Title: Dose escalation using contact X-ray brachytherapy (CXB) following external beam radiotherapy as non-surgical treatment option for rectal cancer: outcomes from a single centre experience.

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Summary

This study reviewed outcomes from 83 rectal cancer patients treated with CXB boost for residual tumour ≤ 3cm following EBRT. Fifty three (63.8%) patients achieved cCR. Local regrowth after cCR was low at 11.3%. All patients had successful salvage surgery. At median follow-up of 2.5 years, 63 (83.1%) patients were cancer free. This approach may provide a non-surgical treatment option to reduce local regrowth after EBCRT in patients not suitable or wish to avoid surgery.

Abstract

Purpose

To review the outcomes of rectal cancer patients treated with a non-surgical approach using contact X-ray brachytherapy (CXB) when there was suspicious residual disease (≤3 cm) following external beam chemoradiotherapy/radiotherapy (EBCRT/EBRT).

Methods and materials

Outcome data for rectal cancer patients referred to our institution from 2003 to 2012 were retrieved from an institutional database. These patients were referred after initial local multidisciplinary team discussion either because they were not suitable for or refused surgery. All selected patients had a CXB boost following EBCRT/EBRT. Most patients received a total of 90Gy CXB delivered in three fractions over 4 weeks.

Results

The median follow up was 2.5 years (range 1.2-8.3 years). Of 345 consecutive patients with rectal cancer who were referred to us, 83 patients with suspicious residual disease (≤3 cm) after EBCRT/EBRT were identified for CXB boost. Median age was 72 years (range 36–87) and 58 (69.9%) were males. Initial tumor stages were cT2 (n=28), cT3 (n=55) and 54.2% were node positive. Complete clinical response (cCR) was achieved in 53 (63.8%) patients after the CXB boost following EBCRT/EBRT. Seven (13.2%) of these 53 patients relapsed after achieving cCR and the six patients (11.6%) who had non-metastatic regrowth had salvage surgery (100%). At the end of the study period, 69 (83.1%) out of 83 patients were cancer free.

Conclusions

Our data suggest that a CXB boost in selected patients with suspicious residual disease (≤3 cm) following EBCRT/EBRT can be offered as an alternative to radical surgery. In our series patients with a sustained cCR had a low rate of local regrowth and those with non-metastatic regrowth could be salvaged successfully. This approach could provide an alternative treatment option for elderly or comorbid patients who are not suitable for surgery, or those with rectal cancer who wish to avoid surgery.

Introduction

Although a decade ago, non-operative management of rectal cancer with complete clinical response to neo-adjuvant chemoradiation seemed anathema, it is now gaining acceptance (1–5). This approach is relevant for individuals where the potential risks of surgery outweigh the benefits, in elderly comorbid patients with rectal cancers, which are increasing as a proportion of all cancers diagnosed due to national bowel cancer screening programmes (6, 7). With conventional external beam chemoradiotherapy (EBCRT) regimens, the true level of complete pathological response is low, occurring in approximately 10–30% of patients who received fluoropyrimidine with radiation (8–10). In addition, published data have shown that around 15–40% of initial complete responders (cCR) will regrow locally and will require surgical salvage for cure (8–10). Therefore, there is a need to increase complete response rates, and reduce local regrowth to enable more patients to benefit from the watch and wait approach after EBCRT.

At our centre we have adopted the strategy of offering patients escalated doses of radiation delivered directly onto the tumor site in an effort to increase the clinical complete response (cCR) rate by using a contact X-ray brachytherapy (CXB) boost. The advantage of this approach is that it can deliver up to additional 90 Gy of radiation with minimal collateral damage to the surrounding normal tissues (11). In this paper, we describe the treatment outcomes of this approach from our centre.

Methods and materials

Patient selection

Eighty three patients were identified from a prospectively maintained institutional database of 345 consecutive patients with rectal cancer who were referred to our centre for CXB between January, 2003, and November, 2012. No ethics approval was necessary for this retrospective audit because CXB has been used since 1993 and is not regarded as an experimental treatment at our institution. However, approval from our regional audit committee was obtained for this retrospective audit (approval number xxx).

Histological diagnosis of adenocarcinoma was confirmed in all patients prior to treatment. Baseline pre-treatment assessment included endoscopy, digital rectal examination (DRE), MRI, computed tomography of chest, abdomen and pelvis, and endorectal ultrasound (if MRI was not possible due to cardiac pacemaker) undertaken at the patients' local referring hospitals. Initial local T and N staging using TNM (AJCC/UICC.v7) was determined by MRI in 87.9% of patients (Table 1). Patients agreed to receive treatment after informed consent and counselling. All patients were fully aware that we did not treat all of those who were referred, that we only selected suitable individuals for CXB boost, that curative treatment might not be possible, and that if there was a residual disease or local regrowth at a later date, salvage surgery might be feasible provided they did not have distant metastases, and that they were fit and agreeable for surgery.

Inclusion and exclusion criteria

We include patients with persistent abnormality suspicious of residual cancer either endoscopically, on DRE or radiologically which was $\leq$ 3cm following EBCRT or EBRT for

consideration of CXB boost in those patients who were not suitable for surgery or refuse surgery. Individuals who achieved a true clinical complete response (cCR) after EBRT or EBCRT were excluded from our present study as this group comprised individuals where there was no mucosal abnormality to be seen or felt and hence no target at which to direct the CXB boost. Some of those who were referred for consideration of CXB boost had a bulkier residual tumor (>3 cm) or a tumor that involved half the rectal circumference (poor responders to EBRT/EBCRT). They were offered HDR endoluminal brachytherapy using a rectal applicator (Elekta, Stockholm, Sweden) and were also excluded from our study (n=46). Patients who had metastatic disease or tumors with regrowth following EBRT/EBCRT were treated palliatively (n=86) and were excluded from this analysis. Patients with cT1 tumors who received CXB alone (n=17) and both cT1 or cT2/cN0 tumors that were mainly adenomas with a small focus of cancer ≤3 cm who received CXB prior to EBRT (n=26) and all other cT1 and cT4 patients (n=6) were excluded from our study. In addition, all patients who received CXB within 4 weeks of completing EBCRT/EBRT (n=26) were also excluded from our study in order to improve the homogeneity of our cohort (Figure 1). Patients with missing data (n=61) were also excluded.

External beam radiation dose and schedule

EBCRT consisted of 45 Gy in 25 fractions over 35 days with concurrent chemotherapy using either 5-fluorouracil infusion 1 g/m^2 day from day 1–4 in week one and five, or in later period of our study, chemotherapy was changed to oral capecitabine 825 mg/m^2 twice a day (Monday–Friday) throughout radiotherapy (n=71). A small number of patients who were not suitable for chemotherapy (due to poor renal function) were treated with radiation (EBRT) alone (n=12). Patients were assessed at 4–6 weeks after EBRT/EBCRT in the earlier time period of this study

but more recently the practice in the UK have changed to assessing patients a little later at 6-8 weeks. This time point is in line with most international watch and wait protocols (10). All patients were discussed again at their local colorectal multidisciplinary team (MDT) meeting after their assessment. This included endoscopy, DRE, and restaging MRI scans to evaluate their response at their local colorectal units. The interval between EBRT/EBCRT and CXB varied, as patients were treated by EBRT/EBCRT at their local cancer units and were subsequently referred to our specialist cancer centre for consideration of CXB. In most cases the interval was within 4-6 weeks during the earlier period of our study and in the later stages it was at 6-8 weeks, with a median of 39 days (range 28–174 days).

Contact X-ray brachytherapy set up, dose, schedule, and rationale

CXB was delivered using a 50 kVp Therapax (Gulmay, UK) machine between 2003 and 2009, and after 2009 by Papillon 50 (Ariane, Derby, UK; Figure 2). The comparison between these two machines (12) and the CXB treatment protocol used in this study have previously been described (13–16). CXB was administered on an outpatient basis every 2 weeks. At each visit 30 Gy of 50 kVp X-rays (HVL 0.64 Al, 2.7 mA) was delivered through a rectal treatment applicator (size 30, 25, or 22 mm) at a focal source surface distance (FSD) of 29, 32, or 38 mm (depending on applicator size chosen). Radiation was targeted straight onto the tumor with a 5-mm margin under direct vision (Figure 2). Most patients received a total of 90 Gy (surface dose) delivered in three fractions (day 0, 14, and 28) over 4 weeks.

Response assessment and surveillance protocol

The most intensive monitoring occurred within the first 2 years when the risk of tumor recurrence was highest. Patients were seen every 3 months for digital rectal exam (DRE) and

sigmoidoscopy. MRI scans were done 4–6 monthly, and computed tomography of chest, abdomen, and pelvis was undertaken at 12, 24, and 36 months. A clinical complete response (cCR) was defined according to the published criteria as a complete absence of palpable, endoscopic or radiological evidence of residual tumor (17). Importantly, the time-point used to establish a true clinical incomplete response was 6 months after the last CXB dose, since in our experience further regression of tumor is not usually observed beyond this time. If a suspicious mucosal abnormality progressed endoscopically, or if induration was felt on DRE, or suspicious changes were observed on MRI then patients were referred for immediate salvage surgery (ISS) provided they were agreeable and fit for treatment (18). Less importance was given to isolated subtle abnormalities on MRI scan or mucosal abnormalities on endoscopy that did not change over time (19). These were regarded as static disease and kept under review with regular endoscopic and radiological assessments at 3 monthly intervals.

All patients who remained on the so-called "watch-and-wait" pathway after 6 months were reassessed as described above every 3 months for the first 2 years. If any active regrowth of tumor was suspected or detected after an initial cCR, the patient was restaged and offered delayed surgical salvage (DSS), provided no inoperable distant metastases were detected, that they were fit and agreeable for surgery (Figure 1). Throughout the disease-monitoring process, clinicians were encouraged not to biopsy the scar if no obvious cancer remained, due to the known low negative predictive value of negative histology (19, 20). When cCR was maintained, the frequency of assessment was reduced to every 6 months in year 3, and every year thereafter for up to 5 years**.**

Data integrity and statistical analysis

Since our data were retrospective and had been accrued over many years, an external independent validator was commissioned to ensure its accuracy and integrity. This process indicated that 94% of initial data entries were accurate. All identified inaccuracies were corrected. The data were analysed using SPSS Version 21 (IBM, Portsmouth, UK). The objective of our paper was to report the outcomes of CXB as a boost following EBCRT or EBRT. We choose our main end point as local regrowth in those who had achieved cCR following CXB after EBCRT or EBRT. Furthermore, disease-free survival (DFS) was estimated using the Kaplan-Meier survival methodology (Figure 3). Univariate and multivariate analyses using logistic regression were used to identify possible clinical factors associated with treatment response and local regrowth (Table 2).

Results

Study group and demographics

Our institutional database identified 83 patients that fulfilled our inclusion and exclusion criteria. The baseline demographics of the study group are shown in Table 1, and their outcomes are shown in Figure 1.

Clinical complete response (cCR)

A cCR after CXB boost in patients with suspicious residual disease following EBCRT/EBRT was observed in 53 patients (63.8%). Univariate logistic regression analysis showed that attainment of cCR was not related to pre-treatment performance status (P=0.62), age (P=0.74), cT stage (P=0.31), size of tumour (0.27), CXB dose (P=0.82), or external beam treatment modality with or without chemotherapy (P=0.56). Importantly, cCR was also not related to pre-treatment clinical nodal status (P=0.10).

Clinical incomplete response

Thirty patients (36.1%) had a clinical incomplete response 6 months after the last dose of CXB. Twenty-two (73.3%) patients from this group subsequently underwent surgery as it was presumed that they had residual cancer. Interestingly 5 (22.7 %) of these patients actually had no residual tumour with pathological stage of ypT0. Eight patients did not proceed to immediate salvage surgery (ISS) mainly because of advanced age and comorbidities, however, two patients chose not to undergo surgery.

Local regrowth after initial complete clinical response

At the study cut-off date, seven (13.2%) patients out of 53 patients who achieved initial cCR after CXB boost following EBRT developed either local regrowth or distant relapse. Therefore, 46 (86.7%) of the 53 patients who achieved cCR had a sustained complete clinical response.

The median time for relapse was 16 months (range 4.0–113). Univariate analysis showed that tumour regrowth was not associated with pre-treatment performance status (P=0.99), age (P=0.69), cT stage (P=0.81), cN stage (P=0.98), original tumour size (P=0.75), treatment modality (P=0.10), or CXB dose (P=0.25; Table 2).

Management of local regrowth

Of the seven patients (13.2%) who developed tumor regrowth after an initial documented cCR, one (1.8%) had distant metastases only. Only 4 patients (7.5%) had local regrowth only and two (3.7%) patients had regional nodal regrowth in addition to their local regrowth. All six patients with potentially salvageable non metastatic local regrowth (100%), underwent delayed salvage surgery (DSS). Interestingly, one (16%) out of the six had no pathological evidence of residual tumor (ypT0).

Distant metastases

In total, 7 (13.2%) patients developed distant metastases. This included one patient after achieving cCR and another two who developed distant metastases after immediate salvage surgery (ISS) for residual disease. Two patients relapsed with distant metastases after delayed salvage surgery (DSS) for local regrowth. Two patients who had persistent tumour in the initial incomplete responder group also developed distant metastases in addition to their local disease (Figure 1). Of those who developed distant metastases, three had a metastectomy and the others received palliative treatments.

Disease-free survival

The Kaplan-Meier probabilities of disease-free survival for the whole group were 70% (95% CI 60–80) at 2 years, 59% (95% CI 47–71) at 3 years, and 46% at (95% CI 31–61) at 5 years (Figure 3). This outcome mainly reflects the elderly nature of this population who also had medical comorbidities and in many cases died from causes unrelated to cancer.

Toxicities and adverse effects of therapy

No patient had to stop CXB because of gastrointestinal toxicity. Rectal ulceration (grade 1) developed in 30% of cases following CXB, but this usually healed within 3-6 months. Twenty three patients (28%) developed bleeding (grade 1) due to telangiectasia, and five (6 %) of the 83 patients needed argon beam therapy (grade 2) for haemostasis (Common Toxicity Criteria Score v 4.0) (21, 22). No patients needed a colostomy due to late gastrointestinal toxicity (grade 3). No deaths were reported related to CXB.

Disease status

At the end of our study period with median follow up of 2.5 years, 69 (83.1 %) of 83 patients were free from cancer; this includes those who had salvage surgical treatment (Figure 1). Sixteen of the 27 patients who died (60 %) had no documented evidence of residual or recurrent cancer, and they died of other causes.

Discussion

Our study constitutes a retrospective analysis of patients from a single institution who underwent non-operative watch-and-wait management for rectal cancer. We acknowledge that there are limitations, uncertainties and a potential selection bias in our data which could skew the initial clinical complete response rate. The difference between this series and the majority of other published series is that all patients received an additional boost of CXB in an attempt to treat any remaining cancer cells that persisted after EBCRT or EBRT with the aim to reduce local regrowth. A further important difference is that the patients included did not have a classical clinical complete response because by definition this would mean nothing visible on the mucosa or on MRI scan and nothing to feel which in this situation is not possible to target CXB. All the patients in our series had a residual mucosal abnormality which meant that they did not have a classical clinical complete response following EBCRT/EBRT. Despite our patients all having an 'clinical incomplete response' following EBCRT/EBRT, we found that after CXB, further 63.8% went on to achieved a classical clinical complete response with no mucosa abnormalities suspicious of residual disease. Of those who achieved cCR after CXB boost, only11% developed a local regrowth and this in turn was salvageable in all 6 non metastatic patients.

Although CXB has been in clinical use for over 80 years, it has not been regarded by many clinicians as a standard of care in Europe (23–27) or in the USA (28, 29). Its use has been restricted to only a few specialist centres due to decommissioning of the Phillips RT50 machine in the 1970s. However, there has since been a revival of interest in CXB with the availability of the Papillon 50 machine (Ariane, Alfreton, UK) and now there are 15 centres in Europe offering CXB for rectal cancer in suitable cases (14). We find that our referrals constitute mostly elderly patients and those that are either unsuitable for surgery or refused surgery. We

are also finding increasing numbers of young and fit patients who wish to explore alternative options to radical surgery because of its side effect profile and the likelihood of a stoma.

As the population is ageing and more patients are been diagnosed with rectal cancer through national bowel cancer screening programmes, the number of patients with rectal cancer who are suitable and likely to benefit from CXB will increase. Therefore, we need a plan to expand the number of centres offering CXB to meet this growing demand in the future.

A Brazilian research group was one of the first to report the results of a watch-and-wait policy for rectal cancer (10). They reported 183 patients who were treated with intensified chemoradiotherapy (54 Gy in 28 fractions over 38 days) followed by four cycles of chemotherapy and achieved a high (49%) cCR. However, 31% of these patients who achieved cCR later developed local regrowth requiring surgical salvage (Table 3). The most comparable group to our cohort was reported in the OnCoRe study. The geographic coverage of the patients referred to our centre were similar to those patients in the OnCoRe study. The patients in the OnCoRe study were those who achieved cCR and were not referred to our centre for CXB boost. However, 38% of the 129 patients who just had watch and wait following EBRT needed surgical salvage for local regrowth. Meta-analysis of watch and wait trials recently published showed lower local regrowths of 15% at a short follow up of 2 years (30). However, the majority of patients in the studies reviewed had much earlier stage rectal cancer unlike patients in the OnCoRe and our study which included much more advanced staged cancer (70% and 66.3% T3, respectively) patients with longer follow up of 33 and 29 months, respectively. In our series, despite including a heterogeneous group of patients, many of whom were elderly with locally advanced disease, six (11%) developed loco regional regrowth, of whom 4 (7.5%) had local regrowth only after a median follow up of 2.5 years following an initial cCR. Our data, therefore, appear to be very favourable when compared to other published series of non-

operative management involving standard neoadjuvant protocols using 50 Gy in 25 fractions over 5 weeks with fluoropyrimidine, where approximately 15-40% of patients developed local tumor regrowth (8–10).

There are several possible reasons for the high levels of sustained cCR observed in our study (Table 3). We believe that dose escalation with CXB boost is an important contributing factor (11). The advantage is that any viable tumor cells beneath the surface of the residual mucosal abnormality (which is usually ≤20 mm) receive a further very high, yet localized, dose of targeted radiotherapy that sterilizes them. The tumor was shaved off layer-by-layer at each fortnightly application until the tumor had regressed to its base. The total dose of 90 Gy seems quite high, but most of this dose was delivered directly onto the tumor, using low-energy X-rays with limited range of penetration, so the surrounding normal tissues including those at a depth received very little of this radiation dose, thus reducing collateral damage which minimised the side effects (15,16).

The randomized trial Lyon 96-02 provided supportive evidence for improved clinical (24% vs 2%) and pathological response (57% vs 34%) in favour of CXB boost in addition to EBRT for more advanced bulky stage T2 and T3 rectal cancers (27). More recently, histological data following EBRT for earlier staged cT1, cT2, and cT3a tumors have been reported from two independent trials. One study from the UK on cT1 and cT2 rectal cancers showed 32% pCR after 8–10 weeks following short course radiotherapy (SCRT), and a similar Dutch study reported 44% pCR following EBCRT for cT1, cT2, and cT3a tumors (31,32). There was histological evidence of residual tumor in 68% and 56% of patients in both trials. Transanal endoscopic microsurgery (TEMS) provided the histological status following either neo-adjuvant SCRT or EBCRT. Our data suggest that the residual disease that remained could be sterilized by CXB to reduce local regrowth down to 11%. Our data concur with those from a

published prospective study on a well-defined group of patients in a single centre in Hull (UK) treated under a strict protocol, which showed reduction in local regrowth to 12% (n=5) when CXB boost was offered in addition to EBRT (32). Moreover, a recent publication from Nice (France) showed 11% predicted local regrowth at 5 years in patients with more advanced cT2/cT3 tumors treated by combination of EBCRT at a higher dose of 50 Gy in 25 fractions over 5 weeks and CXB 90 Gy in three fractions (33). Both these studies used a CXB boost similar to that received by our patients, but both were prospective studies involving patients treated under strict protocol in single institutions. Both studies showed low rates of local regrowth similar to our series, which suggests that CXB is a significant contributor to this observation (Table 3). We are assessing this hypothesis further in an ongoing European multicentre phase 3 randomized trial which started 2 years ago and so far 45 patients have been randomized.

We believe another important clinical finding from our results is that most of our patients (16 of the 27 patients [60%]) who died had no documented evidence of cancer (i.e. they died from other medical causes). As such, our data highlight the importance of competing oncological outcomes against physiological risk involved in decision making for rectal cancer, in comorbid and elderly patient groups who are increasing in number due to an ageing population (27). Furthermore, in patients who had an initial cCR and subsequently developed local and regional regrowth, delayed salvage surgery was possible in the all of six patients (100%) who did not have distant metastatic disease (18). These results mirror those from other specialist centres where reported surgical salvage rates have been around 90% (9, 10, and 30).

There are further limitations in our study as our data was a retrospective analysis of patients treated over many decades with all its drawbacks. We also did not compare our outcomes with patients who received radical surgery, which is the current gold standard treatment. However,

the OnCoRe study did perform this. It compared the oncological outcomes of 129 patients managed by watch-and-wait (38% needed surgical salvage for local regrowth) with a propensity-score matched group of patients that underwent index radical surgery and showed no difference in their survival outcomes (9).

We acknowledge that our follow up was relatively short and we have also not included outcome data concerning bowel function. However, we are in the process of formally prospectively recording functional data for our patients through a national data set as recommended by NICE (National Institute of Health and Care Excellence). In addition, there was a review of acute and long term toxicities of CXB by NICE and their findings were published as IPG 532 (35). Their findings of acceptable safety and toxicity profiles in patients not suitable for surgery were consistent with our experience.

We also accept that our data do not form part of a formal clinical study, that our patients were not randomized, and that this was essentially a retrospective observational study with all its limitations. This is because until recently non-operative management was deemed anathema to conventional treatment for rectal cancer and very few patients were referred for CXB boost after EBRT/EBCRT. We aim to rectify these issues in the trial which is a European multi-centre phase 3 randomized trial, for which we have started recruiting patients. The primary endpoint is organ preservation with local control at 3 years (36).

Conclusions

Our data with all its limitation and uncertainties have shown that patients with clinical incomplete response to ECBRT/EBRT can still achieve a clinical complete response after CXB boost. Of these who achieved cCR, only 11% developed a local regrowth and this percentage is low when compared to other series. All 6 patients with non-metastatic local regrowth could

be salvaged. We do, however, accept that this technique ideally needs to be assessed in a clinical trial of which one is under way. We do believe that CXB is particularly pertinent for older or comorbid patients with rectal cancer who are not suitable for surgical salvage, or for younger stoma-averse patients who wish to avoid surgical salvage (if possible) in the event of local regrowth following EBCRT/EBRT.

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Figure legends

Table 1: Patient characteristics

Table 2: Prognostic factors related to treatment clinical outcomes

Table 3: Comparative local regrowth rates following different treatment modalities

Figure 1: Patient care pathway flow chart

Figure 2: Contact X-ray brachytherapy treatment position and schematic diagram

Figure 3: Disease-free survival

Table 1: Patient characteristics

		N	%
Age median (range)		72 years (36-87)	
Sex	Female	25	30.1%
	Male	58	69.9%
Performance status	0	35	42.2%
	1	34	41.0%
	2	9	10.8%
	3	3	3.6%
	Not Known	2	2.4%
Differentiation	Well	3	3.6%
	Moderate	58	69.9%
	Poor	1	1.2%
	Not Known	21	25.3%
Tumour stage	cT2	28	33.7%
	cT3	55	66.3%
Nodal stage	cN0	38	45.8%
	cN1	32	38.6%
	cN2	12	14.5%
	Not Known	1	1.2%
Metastases stage	M0	83	100%
Tumour size	≤3cm	47	56.6%
	>3 cm	23	27.7%
	Not Recorded	13	15.7%
Distance from anal verge (cm)	<7 cm	61	73.5%
	7-11 cm	16	19.3%
	Not Recorded	6	7.2%

Table 2: Prognostic factors related to treatment response and local regrowth

			Treatment response			Local regrowth		
Prognostic factors		N	HR	95% CI	P	HR	95% CI	P
Performance status	0	35	Ref		0.62	Ref		0.99
	1	34	0.43	0.14-1.35		0.62	0.08-4.64	
	2	9	1.19	0.2-6.94		0.00	0-0	
	3	3	1.22	0.07-21.03		0.00	0-0	
	Not known	2	1.09	0.03-42.78		0.00	0-0	
Age group	<70	33	Ref		0.74	Ref		0.69
	70-79	30	0.66	0.2-2.18		2.49	0.3-20.38	
	80-89	20	1.03	0.24-4.36		1.41	0.08-24.77	
Tumour stage	cT2	28	Ref		0.31	Ref		0.81
	cT3	55	1.87	0.56-6.18		0.76	0.08-6.98	
Nodal stage	cN negative	38	Ref		1.00	Ref		0.98
	cN positive	44	1.01	0.32-3.19		1.25	0.11-13.58	
	Not known	1	0.00	0-0		0.00	0-0	

Distant from anal verge	<7 cm	61	Ref		0.32	Ref		0.63
	7-11 cm	16	0.43	0.1-1.84		3.34	0.28-39.96	
	Not known	6	0.23	0.02-2.85		0.00	0-0	
Tumour size	≤3cm	31	Ref		0.27	Ref		0.75
	>3 cm	34	0.61	0.19-2		0.39	0.03-4.9	
	Not recorded	18	1.99	0.46-8.62		0.88	0.06-12.91	
Treatment modality	Chemoradiation	71	Ref		0.56	Ref		1.00
	RT alone	12	0.58	0.1-3.51		0.00	0-0	
Papillion total dose	≤90 Gy	79	Ref		0.82	Ref		0.25
	>90 Gy	4	0.74	0.05-9.99		8.65	0.22-347.01	

Table 3 Comparison of initial response and local regrowth after cCR

Study	n	Treatment modality	Initial Response (%)	Local regrowth (%)
Habr Gama (10)	183	EBCRT 45Gy +EBRT boost 9Gy	90/183 (49)	28/90 (31 at 5 years)
Appelt (2)	51	EBCRT 60Gy + HDR 5Gy	40/51 (78)	9/40 (25.9 at 2 years)
Renehan (9)	129	EBCRT 45Gy	NA	44/129 (38 at 3 years)
Gerard (34)	45	EBCRT 50Gy + CXB 90 Gy	43/45 (98)	3/43 (11 at 5 years)
Dhadda (33)	42	EBCRT 45 Gy + CXB 90 Gy	NA	5/42 (12 at 2 years)
Present study	83	EBCRT 45Gy + CXB 90 Gy	53/83 (63.8)	6/53 (11.3 at 2.5 years)

Abbreviations HDR =High dose rate brachytherapy; NA=not available.

Figure 1

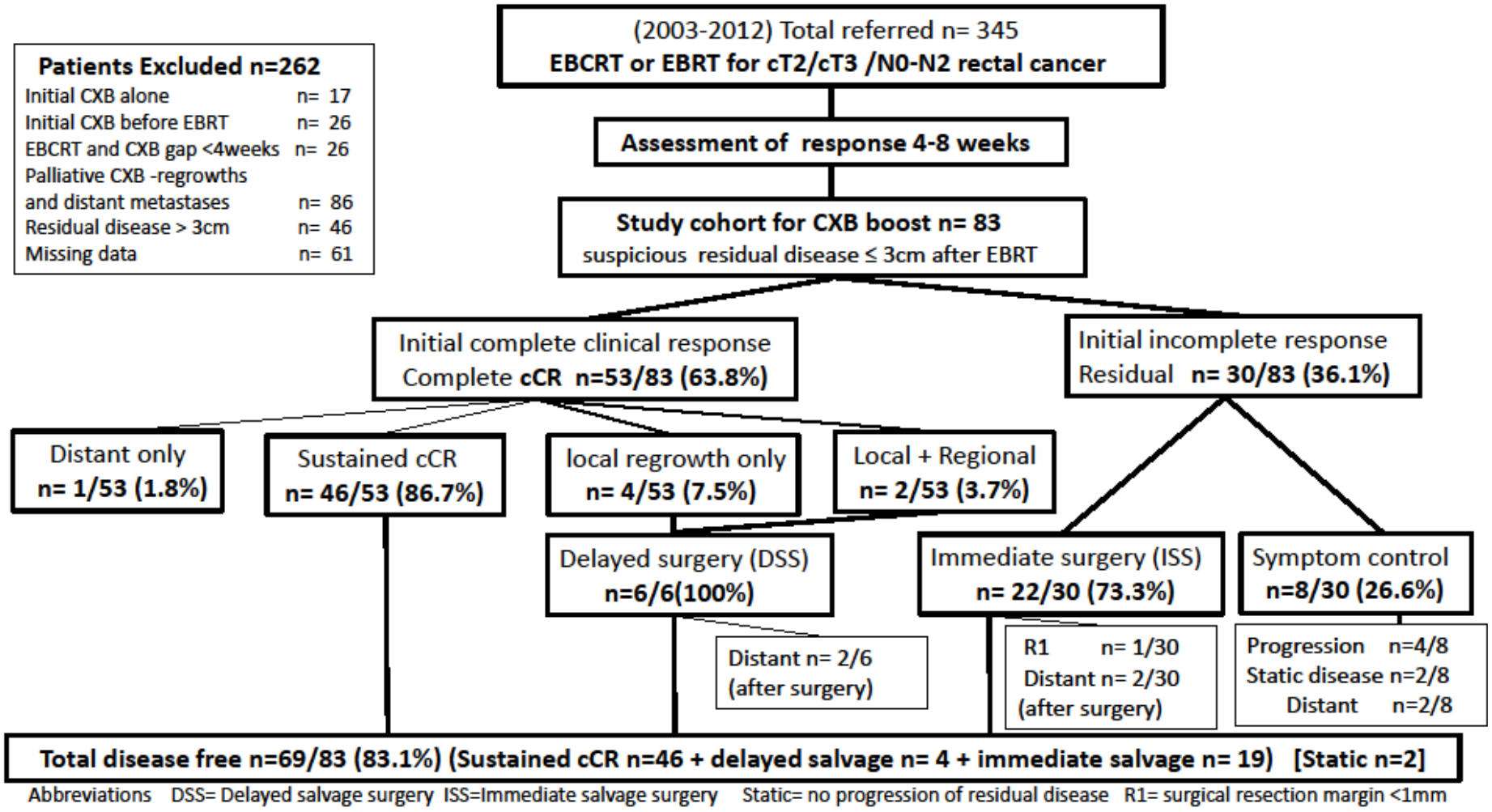
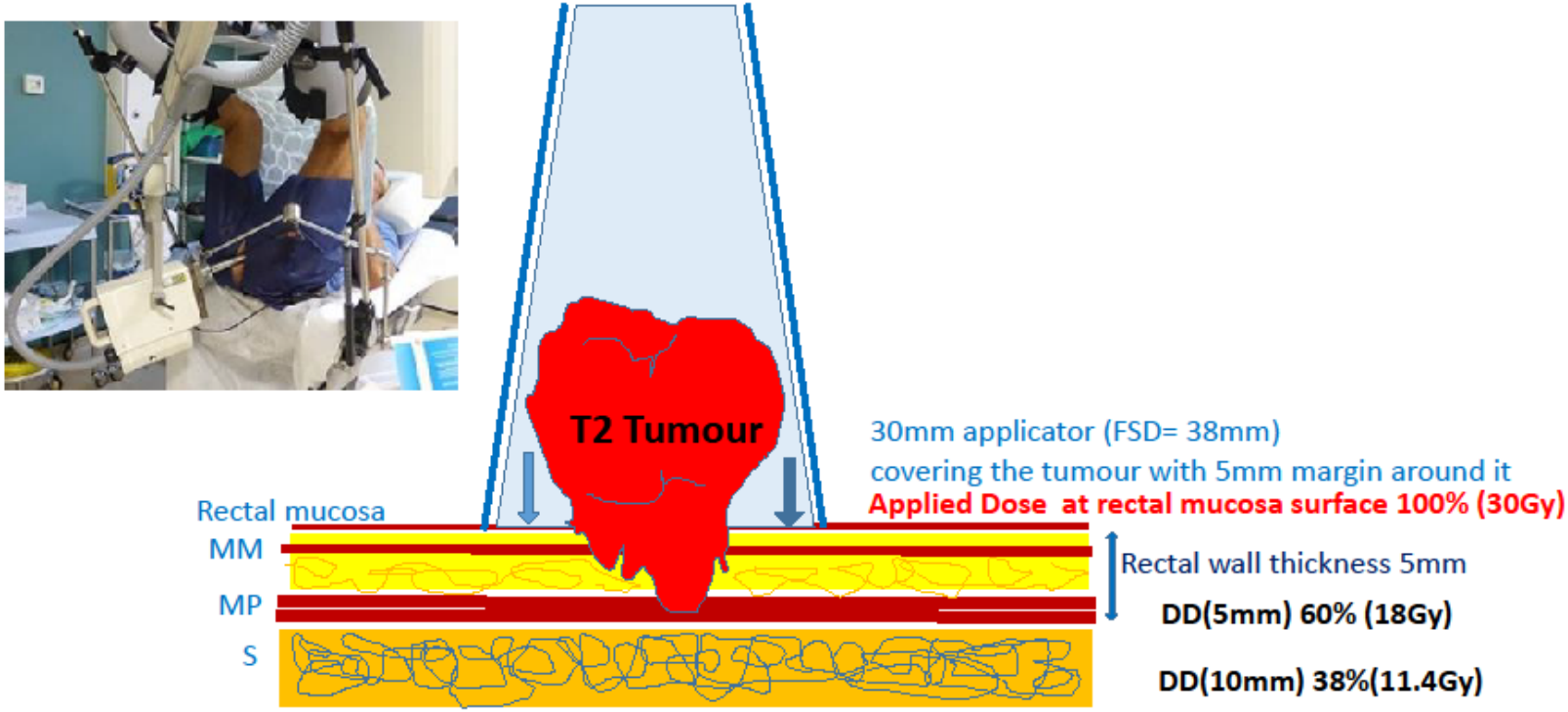
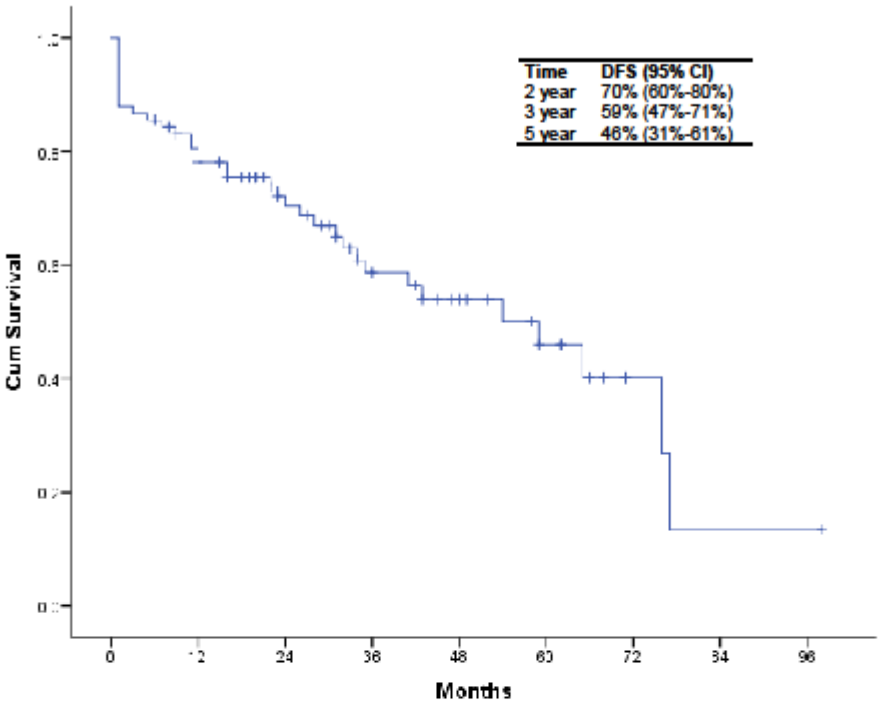

Patients Excluded n=262
Initial CXB alone n= 17
Initial CXB before EBRT n= 26
EBCRT and CXB gap <4weeks n= 26
Palliative CXB -regrowths and distant metastases n= 86
Residual disease > 3cm n= 46
Missing data n= 61
(2003-2012) Total referred n= 345
EBCRT or EBRT for cT2/cT3 /N0-N2 rectal cancer
Assessment of response 4-8 weeks
Study cohort for CXB boost n= 83
suspicious residual disease ≤ 3cm after EBRT
Initial complete clinical response
Complete cCR n=53/83 (63.8%)
Initial incomplete response
Residual n= 30/83 (36.1%)
Distant only
n= 1/53 (1.8%)
Sustained cCR
n= 46/53 (86.7%)
local regrowth only
n= 4/53 (7.5%)
Local + Regional
n= 2/53 (3.7%)
Delayed surgery (DSS)
n=6/6(100%)
Immediate surgery (ISS)
n= 22/30 (73.3%)
Symptom control
n=8/30 (26.6%)
Distant n= 2/6
(after surgery)
R1 n= 1/30
Distant n= 2/30
(after surgery)
Progression n=4/8
Static disease n=2/8
Distant n=2/8
Total disease free n=69/83 (83.1%) (Sustained cCR n=46 + delayed salvage n= 4 + immediate salvage n= 19) [Static n=2]
Abbreviations DSS= Delayed salvage surgery ISS=Immediate salvage surgery Static= no progression of residual disease R1= surgical resection margin <1mm

Figure 2



Abbreviations MM =Muscularis Mucosa, MP =Muscularis Propria, S= Serosa, DD= Depth Dose, FSD= Focal source surface distance T2= stage T2 tumour infiltrating into MP (TNM)

Figure 3


Time DFS (95% CI)
2 year 70% (60%-80%)
3 year 59% (47%-71%)
5 year 46% (31%-61%)
Cum Survival
0.4
0
24
36
48
60
72
84
96
Months