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FULL PAPER

Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: does it improve the chance of organ preservation?

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Objective: A watch and wait policy for patients with a clinical complete response (cCR) after external beam chemoradiotherapy (EBCRT) for rectal cancer is an attractive option. However, approximately one-third of tumours will regrow, which requires surgical salvage for cure. We assessed whether contact X-ray brachytherapy (CXB) can improve organ preservation by avoiding surgery for local regrowth.

Methods: From our institutional database, we identified 200 of 573 patients treated by CXB from 2003 to 2012. Median age was 74 years (range 32–94), and 134 (67%) patients were males. Histology was confirmed in all patients and was staged using CT scan, MRI or endorectal ultrasound. All patients received combined CXB and EBCRT, except 17 (8.5%) who had CXB alone.

Results: Initial cCR was achieved in 144/200 (72%) patients. 38/56 (68%) patients who had residual tumour received immediate salvage surgery. 16/144 (11%) patients developed local relapse after cCR, and 124/144 (86%) maintained cCR. At median follow up of 2.7 years, 161 (80.5%) patients were free of cancer. The main late toxicity was bleeding (28%). Organ preservation was achieved in 124/200 (62%) patients.

Conclusion: Our data suggest that CXB can reduce local regrowth to 11% compared with around 30% after EBCRT alone. Organ preservation of 62% achieved was higher than reported in most published watch and wait studies.

Advances in knowledge: CXB is a promising treatment option to avoid salvage surgery for local regrowth, which can improve the chance of organ preservation in patients who are not suitable for or refuse surgery.

INTRODUCTION

Patients often prefer not to have surgery if they have a choice.¹ Therefore, a watch and wait policy for responders after external beam chemo-radiotherapy (EBCRT) is gaining acceptance as an alternative to radical surgery in patients with rectal cancer, since it avoids extirpative surgery and a stoma.² However, published evidence suggests that local regrowth occurs in up to one-third of patients despite them having achieved an initial clinical complete response (cCR).³ Most patients who are fit and agreeable for surgery have salvage operations for local regrowth, which reduces their overall chance of organ preservation to less than 40%.^{3,4} There is a need to investigate methods to reduce local regrowth rates.

One approach is to offer contact X-ray brachytherapy (CXB) after external beam radiotherapy (EBRT) or external beam chemoradiotherapy (EBCRT).^{5,6} We report our experience in a real-world situation in patients who were either not suitable for surgery or were fit but refused surgery and were referred to our centre for non-surgical treatment. We offered CXB to this group of patients to avoid salvage surgery for local regrowth and to improve their chance of organ preservation.

METHODS AND MATERIALS

We identified 200 consecutive patients with operable rectal cancer from our institutional database of 573 patients who had been referred to our centre from 1 January 2003 to

31 December 2012. CXB was offered with the intent of reducing local regrowth to avoid salvage surgery in patients who were not suitable for or refused surgery within the study period. The selection and exclusion criteria are shown in [Table 1](#). Histological diagnosis of adenocarcinoma was confirmed in all patients. Baseline pre-treatment assessment included endoscopy, digital rectal examination (DRE), MRI, CT scan and endorectal ultrasound (if MRI was not possible owing to cardiac pacemaker), and was undertaken at the patients' local referring centres. Pre-treatment stages cT1–cT4 and cN stages (AJC/UICC v7) are shown in [Table 2](#). All patients were discussed at their local colorectal multidisciplinary team meetings before referral.

17 patients presenting with rectal cancers of 3 cm or smaller (mostly cT1/ early cT2 and cN0; mainly adenomas with small focus of cancer) were referred for consideration for CXB upfront because they were not suitable for surgery and also refused external beam radiotherapy ($n = 17$). All other patients who had advanced tumours larger than 3 cm in diameter (cT2 or cT3/cN1/cN2) had EBRT/EBCRT locally to downsize and downstage their tumours. Our proposed treatment algorithm is shown in [Figure 1](#). All patients had repeat endoscopy, DRE and restaging scans to assess their response to EBRT/EBCRT (usually within 6–8 weeks). They were then discussed again at their local multidisciplinary team meeting, and surgery was offered to all with residual disease, since this was "the standard of care". However, those patients who were not suitable for surgery or those who were fit but refused surgery were referred to us for consideration of CXB boost.

Our study was a retrospective observational audit approved by the audit committee (01-02/26). All patients were consented and agreed to CXB after a full explanation that this treatment might not be curative, and that they may need future salvage

Table 1. Inclusion and exclusion criteria for CXB

Inclusion criteria for CXB	
1.	Histologically proven rectal cancer.
2.	Well to moderately well-differentiated adenocarcinoma.
3.	Stage T1-3 mobile tumour less than 3 cm in size. Any N stage within the mesorectum.
4.	Tumour situated less than 12 cm from the anal verge.
5.	Patients must be suitable for long-term follow up.
Exclusion criteria for CXB	
1.	Poorly differentiated adenocarcinoma.
2.	Presence of lympho-vascular invasion.
3.	Size (largest) of tumour more than 3 cm or over half the circumference of the rectal lumen.
4.	Any lymph node outside the mesorectum.
5.	Presence of proven distant metastases.
6.	Local regrowth after achieving cCR following EBCRT.
7.	Previous surgical excision of tumour.

cCR, clinical complete response; CXB, contact X-ray brachytherapy; EBCRT, external beam chemoradiotherapy.

Table 2. Baseline characteristics

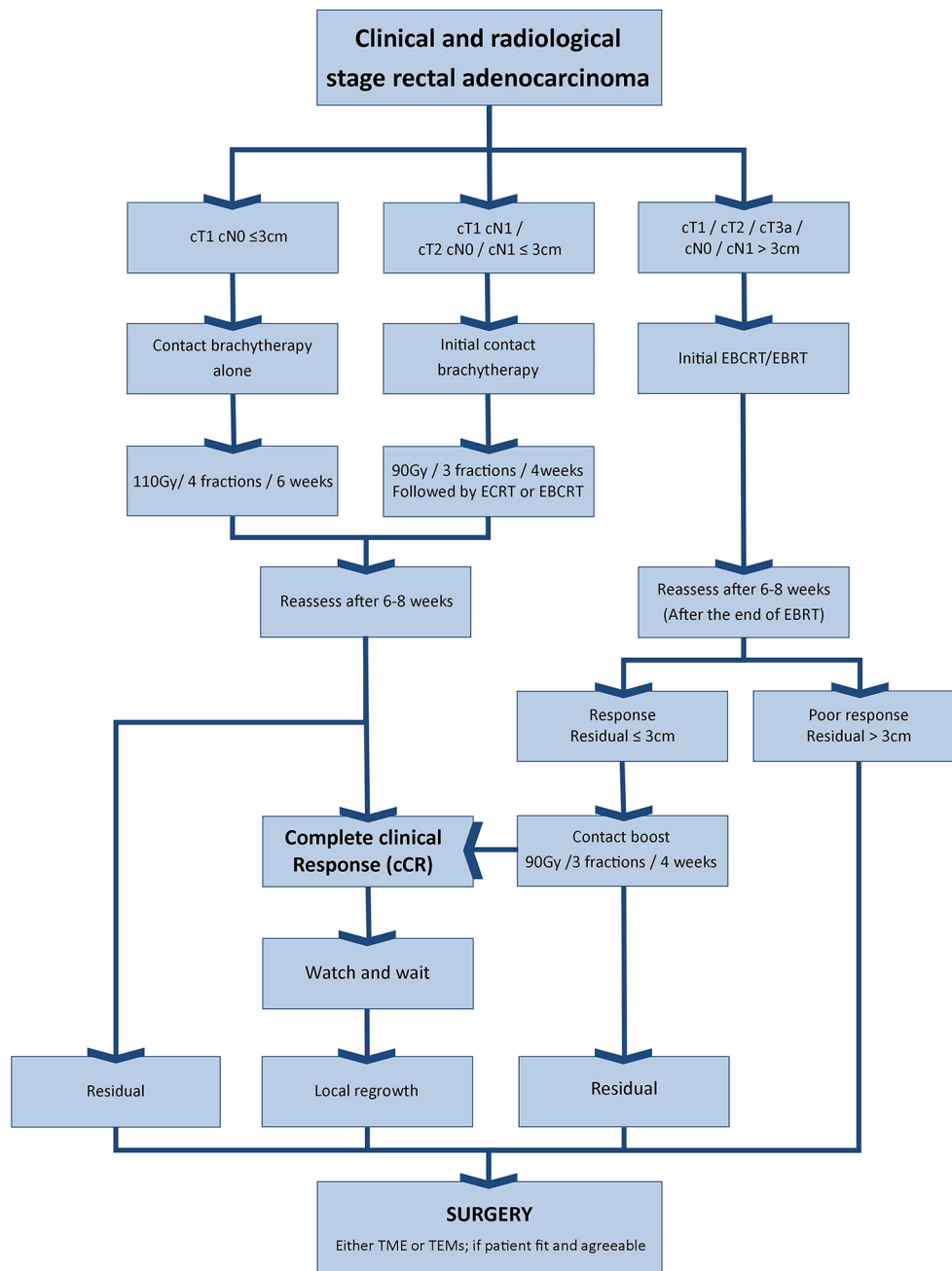
		<i>n</i>	%
Age in years, median (range)		74 (32–94)	-
Sex	Females	66	33.0%
	Males	134	67.0%
Performance status	0	66	33.0%
	1	73	36.5%
	2	41	20.5%
	3	7	3.5%
	Not known	13	6.5%
Differentiation	Well	10	5.0%
	Moderate	121	60.5%
	Poor	6	3.0%
	Not known	63	31.5%
Tumour stage (pre-treatment)	cT1	21	10.5%
	cT2	89	44.5%
	cT3	87	43.5%
	cT4	3	1.5%
Nodal stage	cN0	125	62.5%
	cN1	56	28.0%
	cN2	18	9.0%
	Not known	1	0.5%
Metastases stage	M0	200	100%
Distance from anal verge	<7 cm	144	72.0%
	7–11 cm	47	23.5%
	>11 cm	2	1.0%
	Not recorded	7	3.5%
Tumour size	≤3 cm	107	53.5%
	>3 cm	65	32.5%
	Not recorded	28	14.0%

surgery if there was a residual tumour or local regrowth, provided that they were fit and agreeable for surgery ([Figure 2](#)).

EXCLUSION CRITERIA

We excluded all patients where we could not locate the area to treat with CXB boost after EBRT/EBCRT. They were offered the watch and wait protocol and followed up locally. Some of those patients who were referred were also found to have a bulkier residual tumour at endoscopy (>3 cm) and were instead offered high-dose-rate endoluminal brachytherapy using a rectal applicator (Elekta, Stockholm, Sweden). The decision not to treat residual tumours larger than 3 cm was because the largest rectal applicator that we can use for CXB is 30 mm. These patients were also excluded from our study ($n = 46$). Patients ($n = 180$) who had initial excision of tumour

Figure 1. Treatment algorithm. cCR, clinical complete response; EBCRT, external beam chemoradiotherapy; EBRT, external beam radiotherapy.



by transanal endoscopic microsurgery, transanal resection of tumour or endoscopic mucosal resection were also excluded and reported separately elsewhere ($n=180$). In addition, patients who had tumour regrowth after EBRT/EBCRT and those with metastatic disease were treated palliatively with CXB ($n=86$), and were excluded from our analysis. 61 (10.6%) patients with missing data were also excluded (Figure 2).

External beam radiotherapy

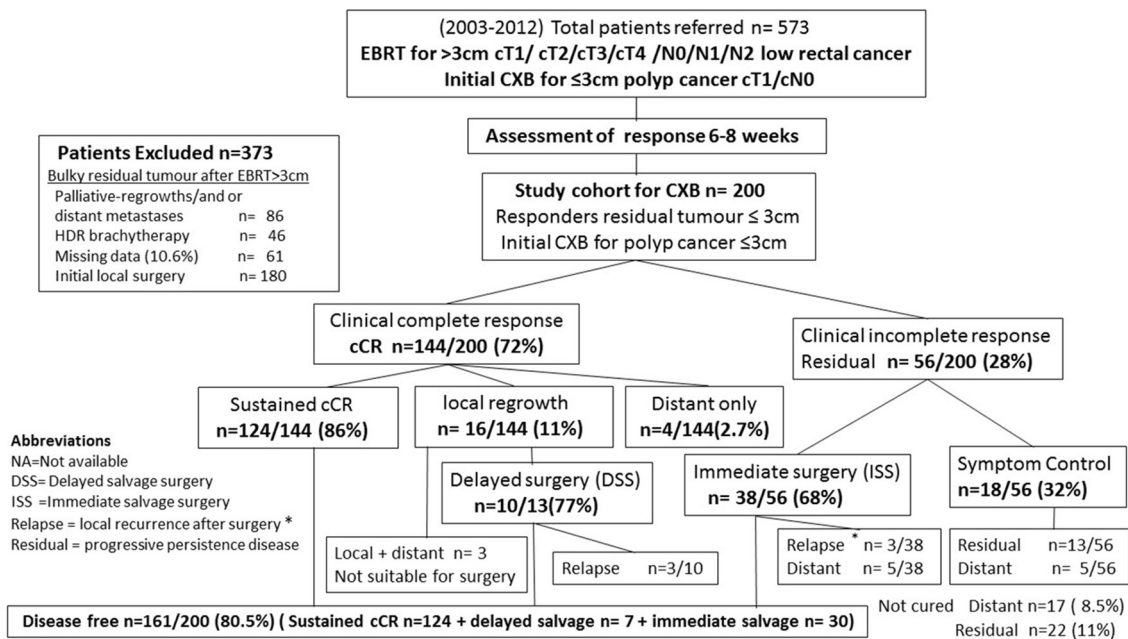
All patients received EBRT/EBCRT except those with polyp cancer of 3 cm or smaller (mainly cT1 / early cT2 and cN0; $n=17$). Patients who were fit for treatment had 45 Gy in 25 fractions over 5 weeks with 5-fluorouracil 1 g m^{-2} (days 1–4 in weeks 1 and 5) or oral capecitabine 825 mg m^{-2}

twice a day on the days of radiation ($n=127$). Patients with poor renal function received EBRT without chemotherapy ($n=56$).

Contact X-ray brachytherapy (Papillon)

Since 2009, CXB was delivered using a Papillon 50 machine (Ariane, Alfreton, UK; Figure 3). However, a Therapax machine (Gulmay, Surrey, UK) was used between 1993 and 2009. The details of the CXB treatment schedule, set up and data comparing the two machines has been described in our earlier publications.^{6–8} CXB was administered as outpatient treatment every 2 weeks. A surface dose of 30 Gy using 50 kVp X-rays (HVL 0.64 Al, 2.7 mA) was delivered through a rectal treatment applicator at each visit. The size of treatment applicator (30, 25 or 22 mm)

Figure 2. Patient care pathway. cCR, clinical complete response; CXB, contact X-ray brachytherapy; DSS, delayed salvage surgery; EBRT, external beam radiotherapy; ISS, immediate salvage surgery.



was chosen to cover the tumour with a 5 mm margin, and was targeted under direct visual guidance (Figure 4). Most patients received no more than a total dose of 90 Gy delivered in three fractions every 2 weeks for 4 weeks.⁶⁻⁸

Surveillance protocol

Close follow-up was done within the first 2 years, when the risk of tumour recurrence was highest. During this period, patients were seen every 3 months for DRE and sigmoidoscopy. MRI and CT scans were done every 4-6 months. A clinical complete response (cCR) was defined as a complete absence of palpable, endoscopic or radiological evidence of a residual tumour.^{3,4,9} If there was a progressive suspicious mucosal abnormality detected endoscopically, or if progressive induration was felt on DRE,

patients were referred for immediate salvage surgery provided they were fit and willing to accept this treatment.^{3,4} Isolated subtle abnormalities on the MRI scan or mucosal abnormalities on endoscopy that did not change or progress over time were regarded as static disease and kept under review.

All patients with a sustained cCR on the watch and wait pathway after CXB were reassessed every 6 months after the first 2 years, alternating with their referring clinician from their local hospitals for up to 5 years. If any active regrowth of the tumour was detected after an initial cCR, the patient was restaged and offered delayed surgical salvage, provided no inoperable distant metastases were present and that the patient was fit and agreeable for surgery (Figure 2). We encouraged clinicians not to biopsy the scar if no obvious cancer remained, owing to the known low negative predictive value of negative histology. Scarring or ulceration resulting from biopsy could also make subsequent endoscopic and MRI appearances difficult to interpret.^{10,11}

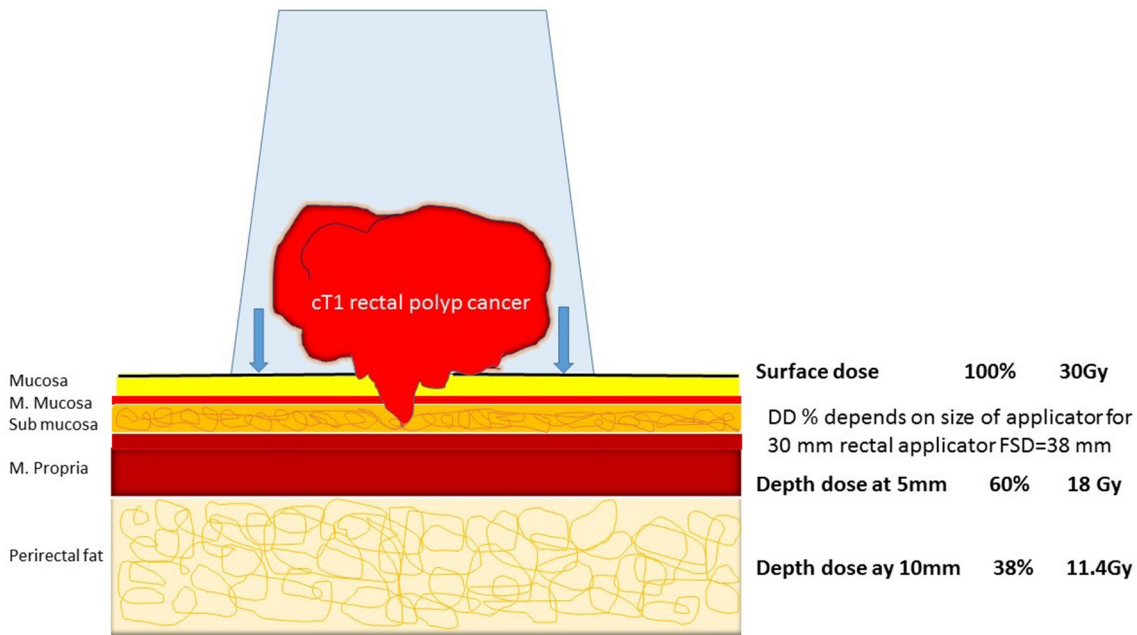
Figure 3. Contact X-ray brachytherapy treatment position.



Statistical analysis

Our main objective was to demonstrate the effectiveness of CXB in reducing local regrowth in our cohort, which have shown to improve the chance of organ preservation by avoiding salvage surgery. The overall survival, local progression free survival and the disease-free survival, were estimated using the Kaplan-Meier survival methodology. Univariate and multivariate analyses using logistic regression were done to identify factors associated with initial response and local regrowth (Table 3). Additionally, Cox regression analysis was done to identify factors associated with disease-free survival (Table 4). An external independent validator was commissioned to ensure the accuracy and integrity of our data, since it had been accrued over many years. This process indicated that 94% of initial data

Figure 4. Contact X-ray treatment schematic diagram. FSD, focal surface distance



entries were accurate. Data were analysed using SPSS v. 21 (IBM, Portsmouth, UK).

RESULTS

Patient characteristics

Our institutional database identified 200 patients who had been diagnosed with either rectal polyp cancer ≤ 3 cm (mainly cT1 / early cT2 and /cN0) or residual rectal cancer measuring ≤ 3 cm after EBRT/EBCRT (cT2, cT3a, cN0, cN1). There were three patients with cT4 tumours but all were downstaged with minimal residual tumour prior to CXB boost. The baseline demographics of our patients are shown in Table 2 and their outcomes are summarized in Figure 2.

Clinical complete response

An initial cCR was seen in 144 (72) of 200 patients following CXB. Examples of responses to CXB for early stage tumour (≤ 3 cm) followed by EBCRT and for more advanced tumours (> 3 cm) treated with initial EBRT or EBCRT followed by CXB boost are shown in Figures 5 and 6. Univariate logistic regression analysis did not identify any prognostic factors related to the initial response (Table 3).

Clinical incomplete response

Despite the high dose received from CXB, 56 (28%) of 200 patients had an clinical incomplete response. This finding suggests that inherent tumour radio-resistance plays an important role. 38 patients (68%) from within this group subsequently underwent immediate salvage surgery. Of these patients, eight (21%) had no pathological evidence of residual disease (ypT0). 16 patients did not proceed to surgery owing to advanced age and comorbidities, and two other patients refused surgery.

Local regrowth after initial clinical complete response

At the study cut-off date, 16 (11%) of the 144 patients who initially achieved cCR developed a local regrowth. The median time for this to occur was 16 months (range 4.0–113). Univariate analysis using logistic regression did not identify any prognostic factors associated with local regrowth (Table 3).

Local regrowth management

Of the 16 patients who developed a local regrowth, 3 had distant metastases in addition to local regrowth. 10 (77%) of 13 patients with salvageable local and regional regrowth underwent delayed salvage surgery.¹² Importantly, 2 of the 10 patients (20%) who underwent salvage surgery for suspected local regrowth seen endoscopically had a pathological stage of ypT0.

Distant metastases

Of the 200 patients in this study, 17 (8.5%) developed metastatic disease. Four patients had lung resections for their metastatic disease, and the others received symptomatic palliative care only owing to their advanced age or comorbidities.

Disease-free survival

The Kaplan–Meier probabilities of disease-free survival for the whole group were 72% (95% CI 66–78) at 2 years, 65% (95% CI 58–72) at 3 years, and 53% (95% CI 44–62) at 5 years (Figure 7). Cox regression analysis was carried out to identify factors associated with disease-free survival (Table 4). Performance status, age at presentation, and treatment modality were found to be significant factors for the disease-free survival. The local progression-free survival and overall survival for the corresponding periods were also estimated using the Kaplan–Meier probabilities (Figures 8 and 9). This outcome highlights the elderly nature

Table 3. Prognostic factors on response and regrowth

		Treatment response			Local regrowth			
		<i>n</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
PS	0	66	Ref		0.15	Ref		0.83
	1	73	0.43	0.20–0.95		1.30	0.39–4.29	
	2	41	0.93	0.40–2.13		2.09	0.59–7.35	
	3	7	0.80	0.14–4.46		0.00	0.00	
	Not known	13	1.71	0.51–5.72		1.02	0.11–9.49	
Age group	<70	72	Ref		0.26	Ref		0.46
	70–79	63	0.48	0.22–1.02		1.41	0.41–4.87	
	80–89	57	0.60	0.60–2.78		1.58	0.46–5.46	
	≥90	8	0.00	0.00		4.47	0.71–28.13	
Tumour stage	cT1	21	Ref		0.20	Ref		0.90
	cT2	89	1.23	0.37–4.08		0.59	0.14–2.46	
	cT3	87	2.35	0.73–7.61		0.61	0.15–2.52	
	cT4	3	2.12	0.15–29.66		0.00	0.00	
Nodal stage	Negative	125	Ref		0.59	Ref		0.63
	Positive	74	1.344	0.72–2.62		1.59	0.61–4.12	
	Not known	1	0.00	0.00		0.00	0.00	
Distance from anal verge	<7 cm	144	Ref		0.88	Ref		0.91
	7–11 cm	47	1.07	0.52–2.20		0.46	1.47–0.53	
	>11 cm	2	0.00	0.00		0.00	0.00	
	Not known	7	0.42	0.05–3.59		0.00	0.00	
Tumour size	≤3 cm	107	Ref		0.28	Ref		0.50
	>3 cm	65	1.56	0.79–3.11		0.80	0.29–2.26	
	Not known	28	1.82	0.75–4.45		0.29	0.04–2.36	
Treatment method	Chemoradiation	127	Ref		0.20	Ref		0.50
	EBRT alone	56	0.51	0.24–1.01		1.03	0.34–3.13	
	CBX alone	17	0.64	0.20–2.10		2.26	0.56–9.09	
Papillion total dose	≤90 Gy	162			0.40	Ref		0.20
	>90 Gy	32	0.68	0.28–1.67		2.04	0.68–6.12	

CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy; PS, performance status.

of our patients who also had medical comorbidities, and many died from other causes unrelated to their cancer.

Toxicities

CXB was well-tolerated and no patient had to stop treatment because of gastrointestinal toxicity. Rectal ulceration (Grade 1) developed in 30% of patients after receiving CXB, but this usually healed within 3–6 months. 56 patients (28%) developed bleeding (Grade 1) owing to telangiectasia, and 21 patients (10.5%) needed argon beam therapy (Grade 2) for haemostasis (common toxicity criteria score v4.0).^{13,14} No patients needed colostomy owing to late gastrointestinal toxicity (Grade 3). No deaths were reported related to CXB.

Outcomes

At the end of study period, with a median follow-up of 2.7 years, 161 (80.5%) of 200 patients were alive and free from cancer, including those patients who had salvage surgery (Figure 2). 22 (11%) of the 200 patients had progressive local disease, and 17 (8.5%) developed distant metastases. Organ preservation with no residual tumour was achieved in 124 (62%) of 200 patients. Of the 136 patients who remained alive, 108 (79.4%) were colostomy-free.

DISCUSSION

Our data show that we achieved organ preservation in 124 (62%) of 200 patients, which was much higher than in most other published series.^{3,4} 108 (79.4%) of 136 patients who were alive at the end of our study period were also colostomy-free.

Table 4. Relationship of disease-free survival to prognostic factors

Prognostic factors		n	Disease-free survival at median time of follow up	Univariate analysis			Multivariate analysis		
				HR	95% CI	p	HR	95% CI	p
Performance status	0	66	76%			<0.001			
	1	73	74%	1.21	0.69–2.14				
	2	41	35%	2.73	1.51–4.96				
	3	9	38%	3.79	1.41–10.17				
	Not known	13	77%	0.52	0.19–1.39				
Age group (years)	<70	72	80%			<0.001			<0.001
	70–79	63	75%	1.39	0.075–2.58		1.39	0.75–2.58	
	80–89	57	42%	4.39	2.47–7.80		4.39	2.47–7.80	
	≥90	8	50%	3.15	1.24–8.00		4.15	1.24–8.00	
Tumour stage	cT1	21	70%			0.79			
	cT2	89	72%	1.31	0.62–2.80				
	cT3	87	59%	1.46	0.67–3.17				
	cT4	3	67%	0.97	0.12–7.78				
Nodal stage	Negative	125	69%			0.99			
	Positive	74	62%	1.01	0.63–1.62				
	Not known	1	–	0.00	0.00				
Distant from anal verge	<7 cm	144	68%			0.28			
	7–11 cm	47	59%	1.47	0.92–2.33				
	>11 cm	2	–	1.43	0.20–10.38				
	Not known	7	71%	0.53	0.13–2.17				
Tumour size	≤3 cm	107	72%			0.44			
	>3 cm	65	60%	1.33	0.83–2.13				
	Not known	28	59%	1.29	0.71–2.36				
Treatment modality	RT alone	127	54%			0.002			
	Chemoradiation	56	71%	2.27	1.44–3.56				
	CXB alone	17	71%	1.47	0.69–3.14				
Papillon total dose	≤90 Gy	168	66%			0.70			
	>90 Gy	32	64%	1.11	0.65–1.92				

CXB, contact X-ray brachytherapy; RT, radiotherapy.

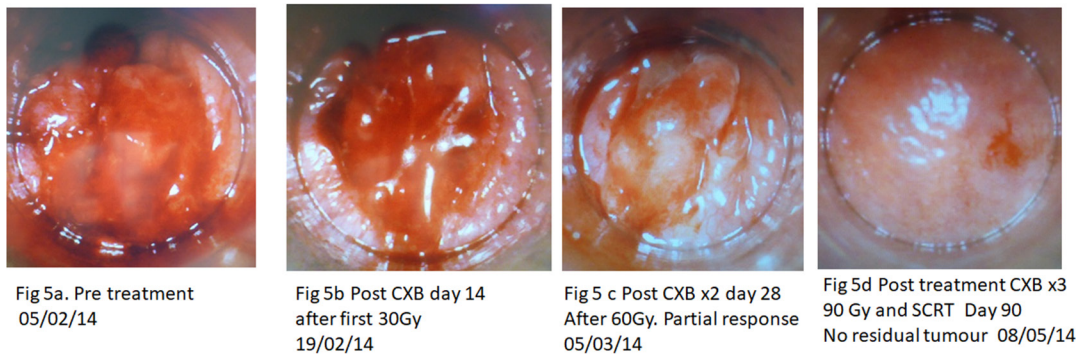
Organ preservation has been achieved with a non-surgical approach using radiation in rectal cancer for many years.¹⁵ Jean Papillon from Lyon advocated the use of non-surgical treatment with CXB for operable rectal cancer in elderly patients, and popularized the radiation technique that bears his name.¹⁵ Papillon treated 312 patients and achieved local control in 91% of cases. His protégé Jean Pierre Gerard continued championing CXB (Papillon) in Lyon and later moved to Nice. He had published many scientific papers including the randomized trial Lyon 96-02.^{16,17} Ben Sischy visited Lyon in the early 70s, and then started a CXB facility in the USA. He was able to replicate both Papillon's and Gerard's results with local control of 95% in

his cohort of 227 patients.¹⁸ Mendenhall et al¹⁹ from Florida also reported their results on patients with rectal cancer treated by CXB. There have also been several publications on its efficacy from the UK.^{6,7} In France, Haute Autorité de Santé has officially recommended CXB for rectal cancer since October 2008,²⁰ and in the UK, National Institute for Health and Care Excellence has recommended CXB for patients with early rectal cancer who are not suitable for surgery since September 2015.²¹

The published evidence suggests that EBRT alone can achieve pathological complete response in about 30–40% of cases if surgery was deferred up to 10 weeks. However, residual disease was still present

Figure 5. Treatment response for early stage malignant polyp. CXB, contact X-ray brachytherapy; .

Case 2 . Endoscopic response for early rectal adenocarcinoma following Papillon and short course radiotherapy



Male, 89 years old retired legal executive diagnosed with low rectal adenocarcinoma. Staging MRI (14.01.14) and CT scan showed 2.3 cm tumour situated at 4.6 cm from anal verge, radiologically staged as cT2 cN0 cM0. APER was suggested but patient was not keen on a stoma and was referred for consideration of CXB. CXB was offered followed by SCRT as the risk of lymph node spread was around 20% . Response to radiotherapy well and the patient achieved cCR which was maintained for 3 years.

in 60–70% of cases.^{22,23} Investigators in a Brazilian study⁴ were one of the first groups to publish the concept of watch and wait in 183 patients who had been treated with EBCRT, and showed 90 (49%) cases achieved cCR. However, at median follow-up of 60 months, 28 (31%) patients developed local regrowth within the first 2 years.⁴ 26 patients had salvage surgery. In total, 70 patients had organ preservation, as some of patients who had surgical salvage had local excision for their recurrences. Therefore, 70 (38%) of 183 patients achieved organ preservation at the end of their treatment. In our study, 124 (62%) of 200 patients achieved organ presentation, which is much higher than that reported by the Brazilian group. Comparable group with our cohort who achieved cCR treated with EBRT alone was reported by Renehan's group which showed local regrowth of 38%.³ To reduce this local regrowth, the authors of a

Danish study used brachytherapy 5 Gy at 10-mm depth to escalate the dose after an initial high dose of 60 Gy EBCRT using intensity modulated radiotherapy with in-field boost technique. Although there was a higher initial response in 40 (78%) of 51 patients, 25.9% of their patients still developed local regrowth within 2 years.²⁴ The Danish group modelled a predictive dose response curve to explain their failure and found that the radiation dose needed to sterilize the tumours (D50) was 92 Gy (95% CI 79–145; Figure 10). This dose is not possible to achieve with EBRT even using modern technology such as stereotactic body radiotherapy.²⁵

One elegant way to improve the dose delivered to the tumour is by CXB, which can be used to escalate the dose up to 90 Gy in addition to the initial EBRT dose of 45 Gy. At each application

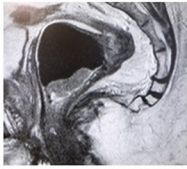
Figure 6. Treatment response for more advanced tumour.

Fig. 6: Showing sustained response to CXB boost for minimal residual tumour following EBCRT

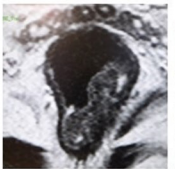
VIGNETTE

Case 1- DW male 67 years rectal adenocarcinoma diagnosed through National Bowel Cancer Screening Programme on 11th July 2011. MRI 21.07.11 showed 45x31x11mm low rectal cancer in left posterior-lateral wall (Fig. 4A, 4B). Radiological stage cT3b cN2 cM0 (TNM). Had neoadjuvant EBCRT completed on 23.09.11. Restaging MRI (4c) showed significant down staging with residual tumour. Recommend APER but refused as the patient was not keen on a permanent stoma. Offered CXB and completed on 01.12.11; achieved cCR maintained for 5 years (11.08.16). Has good quality of life with normal bowel action, no bleeding or pain, not toilet dependant & has good sphincter control. Patient's consent obtained

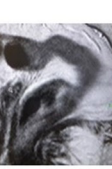
Pre Chemo radiotherapy cT3 cN2 cM0 (21.07.11)




4A- MRI Sagittal view showing tumour




4B- MRI Coronal view Pre treatment



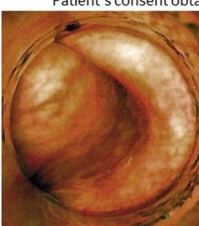
4c- post treatment



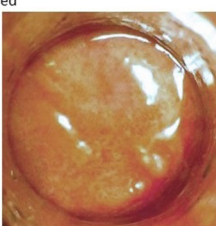
4d. Residual tumour after EBCRT
22.8.11- 26.9.11 Pre CXB boost
Day 0 - (18.10.11) 30Gy



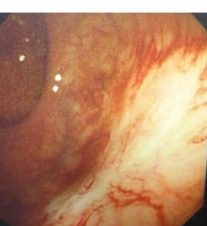
4e. Regression of tumour
Week 2 after 1st CXB
Day 14 - (16.11.11) 30Gy (22mm)



4f. Further regression
Week 4 after 2nd CXB
Day 28 - (01.12.11) 30Gy



4g. Complete regression (cCR)
Week 6 after 3rd CXB
Day 42 - (15.12.11) 20Gy

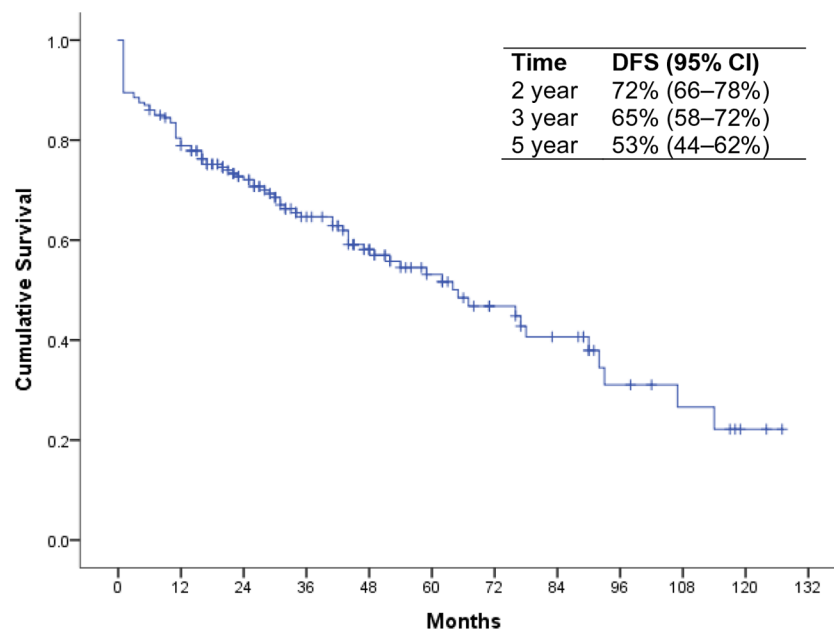


4h. Post treatment scar
24 months 29.08.13
maintained cCR 11.08.16 (5yrs)

Abbreviations: cCR =complete clinical response; CXB= contact X-ray brachytherapy; EBCRT=external beam chemo radiotherapy (long course);APER= Abdominal-perineal excision of rectum.

clinical response

Figure 7. Disease-free survival.



of 30 Gy, every 2 weeks, layer by layer the tumour is shaved off from the top until it reaches its base (at the end of treatment) in responders.²⁶ Although the dose of 90 Gy seems quite high, most of the dose is deposited within a small treatment volume (5 ml) that is applied directly to the tumour. In addition, owing to its low energy (50 kVp) and short focal surface distance, the penetration into the tissues is limited, which spares the normal tissues around the tumour.^{26,27}

The published evidence on the combination of EBRT with CXB in two prospective studies has shown that local regrowth rates can be significantly reduced. Data from a UK study showed reduced local regrowth of 12% at 2 years,²⁸ and data from a French study also predicted a reduction in local regrowth to 11% at 5 years.²⁹ Both series reported similar results to our study (11% local regrowth at 2.7 years). Therefore, we postulate that CXB plays a significant part in reducing the likelihood of local regrowth. The reasoning behind

Figure 8. Local recurrence free survival.

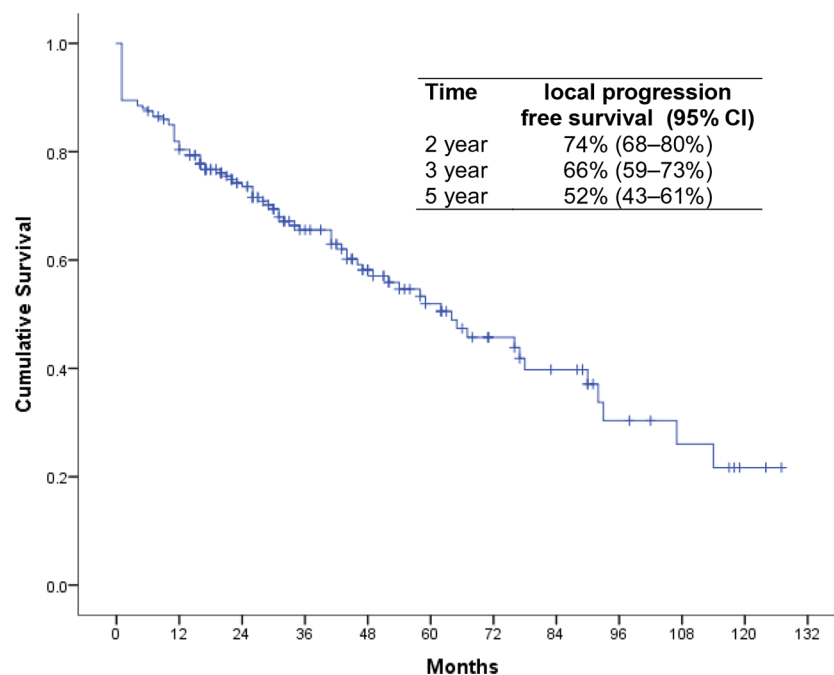
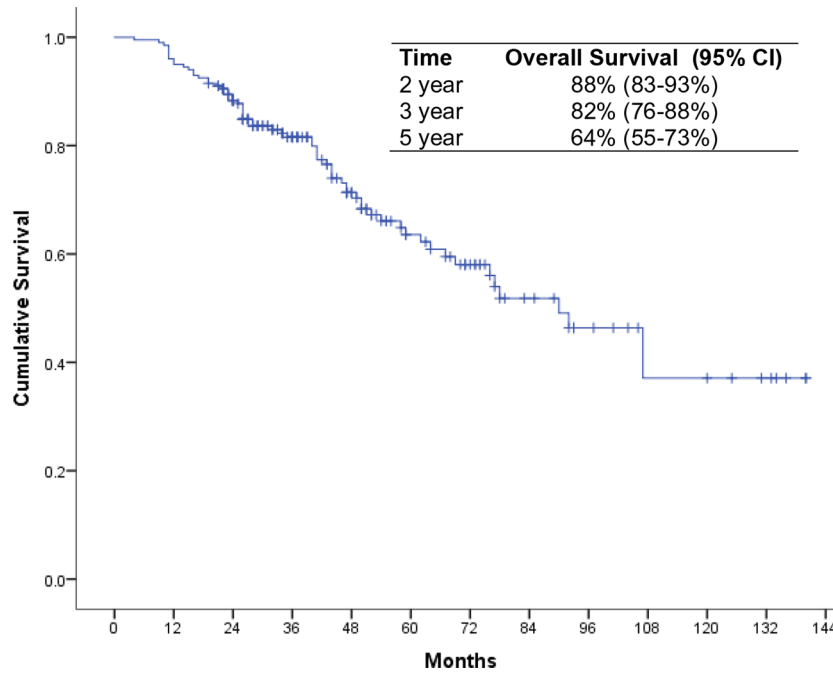


Figure 9. Overall survival.



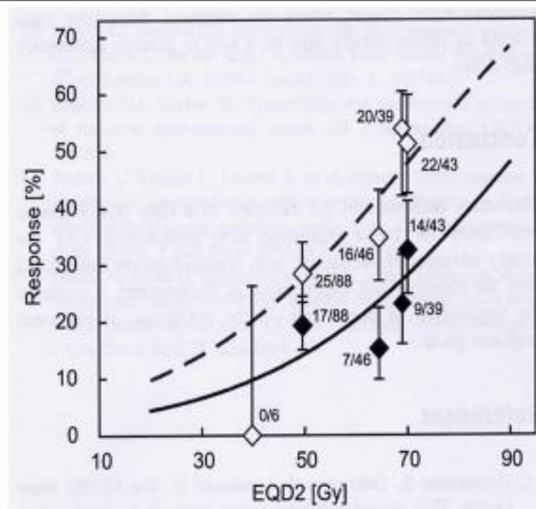
this postulate is that the additional high dose of focused radiation using CXB to a small targeted area enables eradication of residual nests of tumour cells that lie at the base of the tumour beneath the rectal mucosa.²⁷ There was additional evidence to support this hypothesis from a randomized trial (Lyon 96-02), which showed improved clinical (24 vs 2%) and pathological response (57 vs 34%) in favour of a CXB boost in addition to EBRT alone.¹⁶

We accept that there were several limitations to our study. Our study was not randomized and was merely a retrospective audit of

patients who had been treated over many years, with all the drawbacks associated with such a retrospective study. The follow-up period was short, and we do not know the exact number of patients who had EBRT/EBCRT but were not referred to our centre for CXB boost. We hope to address these limitations with the European multicentre prospective randomized trial (OPERA), which is ongoing and which will assess the role of CXB boost in addition to EBCRT. This study is registered with ClinicalTrials.gov, number NCT02505750. Organ preservation at 3 years will be the primary endpoint.³⁰

Figure 10. Radiation dose response model. EBRT, external beam radiotherapy.

Radiation Dose-Response Model (EQD 2)



ypCR (TRG 1)
EBRT + Brachy Ir
D 50% = 92 Gy

95% CI 79-145

A Appelt, S. Bentzen, A. Jakobsen *Int J Rad OBP* 2013 ; 85: 74

CONCLUSION

Our data showed that when CXB was used alone for small rectal cancer or as a boost in combination with EBRT/EBCRT for more advanced rectal tumours, it could reduce local regrowth rates. Therefore, CXB can be considered as a viable treatment option to reduce local regrowth in patients with rectal cancer who are not suitable for salvage surgery or who are fit but refuse surgery because they are stoma averse. This option could improve their chance of organ preservation by avoiding surgical salvage and a stoma.

PREVIOUS PRESENTATION OF DATA

ESTRO 35 Turin (May, 2016) Abstract selected for oral presentation at “Highlights of proffered papers” and oral presentation

at “RCR proffered papers” at NCRI meeting (Liverpool, 2016).

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