Title: Dose escalation using contact x-ray brachytherapy (Papillon) for rectal cancer. Does it improve the chance of organ preservation?

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Short Title: ***Contact X-ray brachytherapy for organ preservation in rectal cancer***

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Dose escalation using contact x-ray brachytherapy (Papillon) for rectal cancer. Does it improve the chance of organ preservation?

Abstract

Objectives

A watch and wait policy for patients with a complete clinical response (cCR) after external beam chemoradiotherapy (EBCRT) for rectal cancer is an attractive option. However, approximately a 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 men. 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 regrowth 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 chemoradiotherapy (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 a 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.

Materials and methods

We identified 200 consecutive patients with operable rectal cancer from our institutional database of 573 patients who had been referred to our centre from January 1, 2003, to December 31, 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 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 due 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.

Seventeen patients presenting with rectal cancers of 3 cm or smaller (cT1 or cN0; mainly adenomas with small focus of cancer) were referred for consideration for CXB upfront because they were not suitable for surgery (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 agreed to CXB after a full explanation that this treatment might not be

curative, and that they may need future salvage 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 by TEMS (transanal endoscopic microsurgery), TART (transanal resection of tumour), or EMR (endoscopic mucosal resection) were also excluded. 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. Sixty-one (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 (cT1 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, Derby, 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) 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 digital rectal examination (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, due 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]

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

Results

Patient characteristics

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

Complete clinical 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).

Incomplete clinical response

Despite the high dose received from CXB, 56 (28%) of 200 patients had an incomplete clinical 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). Sixteen patients did not proceed to surgery due to advanced age and comorbidities, and two other patients refused surgery.

Local regrowth after initial complete clinical 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, three had distant metastases in addition to local regrowth. Ten (77%) of 13 patients with salvageable local and regional regrowth underwent delayed salvage surgery.[12] Importantly, two of the ten 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 due 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 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. Fifty-six patients (28%) developed bleeding (grade 1) due 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 due 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] One hundred and eight (78.6%) out of 136 patients who were alive at the end of our study period were also colostomy-free.

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 popularised 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 contact x-ray brachytherapy (Papillon) in Lyon and later moved to Nice. He had published many scientific papers including the randomised trial Lyon 96-02.[16, 17] Ben Sischy visited Lyon in the early seventies, 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] WM Mendenhall and colleagues from Florida also reported their results on patients with rectal cancer treated by CXB.[19] There have also been several publications on its efficacy from the UK.[6,7] In France, HAS (Haute Autorité de Santé) has officially recommended CXB for rectal cancer since October 2008,[20] and in the UK, NICE (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 in 60–70% of cases.[22, 23] Investigators in a Brazilian study[4] 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 two years.[4] Twenty-six patients had salvage surgery. In total, seventy 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 to 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 (IMRT) 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 sterilise 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 (SBRT).[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 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, due to its low energy (50 kVp) and short focal surface distance (FSD), 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 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 randomised 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 randomised 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 randomised trial (OPERA), which is on-going 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]

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.

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Table and Figure legends

Table 1 Inclusion and exclusion criteria for CXB

Table 2 Patient characteristics

Table 3 Prognostic factors related to treatment response and local regrowth

Table 4 Prognostic factors related to disease-free survival

Figure 1 Treatment algorithm

Figure 2 Patient care pathway

Figure 3 Contact x-ray brachytherapy treatment position

Figure 4 Contact x-ray treatment schematic diagram

Figure 5 Treatment response for early stage malignant polyp

Figure 6 Treatment response for more advanced tumour

Figure 7 Disease-free survival

Figure 8 Local recurrence free survival

Figure 9 Overall survival

Figure 10 Radiation dose response model

Table 1

Inclusion criteria for CXB

1. Histologically proven rectal cancer.
2. Well to moderately well differentiated adenocarcinoma.
3. Stage T1-3 mobile tumour less than 3cm 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.

Table 2: Baseline characteristics

		N	%
Age in years, median (range)		74 (32–94)	..
Sex	Women	66	33.0%
	Men	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	$\leq$3 cm	107	53.5%
	>3 cm	65	32.5%
	Not recorded	28	14.0%

Table 3: Prognostic factors on response and regrowth

			Treatment response			
		N	HR	95% CI	p	
PS	0	66	Ref		0.15	
	1	73	0.43	0.20–0.95		1
	2	41	0.93	0.40–2.13		2
	3	7	0.80	0.14–4.46		0
	Not known	13	1.71	0.51–5.72		1
Age group	<70	72	Ref		0.26	
	70–79	63	0.48	0.22–1.02		1
	80–89	57	0.60	0.60–2.78		1
	≥90	8	0.00	0.00		4
Tumour stage	cT1	21	Ref		0.20	
	cT2	89	1.23	0.37–4.08		0
	cT3	87	2.35	0.73–7.61		0
	cT4	3	2.12	0.15–29.66		0
Nodal stage	Negative	125	Ref		0.59	
	Positive	74	1.344	0.72–2.62		1
	Not known	1	0.00	0.00		0
Distance from anal verge	<7 cm	144	Ref		0.88	
	7–11 cm	47	1.07	0.52–2.20		0
	>11 cm	2	0.00	0.00		0
	Not known	7	0.42	0.05–3.59		0
Tumour size	≤ 3 cm	107	Ref		0.28	
	>3 cm	65	1.56	0.79–3.11		0
	Not known	28	1.82	0.75–4.45		0
Treatment method	Chemoradiation	127	Ref		0.20	
	EBRT alone	56	0.51	0.24–1.01		1
	CBX alone	17	0.64	0.20–2.10		2
Papillion total dose	≤90 Gy	162			0.40	
	>90 Gy	32	0.68	0.28–1.67		2

PS=performance status.; EBRT= external beam radiotherapy; CXB=contact x-ray brachytherapy.

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	0075-2.58		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	≤3cm	107	72%			0.44			
	>3cm	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			
	Chemo-radiation	56	71%	2.27	1.44-3.56				
	CXB alone	17	71%	1.47	0.69-3.14				
Papillion total dose	≤90 Gy	168	66%			0.70			
	>90 Gy	32	64%	1.11	0.65-1.92				

Figure 1

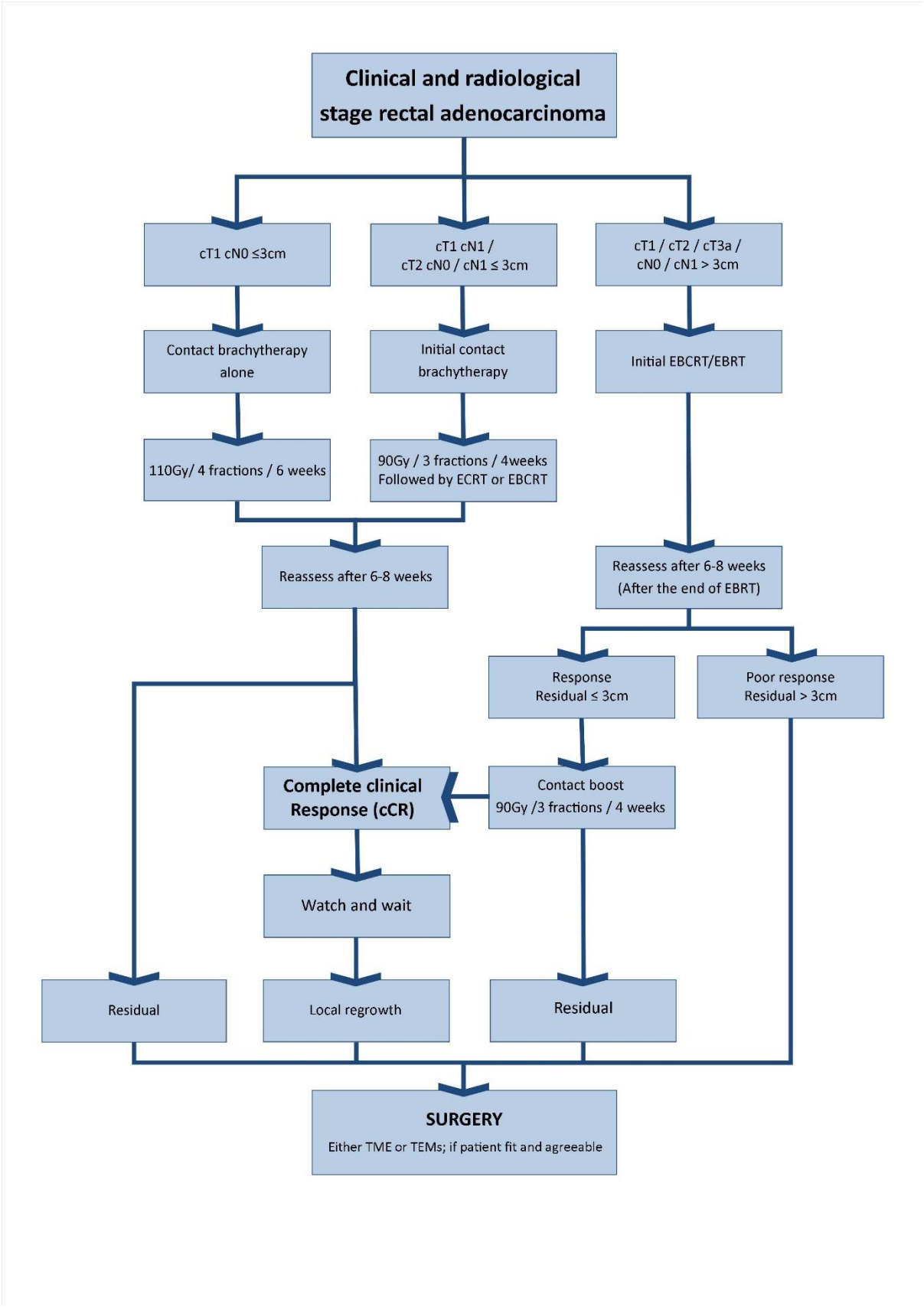

Clinical and radiological stage rectal adenocarcinoma
cT1 cN0 ≤3cm
cT1 cN1 / cT2 cN0 / cN1 ≤ 3cm
cT1 / cT2 / cT3a / cN0 / cN1 > 3cm
Contact brachytherapy alone
Initial contact brachytherapy
Initial EBCRT/EBRT
110Gy/ 4 fractions / 6 weeks
90Gy / 3 fractions / 4weeks Followed by ECRT or EBCRT
Reassess after 6-8 weeks
Reassess after 6-8 weeks (After the end of EBRT)
Response Residual ≤ 3cm
Poor response Residual > 3cm
Complete clinical Response (cCR)
Contact boost 90Gy /3 fractions / 4 weeks
Watch and wait
Residual
Local regrowth
Residual
SURGERY
Either TME or TEMs; if patient fit and agreeable

Figure 2

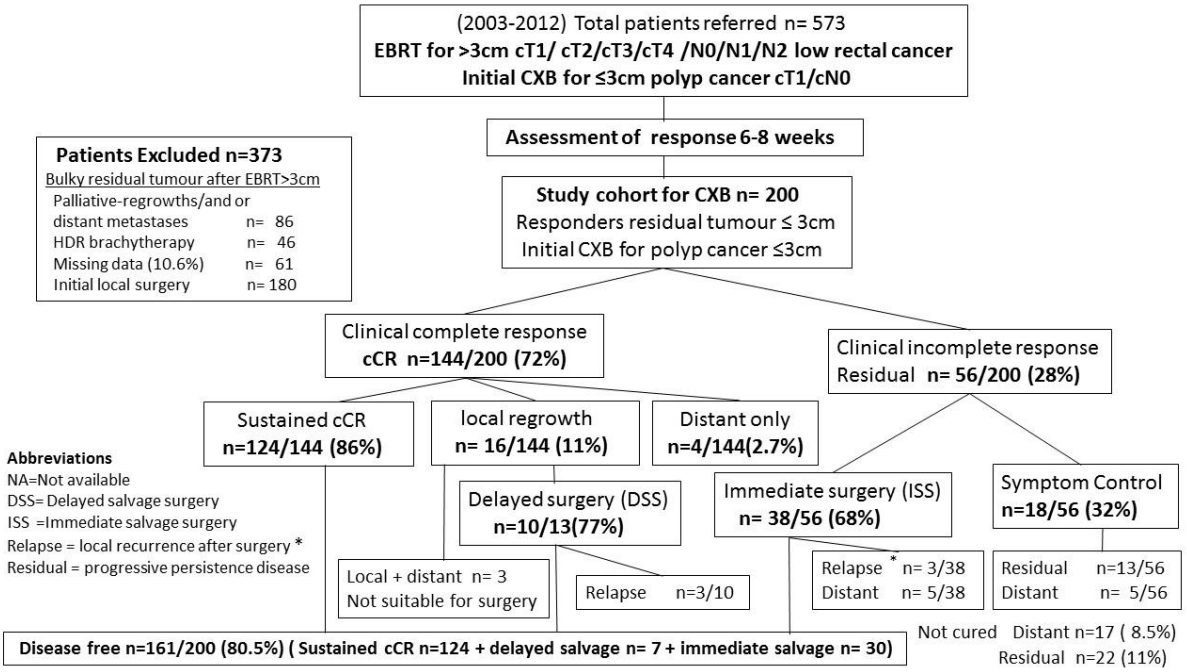

(2003-2012) Total patients referred n= 573
EBRT for >3cm cT1/ cT2/cT3/cT4 /N0/N1/N2 low rectal cancer
Initial CXB for ≤3cm polyp cancer cT1/cN0
Assessment of response 6-8 weeks
Patients Excluded n=373
Bulky residual tumour after EBRT>3cm
Palliative-regrowths/and or distant metastases n= 86
HDR brachytherapy n= 46
Missing data (10.6%) n= 61
Initial local surgery n= 180
Study cohort for CXB n= 200
Responders residual tumour ≤ 3cm
Initial CXB for polyp cancer ≤3cm
Clinical complete response
cCR n=144/200 (72%)
Clinical incomplete response
Residual n= 56/200 (28%)
Sustained cCR
n=124/144 (86%)
local regrowth
n= 16/144 (11%)
Distant only
n=4/144(2.7%)
Abbreviations
NA=Not available
DSS= Delayed salvage surgery
ISS =Immediate salvage surgery
Relapse = local recurrence after surgery *
Residual = progressive persistence disease
Delayed surgery (DSS)
n=10/13(77%)
Immediate surgery (ISS)
n= 38/56 (68%)
Symptom Control
n=18/56 (32%)
Local + distant n= 3
Not suitable for surgery
Relapse n=3/10
Relapse * n= 3/38
Distant n= 5/38
Residual n=13/56
Distant n= 5/56
Disease free n=161/200 (80.5%) (Sustained cCR n=124 + delayed salvage n= 7 + immediate salvage n= 30)
Not cured Distant n=17 (8.5%)
Residual n=22 (11%)

Figure 3

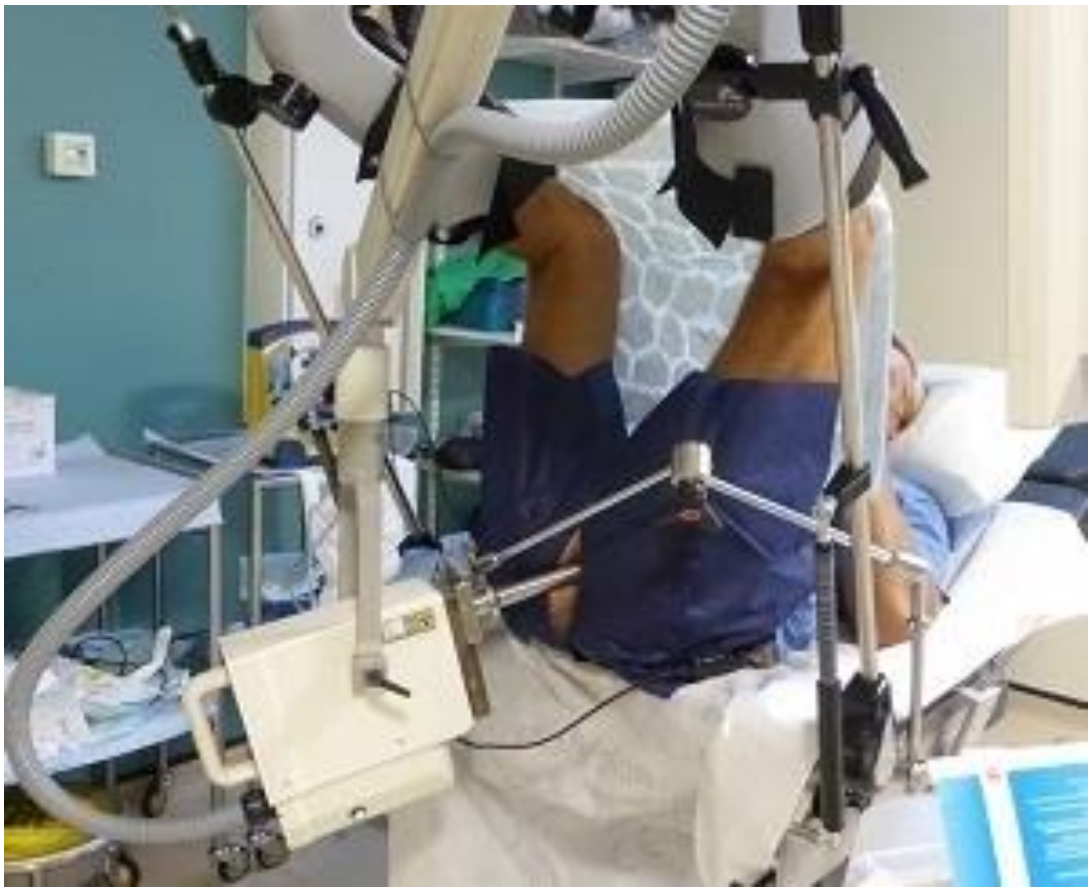


Figure 4

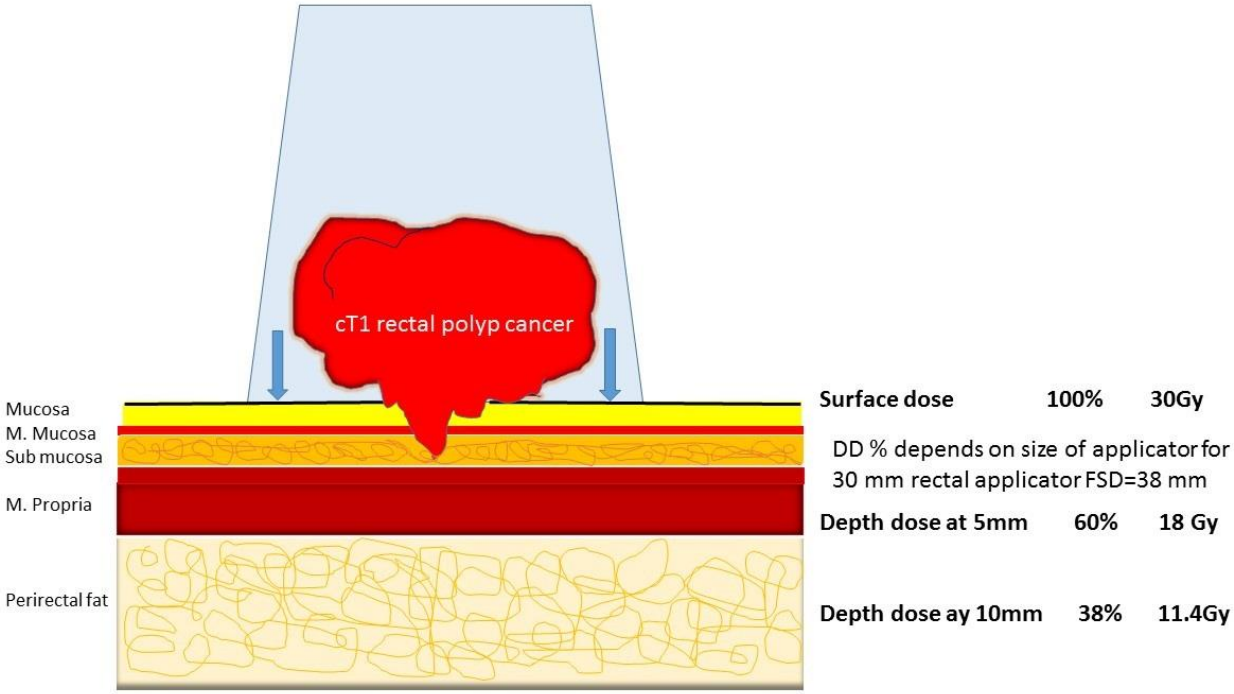

cT1 rectal polyp cancer
Mucosa
M. Mucosa
Sub mucosa
M. Propria
Perirectal fat
Surface dose 100% 30Gy
DD % depends on size of applicator for
30 mm rectal applicator FSD=38 mm
Depth dose at 5mm 60% 18 Gy
Depth dose ay 10mm 38% 11.4Gy

Figure 5

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

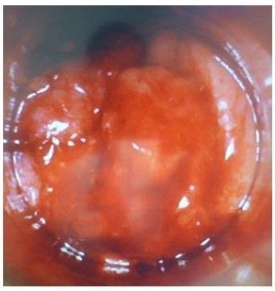


Fig 5a. Pre treatment
05/02/14

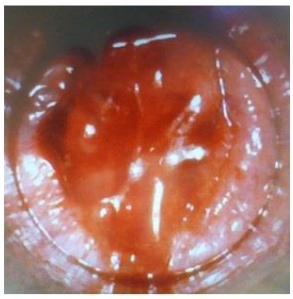


Fig 5b Post CXB day 14
after first 30Gy
19/02/14

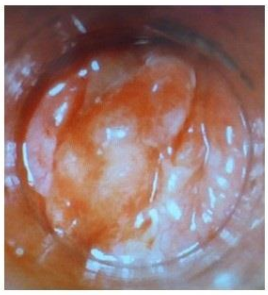


Fig 5 c Post CXB x2 day 28
After 60Gy. Partial response
05/03/14

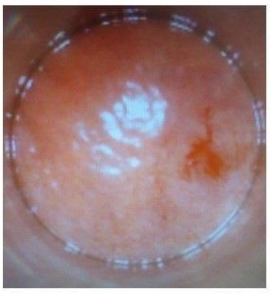
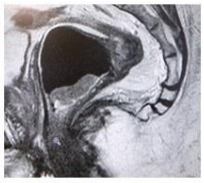


Fig 5d Post treatment CXB x3
90 Gy and SCRT Day 90
No residual tumour 08/05/14

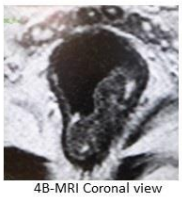
Male, 89 years old retired legal executive diagnosed with low rectal adenocarcinoma. Staging MRI (14.01.14) and CT scan showed 2.3 cm tumour situated at 4.6 cm from anal verge, radiologically staged as cT2 cN0 cM0. APER was suggested but patient was not keen on a stoma and was referred for consideration 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.

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

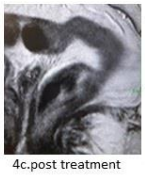
Pre Chemo radiotherapy cT3 cN2 cM0 (21.07.11)



4A- MRI Sagittal view showing tumour



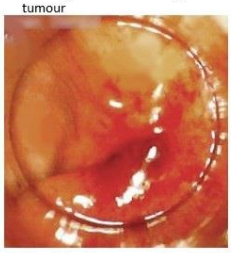
4B-MRI Coronal view Pre treatment



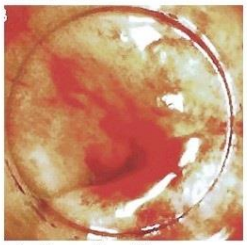
4c.post treatment

VIGNETTE

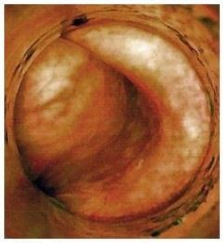
Case 1- DW male 67 years rectal adenocarcinoma diagnosed through National Bowel Cancer Screening Programme on 11th July 2011. MRI 21.07.11 showed 45x31x11mm low rectal cancer in left posterior-lateral wall (Fig. 4A ,4B). Radiological stage cT3b cN2 cM0 (TNM). Had neoadjuvant EBCRT completed on 23.09.11. 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



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

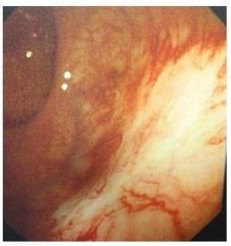


4e.Regression of tumour
Week 2 after 1st CXB
Day 14 -(16.11.11) 30Gy (22mm)



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

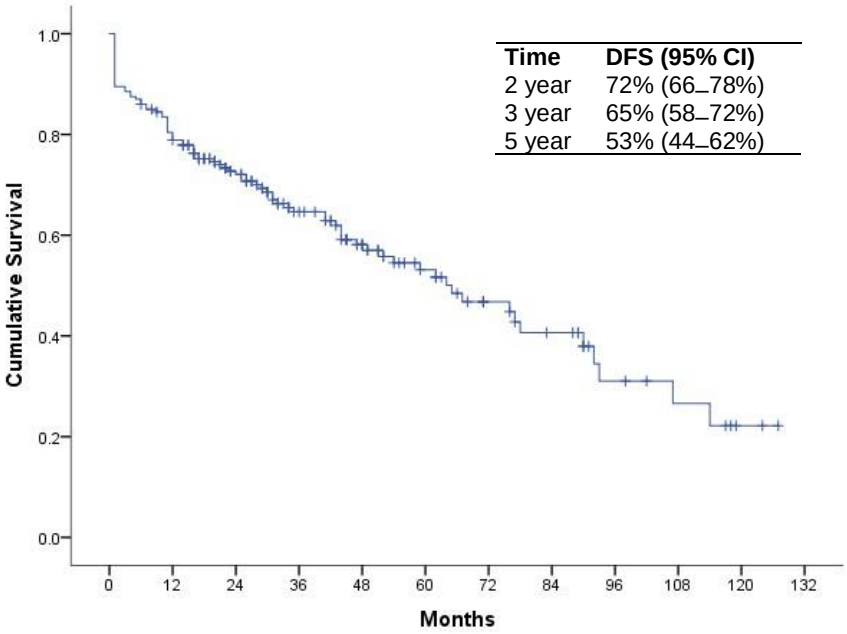
4g.Complete regression (cCR)
Week 6 after 3rdCXB
Day 42-(15.12.11) 20Gy



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

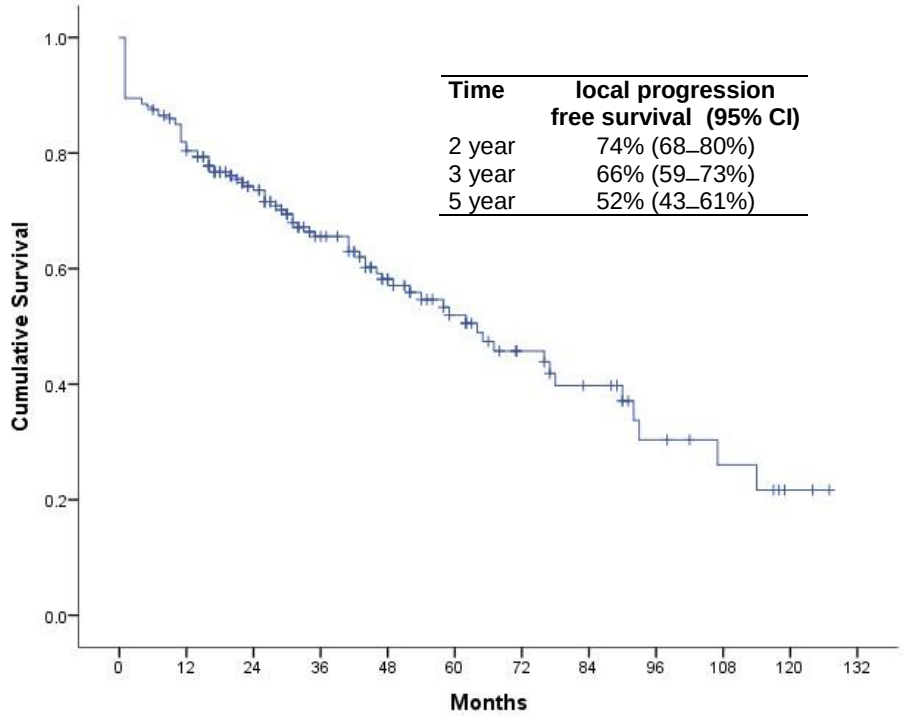
Abbreviations: cCR =complete clinical response; CXB= contact X-ray brachytherapy; EBCRT=external beam chemo radiotherapy (long course);APER= Abdominal-perineal excision of rectum.

Figure 7



Time	DFS (95% CI)
2 year	72% (66–78%)
3 year	65% (58–72%)
5 year	53% (44–62%)

Figure 8



Time	local progression free survival (95% CI)
2 year	74% (68–80%)
3 year	66% (59–73%)
5 year	52% (43–61%)

Figure 9

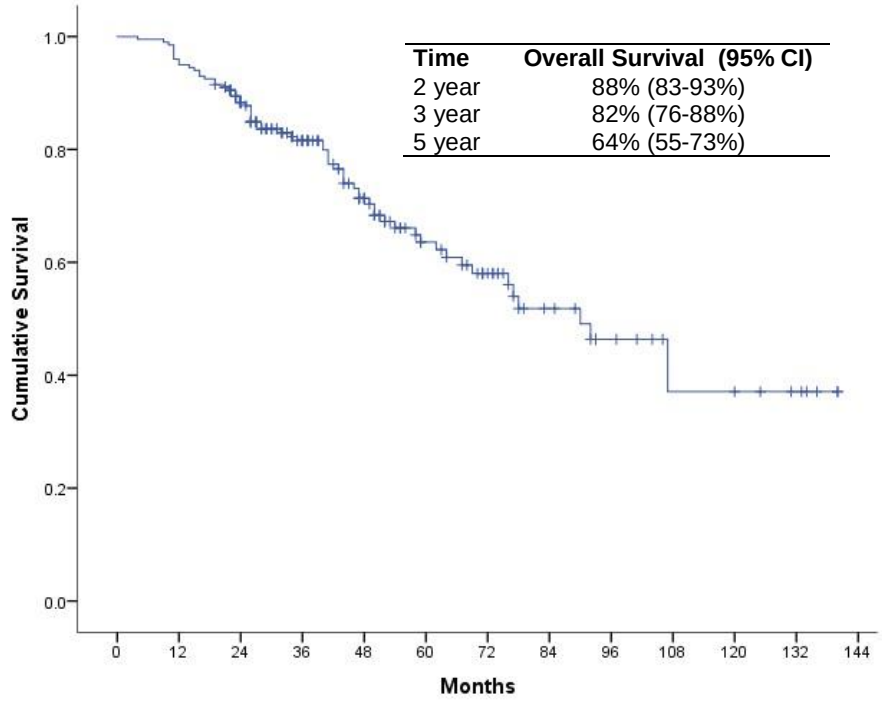

Time
Overall Survival (95% CI)
2 year
88% (83-93%)
3 year
82% (76-88%)
5 year
64% (55-73%)
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
132
144
Months

Figure 10

95% CI 79-145