

# Adaptive radiation dose escalation in rectal adenocarcinoma: a review

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**Abstract:** Total mesorectal excision (TME) after neoadjuvant chemoradiotherapy (CRT) has offered superior control for patients with locally advanced rectal cancer, but can carry a quality of life cost. Fortunately, some patients achieve a complete response after CRT alone without the added morbidity caused by surgery. Efforts to increase fidelity of radiation treatment planning and delivery may allow for escalated doses of radiotherapy (RT) with limited off-target toxicity and elicit more pathological complete responses (pCR) to CRT thereby sparing more rectal cancer patients from surgery. In this review, methods of delivering escalated RT boost above 45–50.4 Gy are discussed including: 3D conformal, intensity-modulated radiotherapy (IMRT), and brachytherapy. Newly developed adaptive boost strategies and imaging modalities used in RT planning and response evaluation such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are also discussed.

**Keywords:** Rectal cancer; radiotherapy; adaptive dose escalation; rectal organ preservation

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## Introduction

The role of radiation therapy in the treatment of rectal cancer has evolved over the past several decades. The current standard of care consists of pre-operative concurrent chemotherapy and radiotherapy (chemo-RT). Such a treatment strategy has further enhanced the pelvic tumor control of advanced surgical techniques such as total mesorectal excision (TME) and offered greater chance for sphincter preservation with lower rates of toxicity compared to post-operative radiotherapy, or TME alone (1,2).

Unfortunately, the inclusion of surgical resection as standard of care for rectal cancer patients carries implications for quality of life and toxicity (3). The concept of organ preservation in rectal cancer treatment was pioneered by surgeon Angelita Habr-Gama

who noted that a subset of patients (about 27%) achieved a complete response after chemoradiation alone and had similar outcomes as those who underwent chemoradiation and subsequent TME, but without the added morbidity that came with surgery (4,5). Their group validated the ‘watch and wait’ strategy by showing that recurrences in the non-operative groups could be managed by salvage surgery with over 90% success (6). Multiple series have been published over the past five years that have demonstrated the efficacy and safety of a ‘watch and wait’ strategy (7).

The efficacy and safety of neoadjuvant chemoradiotherapy (CRT) have been demonstrated by a number of studies, most of which utilize low doses of radiation from 45–50.4 Gy. Indeed, several of the non-operative series have used these moderate doses. Despite these relatively low doses of radiation therapy, such studies, on average, produce

pathologic complete responses (pCR) in 10–27% of patients, with clusters of studies reporting closer to 10% (8-11), and few at 27% and above (5,12). The value of a pCR after CRT has been validated as an indicator of increased chance for disease-free survival (13). Efforts to optimize the pCR rate from chemoradiation in rectal cancers have been ongoing. The impact of multiple factors, such as chemotherapy type and radiation dose escalation above 45 Gy have been postulated to be correlated with the degree of response (14).

Of interest, the impact of radiation dose escalation beyond 50.4 Gy on pCR rates has been examined with a recent meta-analysis of patients treated with doses over 60 Gy which showed increased pCR rates (20%) and acceptable short-term toxicity (15). This same group is furthering their investigation into radiotherapy dose escalation in an ongoing prospective trial (16). The rationale behind radiation dose escalation as an avenue to increase pCR rates is based on studies that have shown increased pCR rates and long-term survival in a dose-dependent manner (17), and a trend toward increased pCR rates and disease-free survival with increasing dose (18). Furthermore, a dose-response model derived from patients treated with a combination of external-beam radiation and brachytherapy to doses of 50.4–70 Gy showed a clear dose-response with a predicted pCR rate of 50% at 92 Gy (19).

While the effect of a boost beyond historic doses of 45–50.4 Gy is under current investigation, there remains a gap in the literature delineating effective methods of planning and applying a radiotherapy boost. Specifically the integration of novel imaging techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI), into selective application of a radiation boost strategy is poorly understood. We sought to review the existing literature of contemporary and personalized radiation therapy boost strategies. Moreover, we aim to provide potential future directions for the integration of innovative response assessment strategies into selective radiation therapy dose escalation for patients with rectal adenocarcinoma.

## **Radiographic assessment of rectal cancer response to therapy**

### ***Magnetic resonance imaging (MRI) response assessment***

Monitoring the response of rectal cancer to chemoradiation by non-invasive methods is a vital component of a non-operative management strategy along with a selective

and personalized radiation boost strategy. The ability to assess rectal tumors for their treatment response is an area of research that has expanded dramatically over the past 5 years (20). MRI presents a particularly novel and appealing modality to enable such response assessment and an adaptive radiation therapy boost strategy. This is particularly true secondary to the rapid expansion of image guided radiation therapy and specifically linear accelerators equipped with MRI guidance (21,22). MRI offers several considerable advantages over traditional computed tomography (CT) based imaging, particularly for primary tumor response assessment with quantitative sequences (23). One such example is the “apparent diffusion coefficient” (ADC), which is a quantitative value derived from diffusion weighted imaging (DWI) MRI that reflects tissue cellularity, organization and cell membrane permeability (24). This technique has shown promise in predicting complete responses of rectal cancer to CRT in recent years, and poses the benefit of being a quantitative method which is preferred for longitudinal studies and meta-analysis. Overall, DWI MRI is an attractive imaging modality for cancer staging and re-staging because it is noninvasive, relatively quick and does not utilize additional contrast agents or ionizing radiation (25). Multiple studies have shown significant differences in mean tumor ADCs between responders and non-responders after CRT treatment, and that a lower mean pre-treatment ADC correlates to better responses to CRT (26-29). One such example shows the potential of MRI integration into a course of radiation therapy treatment (30). Sun *et al.* showed that an increase in mean tumor ADC at approximately one week into CRT, along with a low pre-CRT mean ADC correlated with higher rates of response to chemo-RT (30). However, data examining the acquisitions of rectal MRI during a course of radiation therapy are limited.

### ***Positron emission tomography (PET) based response assessment***

<sup>18</sup>F-fluorodeoxyglucose PET (<sup>18</sup>F-FDG PET) allows for visualization of fluorinated glucose concentrations, indicating tissue with high metabolic activity, including cancers. For this reason, FDG PET is a powerful tool for tumor staging. Additionally, changes in metabolic activity can be monitored after treatments, and can be tracked with the semi-quantitative standardized uptake value (SUV). FDG SUV changes have been correlated with pathologic response to treatment in multiple cancers, including rectal

cancer (31). The specific utility of PET, and PET combined with CT in predicting response to chemoradiation is a subject currently under intense investigation. Recent analysis of pooled individual patient data showed that pre-CRT PET/CT had a low positive predictive value for pCR (44%). Moreover, the absence of FDG avidity early in treatment with Chemo-RT has been shown to be indicative of non-responders (31-33). Interestingly, combining the ADC from DW-MRI and the SUVmax from PET to detect changes in tissue structure at the cellular level appears to more accurately reflect rectal cancer response to chemo-RT (34). Unfortunately, PET/CT has proven unreliable in providing accurate re-staging at the completion of chemo-RT (35-37). Additionally, PET/CT provides a difficult logistical and economic barrier to routine acquisition during the course of chemo-RT as radioisotopes carry considerable cost and logistical burden to their use.

## Methods of radiation therapy dose escalation

### *3-dimensional conformal radiation therapy (3D-CRT)*

The use of 3D-CRT represents the historical standard of care for patients with rectal adenocarcinoma. 3D-CRT utilizes CT to map a 3D target volume, and deliver conformal radiation beams in the shape of the tumor. This advancement allows for decreased toxicity to normal surrounding tissues and boosting of the tumor to higher radiation doses (38). Recent dose escalation studies using 3D-CRT have shown promise as a key component of achieving higher rates of pathological complete responses than with traditional chemoradiation alone (39).

In a study by Mohiuddin *et al.*, patients treated up to 60 Gy by 3D-CRT with 5-FU chemotherapy had favorable responses, with an acceptable toxicity profile. Diarrhea was the most common acute toxicity at a grade 3, with no grade 4 or 5 toxicities in any category observed. This study illustrates a potential opportunity for dose escalation by 3D-CRT. The total reported pCR rates were 13% (2/15) in patients who received less than 55 Gy, and 44% (8/18) in patients who received over 55 Gy. Interestingly higher pCR rates occurred (66%) with continuous infusion vs bolus of 5-FU (9.5%) (40). In a phase 2 follow-up study by Mohiuddin *et al.*, 106 patients were randomized to continuous venous infusion of 5-FU plus RT boosted to 55.2 for T3 cancers and 60 Gy for T4 cancers. The second treatment arm consisted of 5-FU plus irinotecan and

50.4 Gy for T3 and 54 Gy for T4 tumors. PCR rates were 30% in Arm 1 and 26% in Arm 2 (41).

Closely reproducing these results, is a series by Pfeiffer *et al.*, in which 18 patients with unresectable or recurrent tumors underwent 60 Gy of radiation in 30 fractions with tegafur/uracil (UFT) chemotherapy. Of the 18 patients, 2 (11%) experienced a pathological complete response (42). In a phase II clinical trial by Movsas *et al.*, a 3D-CRT boost was taken to 61.8 Gy with 5-FU in patients with bulky, locally advanced rectal cancer. They found downstaging in 50% of patients (43). In a study by Vestermark *et al.*, rectal cancer patients were treated with a 60 Gy boost to the gross tumor volume in 30 fractions with concurrent chemotherapy. Of the patients who underwent resection, 33% (5/15) had a pathological complete response (39). In a unique study by Engineer *et al.*, patients with clinically unresectable rectal cancer received 45 Gy of EBRT with concurrent oral capecitabine or EBRT alone boosted to 60 Gy. Patients experienced a pCR rate of 7% and 11% for radiation alone *vs.* radiation + chemo (44). The lower pCR rate in this study is perhaps not unexpected, as the dose escalated treatment arm did not include concurrent chemotherapy.

Together, these studies are difficult to interpret with radiation doses up to 60 Gy yielding dramatic ranges of pCR rates between 11% and 66%. Heterogeneity of patient populations, pathologic specimen processing, and treatment protocols make direct comparisons between studies difficult, although it is clear that escalated doses of radiation delivered by 3D-CRT trend toward higher pCR rates often with acceptable toxicity profiles. This group of studies also emphasizes the importance of optimizing chemotherapy regimens in concert with radiotherapy. This paradigm was also supported by the result of Engineer's study, in which chemoradiation outperformed radiation alone (44). However, 3D-CRT strategies carry limitations in their ability to conformally address a circumferential target. In addition, they provide higher doses to critical local structures, such as the femoral necks and urinary bladder, which may limit the total radiation dose achievable when embarking upon dose escalation (45).

### *Intensity modulated radiotherapy (IMRT) boost strategies*

IMRT is an advanced form of 3D-CRT in which the radiation beam intensity can be changed, or modulated, during treatment. The ability to deliver a range of radiation doses to the tumor bed allows for a simultaneous integrated

boost (SIB) as well as minimizing doses to organs at risk, potentially enabling dose escalated radiation therapy to the tumor (46). In a study by Alongi *et al.*, patients treated with IMRT boosting to 60 Gy in 30 fractions with concurrent capecitabine, resulted in a pCR rate of 17.5% with no grade 3 or higher toxicities (47). The low toxicity profile of this treatment regimen suggests that higher dose escalation via IMRT could be an appealing strategy. Two very similar studies by Ballonoff *et al.*, and Freedman *et al.*, analyzed dose escalation to 55 Gy using IMRT with oral capecitabine (48,49). Interestingly, the main difference between the studies, was that in the Freedman *et al.* study, capecitabine was administered 7 days per week, while in the Ballonoff study, it was administered 5 days per week with radiation therapy. Reasons for the divergent responses to similar treatments in pCR rates were attributed to the subjectivity of pathological evaluation, coupled with an early termination of the Freedman study due to acute toxicities (48,49). These two examples illustrate that escalating radiation therapy doses with IMRT may be feasible, however toxicity must be carefully monitored in such an approach. A phase II trial by Zhu *et al.*, showed a promising pCR rate of 23.7% in stage II and III rectal cancer with a treatment regimen of 55 Gy to the primary tumor via IMRT, concurrent oxaliplatin and capecitabine and an additional course of Xelox 2 weeks post chemo-RT (50). Cubillo *et al.* examined patients treated with 57.5 Gy by SIB IMRT with chemotherapy tailored to tumor genotypes. In addition, they monitored PET SUV response before and after chemo-RT. Of the 16 patients, 8 (50%) experienced a pCR. Interestingly, the PET SUV change was a poor predictor of pCR, with only 2 of the 8 patients who experienced a tumor regression grade 4 showing a complete PET response. Additionally, one individual experienced a pCR with a negligible change of PET SUV (51). In a follow-up study Hernando *et al.* used the same IMRT radiation boost technique with the substitution of a standardized chemotherapy regimen of capecitabine for the customized regimens used previously. The results were understandably less dramatic than for the customized chemotherapies, with a pCR rate of 30.6% (51). These two series illustrate nicely the value of simultaneous integrated boost via IMRT for rectal cancer, which achieved a higher than average 30.6% pCR rate. On the other end of the spectrum, the only study with a radiation boost by IMRT without chemotherapy is a Belgian study in which patients were treated with up to 55.2 Gy. The pCR rate was low at 8% of the 108 participants, again illustrating

the importance of concurrent chemotherapy (52). Finally, a recently published single arm phase II trial, Hong and colleagues evaluated the toxicity of IMRT, which did not appear to reduce the rates of GI toxicity, however a selective dose escalation strategy was not attempted in this series (53).

### **Brachytherapy boost strategies**

Endorectal brachytherapy involves temporary insertion of radioactive material into the rectal lumen, delivering therapeutic radiation to the tumor. This technique has largely been used for adjuvant or palliative treatment in patients with rectal cancer (54). Endorectal brachytherapy has advanced from a relatively crude procedure that irradiates the entire rectum circumference, to a highly conformal technique with the use of 3D-CT planning and partial shielding to spare normal tissue adjacent to and opposite the rectal tumor (55). Studies on the use of brachytherapy as the sole neoadjuvant radiation treatment for rectal cancer are limited with the total doses reaching 26 Gy (56,57). Endorectal brachytherapy has also been used to escalate radiation doses beyond 50.4 Gy in conjunction with EBRT with mixed results. In 2006, Jakobsen *et al.* used EBRT boosted to 60 Gy, plus an additional boost of 5 Gy via brachytherapy. Results were promising with a pCR rate of 27%, attributed by the authors to the high doses of radiation used, with a favorable side-effect profile consisting of diarrhea as the only grade 3 toxicity. In a follow-up study, Jakobsen *et al.* added a COX-2 inhibitor to the regimen. The goal of the study was to determine the feasibility of adding a COX-2 inhibitor as a radiosensitizing agent to CRT. The COX-2 inhibitor was found to cause a severe maculopapular rash. However, the toxicity profile aside from the skin manifestations was reasonably low, with only 1 incidence of grade 3 diarrhea and leukopenia, while 21% of the patients experienced a pCR, a result that is comparable to the prior study considering the larger tumors treated in the second series (24% T4). Sun Myint *et al.* followed 34 patients treated with CRT consisting of 45 Gy EBRT, and a boost of 10 Gy via high dose rate brachytherapy. Patients experienced a favorable 31% pCR rate, with acceptable toxicity (58). A randomized trial published in 2012 by a Danish group authored by Jakobsen *et al.* enrolled 248 patients with T3-T4 tumors, and treated them with 50.4 Gy by EBRT, with an additional 10 Gy brachytherapy boost in the experimental arm. The group found a pCR



rate of 18% in both arms, with only one notable difference in response: a 28% to 48% increase in response rate in T3 tumors (59). Published in 2014, a follow-up of the same patients showed that despite improved initial responses, these results did not correspond to long-term responses, and the lack of difference in pCR rate between the groups was reflected in the similar 5-year survival of the patients (60). A subsequent prospective trial by the Danish group utilized 60 Gy via IMRT, with an additional 5 Gy brachytherapy boost to test the watchful waiting strategy in patients with T2-T3 tumors. The outcomes were excellent with a 78% clinical complete response rate, and local control in 58% of patients at 2 years without surgical intervention (61). Together, these studies indicate that brachytherapy may have a role in an organ sparing strategy, particularly when used to add to an already escalated dose delivered by external beam radiation therapy. Additionally, and unsurprisingly, the effect of brachytherapy boost may be most effective with smaller tumors, a partial explanation to this is the fact that brachytherapy is an inherently local treatment, and does not effectively treat at-risk or involved lymph nodes, necessitating an additional boost strategy (55).

### *Selective and adaptive boost strategies*

Patients receiving escalated doses of radiation typically receive a boost to the gross tumor volume (GTV) (42). Delivery of a radiotherapy boost has evolved with the advancement of radiotherapy delivery techniques to a simultaneous integrated boost (SIB) which allows for boost to the GTV without extending the overall treatment period, as utilized with the IMRT strategies mentioned in the above studies (62). In general, the imaging modality used in the dose-escalation planning and adaption for rectal cancer has not been emphasized in the literature as shown in *Table 1*. This is surprising, due to the advantages of using MRI in staging and planning RT for rectal cancer (63). It seems that rectal adenocarcinoma would be optimally suited for an adaptive boost strategy using radiologic response through either PET or MRI acquired during the course of chemo-RT. In one such example, Alongi *et al.*, utilized PET/CT to plan the radiotherapy boost, and identified hypermetabolic areas that included primary tumor, mesorectum and involved lymph nodes. Patients treated with this protocol received 60 Gy of boost to identified targets yet had a 17.5% pCR rate. The boost strategy did

not appear to impact tumor down-staging and PET/CT was not predictive of pCR, as there was no correlation between pre-treatment SUV-max and pCR (47). However, this boost strategy did not incorporate an intra-treatment assessment of rectal tumor response to therapy. An example of a truly adaptive strategy was presented by Avallone *et al.* who showed that early changes in mean PET SUV after 12 days of CRT, correlated with improved tumor responses, and 5-year relapse-free survival (64). Furthermore, Leccisotti *et al.* showed that a lack of early changes in SUV in response to CRT correlates with non-responders, and could be used to rapidly adapt the treatment course (65). One considerable limitation of PET is the cost and logistical challenge associated with the acquisition of these images. Alternatively, MRI may prove a powerful tool in selective dose escalation for patients with rectal adenocarcinoma. As the availability of MR guided radiation therapy systems expands, this may allow for real time adaptive treatment strategies. In one such early example, Passoni *et al.* employed a unique adaptive strategy that involved re-imaging with CT and MRI mid-treatment, and re-planning the target volume based on the residual tumor (66). As MR guided radiotherapy therapy systems become increasingly common, further investigation into adaptive boost strategies using MR guided systems presents a unique and promising opportunity.

### **Conclusions and future directions**

There appears to be a role for further evaluation of dose escalation in patients with rectal adenocarcinoma, particularly as it relates to organ preservation. With respect to the optimal RT planning strategy for rectal cancer, further investigation into the value of MRI-predominant adaptive treatment strategies should be considered based on superior soft-tissue detail along with the biological adaptation provided with advanced MR techniques (67,68). Delivery of highly conformal and adaptive doses of radiotherapy, coupled with MRI-guided therapy systems, may allow for higher rates of pCR and may offer improved rates of organ preservation. A list of ongoing clinical trials can be found in *Table 2*. While many boost trials for rectal cancer are ongoing, few use a true biologically adaptive or selective approach for the incorporation of radiation dose escalation. There is room for further investigation into novel methods of adaptive boost strategies and incorporation of novel imaging techniques for patients with rectal

**Table 1** Summary of existing rectal dose escalation series

First author	Radiation/modality	Imaging used in planning/delivery	Chemotherapy	Response assessment	pCR or cCR	> or = G3 toxicity	Tumor stages	# of patients
Mohiuddin 2000	EBRT 3D-CRT: 45–60 Gy	Evaluation with CT abdomen/pelvis; sigmoidoscopy with biopsy and colonoscopy	1,000 mg/m <sup>2</sup> 3–5x per week; or continuous IV 225 mg/m <sup>2</sup>	Surgery 6–8 weeks post CRT	pCR 10% with 5-FU bolus; 67% with continuous infusion; 13% with 45–50 Gy; 44% with 55–60 Gy	18% [6] G3 diarrhea; 15% [5] enteritis; 12% [4] oral mucositis; 9% [3] cystitis	T1–T3	33
Pfeiffer 2005	EBRT 3D-CRT: 48.6 Gy to CTV in 27 fractions, 60 Gy to GTV in 30 fractions	GTV defined by integrated CT and MRI images	Oral UFT 150–300 mg/m <sup>2</sup> 5 days per week + 7.5 mg Isovorin	Eval with CT and DRE 4 weeks post CRT. Resection 6 weeks post CRT	pCR: 11% (2/18)	39% (7/18) diarrhea	Primary unresectable and local recurrent rectal cancer	18
Movsas 2006	EBRT 3D-CRT: 45 Gy to pelvis with 61.8 Gy to GTV	Pretreatment evaluation by CT, MRI, transrectal ultrasound	5 FU 1 g/m <sup>2</sup> per 24 hours x4 d in 1st and 6th week of RT	Surgery 4–6 weeks post CRT with pathologic evaluation	pCR: 0%. Downstaging in 50% (10/20) of evaluated patients	14%	T3 and T4	22
Vestermark 2012	EBRT 3D-CRT: 48.6 Gy to CTV in 27 fractions, 60 Gy to GTV in 30 fractions	GTV determined by MRI	Oral UFT 300 mg/m <sup>2</sup> + 22.5 mg Leucovorin and 10 mg/m <sup>2</sup> per week of Oxaliplatin escalated to 60 mg/m <sup>2</sup> over the treatment course	Surgery 6 weeks post CRT with pathologic evaluation	pCR: 33% (5/15)	17%	Primary or recurrent unresectable rectal cancer	18
Mohiuddin 2013	EBRT 3D-CRT: Arm 1: 45.6 Gy + 9.6 Gy boost for T3, and 14.4 Gy boost for T4; Arm 2: 45 Gy + 5.4 Gy for T3 and 9 Gy for T4 tumors	Optional MRI for TNM staging	Arm 1: CVI of 5-FU 225 mg/m <sup>2</sup> per day; Arm 2: CVI 5-FU M-F (120 hr/wk) + Irinotecan 50 mg/m <sup>2</sup> once per week	Surgery 4–10 weeks post-CRT	pCR – 30% (15/50) in Arm 1; 29% for T3 and 31% for T4; 26% (14/53) in Arm 2; 31% for T3 and 14% for T4 tumors	42% in Arm 1; 51% in Arm 2; consisting mostly of dermatological, gastrointestinal and bone marrow /blood toxicity	T3 and T4	103
Engineer 2013	EBRT 3D-CRT: Arm 1: 45 Gy to pelvis; Arm 2: (radiation only) 45 Gy to pelvis with 20 Gy boost to tumor	CT or MRI for treatment planning	Arm 1 only: oral Capecitabine 1.7 g/m <sup>2</sup> BID in 2 cycles	Clinical evaluation with CT 6–8 weeks post CRT, followed by surgery and pathologic evaluation	pCR – Arm 1: 7%; Arm 2: 11%	Arm 1: 8.8% (4/45); Arm 2: 4.8% (2/42)	"clinically unresectable rectal cancer"	90
Freedman 2007	IMRT 45 Gy boosted to 55 Gy by SIB	CT and/or MRI	Capecitabine (PO 825 mg/m <sup>2</sup> ) 7 days per week	PET SUV pre and post RT	pCR = 0%	Acute GI 13%, anemia 13%, fatigue 13%, pain 13%, ileus 13%, dehydration 13%	cT3–T4/N+	8

**Table 1** (continued)

Table 1 (continued)

First author	Radiation/modality	Imaging used in planning/delivery	Chemotherapy	Response assessment	pCR or cCR	> or = G3 toxicity	Tumor stages	# of patients
Ballanoff et al. 2008	SIB IMRT: 55 Gy (2.2 Gy/fraction) to GTV + 45 Gy pelvis and regional LN in 1.8 Gy fractions	CT, EUS, MRI and/or PET	Capecitabine (PO 825 mg/m <sup>2</sup> ) 5 days per week with RT	6 weeks post-chemoradiation: TME and pathologic evaluation	pCR =38%	Grade 4 diarrhea in 1 of 8 patients (13%)	Locally advanced	8
Zhu 2013	IMRT 55 Gy	Planning: CT, MRI, some PET-CT	625 mg/m <sup>2</sup> capecitabine BID, + oxaliplatin 50 mg/m <sup>2</sup> weekly	Evaluation with MRI at the conclusion of CRT, and every 2 mo until 6 mo. CT to confirm	cCR 4/32; pCR 5/14	Grade 3: Radiation dermatitis 18.8%, GI toxicity 15.6%	cT3-T4 cN+	32 total; 14 underwent surgery
Hernando 2014	IMRT 46 Gy boosted to 57.5 Gy by SIB	CT, PET-CT in all but 4 patients. MRI for staging, and CT image-guided delivery	Capecitabine 825 mg/m <sup>2</sup> BID	Blood count, tumor markers, CT, PET-CT, MRI, echoscopy. Surgery 8 weeks post treatment. Median 67.6 days.	Downstaging in 55/72 (76.38%); ypCR in 22/72 30.6%	Acute: GI 10%, GU 5%	cT2-4 N+	74
Cubillo 2014	IMRT 46 Gy boosted to 57.5 Gy by SIB	ERUS, MR, CT, PET with SUV	625 to 825 mg/m <sup>2</sup> capecitabine 5 days per week. Alone, or with 50 mg/m <sup>2</sup> irinotecan, oxaliplatin, cetuximab, or bevacizumab depending on tumor genotype	EUS, PET SUV change, TNM staging. Surgery 6-8 weeks post CRT	50% pCR	Diarrhea 6%, proctitis 19%	cT3-T4/N1	16
Picardi 2016	VMAT-SIB: 45 Gy, boost to 57.5 Gy (2.3 Gy/fraction)	MRI	Oxaliplatin and capecitabine	Clinical restaging 5-6 weeks after CRT by physical exam and pelvic MRI. Surgery 8 weeks after CRT	pCR: 4 of 16 patients who underwent surgery (25%); CR =4 of total 18 (22%)	Leukopenia =1; skin =1; GU =1; GI =5; overall 44.4%	T2-T4; N0-N2	18
Alongi et al. 2016	VMAT: 60 Gy in 30 fractions to PTV-SIB; 54 Gy to remaining PTV	MRI merged with 18-FDG-PET/CT. PTV defined by hypermetabolic areas with standard uptake value of 5 or greater. 54 Gy to areas of CTV with uptake value below 5	Capecitabine (825 mg/m <sup>2</sup> ) BID 5 days per week during RT	Restaging after 8-10 weeks, just prior to surgery	pCR: 17.5%. Downstaging in 63% of patients evaluated at 8-10 weeks. 5 patients from T3 to T0. 3 patients from T3 to T1. 10 patients from T3 to T2 and 10 patients Remained at T3. 1 patient from T4 to T3 and 1 patient remained at T4	No Grade 3 or greater toxicity noted	T2-T4; N0-N1	40
Appelt et al. 2015	60 Gy in 30 fractions by IMRT. 15 Gy brachytherapy dose on final day of RT	CT with MRI to aid in target planning	Oral tegafur-uracil 300 mg/m <sup>2</sup>	6 weeks post treatment determined by clinical exam, endoscopy with negative biopsy from primary tumor site, plus pelvic MRI	cCR 40 (78.4%)	Nausea 2 (4%); Diarrhea 4 (8%); Anemia 1 (2%); Leukopenia 1 (2%); Other 2 (4%)	Primary, resectable T2-T3 N0-N1	51

Table 1 (continued)

Table 1 (continued)

First author	Radiation/modality	Imaging used in planning/delivery	Chemotherapy	Response assessment	pCR or cCR	> or = G3 toxicity	Tumor grade	# of patients
Jakobsen 2006	EBRT 27 fractions, total dose of 54 Gy to CTV1, and CTV2 boosted to 60 Gy + 5 Gy brachytherapy	Staging with endorectal ultrasound and MRI	Uracil-tegafur 300 mg/m <sup>2</sup> per day	Histopathologic assessment with tumor regression grade system	27%	Diarrhea (6%)	T3; NO-N2	50
Jakobsen 2008	EBRT 27 fractions, total dose of 54 Gy to CTV1, and CTV2 boosted to 60 Gy + 5 Gy brachytherapy	endorectal ultrasound and MRI	Uracil-tegafur 300 mg/m <sup>2</sup> per day + celecoxib 400 mg BID	Surgery 8 weeks post CRT, evaluated with tumor regression grade system	7/33 (21%) pCR	Diarrhea (2.9%); leucopenia (2.9%)	T3-T4	35
Sun Myint 2010	EBRT 45 Gy in 25 fractions over 5 weeks. Repeat MRI and endoscopy at week 4; good responders receive Brachytherapy boost of 10 Gy at 10 mm	Tumor staged with CT, MRI	5-FU 750 g/m <sup>2</sup> x4 days in weeks 1 and 5; or oral capecitabine 625-825 mg/m <sup>2</sup> M-F with RT	MRI and endoscopy. Surgery 6-8 weeks post CRT	>80% regression in 12 (35%). pCR in 9 patients (31%)	2 (5.8%) delayed wound healing; 2 (5.8%) anastomotic leakage; 1 (3.4%) small bowel obstruction; 1 (3.4%) stricture	T2-T4; NO-N2	34
Appelt 2014 /Jakobsen 2012	Arm A: 50.4 Gy EBRT; Arm B: 50.4 Gy EBRT +2 fractions of 5 Gy Brachy	Tumor staged with MRI, CT, rectal U/S and rectoscopy. Treatment planning with CT	Oral tegafur-uracil 3x 100 mg/m <sup>2</sup> ; and oral l-leucovorin 3x 7.5 mg with RT	Surgery 8 weeks post-treatment, with histological evaluation	PCR 18% in both Arms. T3 tumors treated with brachytherapy boost had a 50% higher rate of major response. Appelt et al. 2014 showed no difference in 5-year survival despite better initial response in T3 tumors	Reported, but not itemized	T3-T4; NO-N2	248; 111 in EBRT arm 110 in brachytherapy boost arm
Appelt 2015	60 Gy to tumor via EBRT in 30 fractions, with 1 dose of 5 Gy via Brachytherapy	Dx confirmed with transrectal US, MRI, whole-body PET-CT. Treatment planning with CT, with MRI as an aid	UFT 300 mg/m <sup>2</sup> on RT days (daily for 6 weeks)	Tumor monitored by endoscopy with tattoo at 2, 4 and 6 weeks. After 6 weeks clinical complete response and allocation to watchful waiting by clinical exam, endoscopy, and MRI. CT for distant metastasis.	40/51 cCR 78%	Nausea: 4%; diarrhea: 8%; anemia: 2%; leucopenia: 2%; other: 4%	T2-T3; NO-N1	51

IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiation therapy; pCR, pathological complete responses; UFT, tegafur/uracil; GTV, gross tumor volume; PET, positron emission tomography; FDG, fluorodeoxyglucose; SUV, standardized uptake value.



**Table 2** Ongoing trials related to rectal dose escalation

Sponsor institution (reference)	Experimental Arm	Control arm	Intra-radiation response assessment	Primary outcome measures	Eligibility/tumor stage	Estimated enrollment/status	Clinical trial number
UMC Utrecht (16)	50 Gy with Capecitabine + 15 Gy boost	50 Gy with Capecitabine	MRI at week 2 of chemo-RT and week 7 post chemo-RT	Complete response rate (in surgical patients). 2-year LRFS in those who open for watchful waiting	"Indication for chemo-RT"	94/Recruiting	NCT01951521
Zhongnan Hospital (69)	25Gy to with a boost to 30 Gy/ 5 fractions	25 Gy	–	Pathologic complete remission rate (4 weeks post op)	T3-4NxM0, tumor ≤12 cm from anal edge	100/Pre-recruitment	NCT02498353
Grupo de Investigación Clínica en Oncología Radioterapia (70)	53.75 Gy to tumor and nodes by IMRT (concomitant boost) with chemo	50.4 Gy by 3DRT (sequential boost) with chemo	–	pCR. Gastrointestinal toxicity	T3-4, N0-N2, and M0	525/Recruiting	NCT02964468
University of Brasilia (71)	45 Gy to pelvis + 14.4 Gy to GTV by 3DCRT with chemo	–	–	pCR	T3-4, N+	48/Recruiting	NCT02603302
Chinese Academy of Medical Sciences (72)	50 Gy, + SIB up to 56 Gy to tumor + capecitabine	50 Gy + capecitabine	–	pCR	T3-4, 15 cm from anal verge	104/Recruiting	NCT02195141
McGill University Health Center (73)	45 Gy to pelvis + boost to 54 Gy total + institutional standard chemotherapy	–	–	Feasibility of a "wait and see" approach	T3-T4	48/Recruiting	NCT03001362
Centre Antoine Lacassagne (74)	45 Gy with capecitabine + contact X-ray Brachytherapy boost 50 kV (90 Gy in 3 fractions)	45 Gy by EBRT boosted to 54 Gy	Week 14 after treatment initiation, tumor response evaluation, continue Watch and wait, or surgery	Rate of rectum preservation with watch and wait or local excision	T2, T3a, T3b, N0, N1	236/Recruiting	NCT02505750

IMRT, intensity-modulated radiotherapy; Chemo-RT, radiation therapy and concurrent chemotherapy; LRFS, local recurrence free survival; GTV, gross tumor volume; pCR, pathologic complete response.

adenocarcinoma.

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