of overtreatment, especially in older patients.[32]

It is unlikely that patients with so-called ugly locally advanced rectal cancer[1] (cT3–cT4 >6 cm diameter or occupying more than two-thirds of the rectal circumference, or large metastatic nodes) will be suitable candidates for organ preservation. However, in select patients with mismatch repair-deficiency, the use of PD-1 blockade given as a total neoadjuvant therapy is showing promising results for these advanced rectal cancers.[33] For intermediate tumours,[1] further clinical research into various other treatment options for reaching cCR should be encouraged. Longer surveillance might be relevant after neoadjuvant external beam chemoradiotherapy before decision for total mesorectal excision is made in patients who are reluctant to undergo surgery.[5]

Organ preservation is a promising new frontier in the management of rectal cancer and could be planned for select tumours using dose escalation with contact x-ray brachytherapy. Although surgery remains the standard of care, tailored organ preservation strategies could be discussed and offered to well-informed patients who wish to avoid radical surgery, mainly when presenting with cT2, cT3a, or cT3b tumours of less than 3 cm in size.

Declaration of interests

J-PG is a medical advisor for Ariane Medical Systems (UK) and Clerad (France). IM reports honoraria form AstraZeneca and MSD. MD reports honoraria from Elekta. TZ reports grants from Varian and Debiopharm, and honoraria from Astellas, Janssen, Telix, Debiopharm, and Varian. All other authors report no competing interests.

Contributors

J-PG, RS, and ASM designed the study, and J-PG and RS designed the case report form. J-PG, NB, NM, IM, LM, MD, TZ, AD, and ASM treated patients. J-PG, NB, NM, IM, LM, MD, TZ, AD, and ASM collected data, with the help of research technicians and monitors, which were managed by RS and analysed by J-PG, RS, and ASM. J-PG, RS, and ASM wrote the manuscript, which was read by all authors. RS and J-PG had access to and verified the raw data. J-PG had the final responsibility to submit the manuscript for publication.

Data sharing statement

No additional data are available. Questions regarding the technical procedures, statistical code, and data can be addressed to the corresponding author. Collected data will be available upon request in the form of Excel tables saved as .xls or .xlsx. These files will be shared after approval of a proposal submitted to the trial sponsor by email (drci-promotion@nice.unicancer.fr) and with a signed data access agreement.

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