Adaptive radiation dose escalation in rectal adenocarcinoma: a review.

Jonathan D. Van Wickle, Medical College of Wisconsin
Eric S. Paulson, Medical College of Wisconsin
Jerome Landry, Emory University
Beth A. Erickson, Medical College of Wisconsin
William A. Hall, Medical College of Wisconsin

Journal Title: Journal of Gastrointestinal Oncology
Volume: Volume 8, Number 5
Publisher: Pioneer Bioscience Publishing Company | 2017-10, Pages 902-914
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.21037/jgo.2017.07.06
Permanent URL: https://pid.emory.edu/ark:/25593/s6n5v

Final published version: http://dx.doi.org/10.21037/jgo.2017.07.06

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Accessed August 1, 2019 7:44 AM EDT
Adaptive radiation dose escalation in rectal adenocarcinoma: a review

Jonathan D. Van Wickle 1, Eric S. Paulson 1, Jerome C. Landry 2, Beth A. Erickson 1, William A. Hall 1

1Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; 2Department of Radiation Oncology, Emory University, Atlanta, GA, USA

Contributions: (I) Conception and design: JD Van Wickle, WA Hall; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor William A. Hall, MD. Assistant Professor, Department of Radiation Oncology, Medical College of Wisconsin, 8701 W Watertown Plank Rd, Milwaukee, WI 53226, USA. Email: whall@mcw.edu.

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

Submitted May 02, 2017. Accepted for publication Jun 19, 2017.
doi: 10.21037/jgo.2017.07.06
View this article at: http://dx.doi.org/10.21037/jgo.2017.07.06

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**

18F-fluorodeoxyglucose PET (18F-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 SUV_max 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-dimentional 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 chemoradiation 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 irraditates 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 10% 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).
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>
<thead>
<tr>
<th>First author</th>
<th>Radiation/modality</th>
<th>Imaging used in planning/delivery</th>
<th>Chemotherapy</th>
<th>Response assessment</th>
<th>pCR or cCR</th>
<th>&gt; or = G3 toxicity</th>
<th>Tumor stages</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohiuddin 2000</td>
<td>EBRT 3D-CRT: 45-60 Gy</td>
<td>Evaluation with CT abdomen/pelvis; sigmoidoscopy with biopsies and colonoscopy</td>
<td>1,000 mg/m² 3–5x per week; or continuous IV 225 mg/m²</td>
<td>Surgery 6–8 weeks post CRT</td>
<td>pCR 10% with 5-FU bolus; 67% with continuous infusion; 13% with 45–50 Gy; 44% with 55–60 Gy</td>
<td>pCR or cCR</td>
<td>T1–T3</td>
<td>33</td>
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<td>Pfeiffer 2005</td>
<td>EBRT 3D-CRT: 48.6 Gy to CTV in 27 fractions, 60 Gy to GTV in 30 fractions</td>
<td>GTV defined by integrated CT and MRI images</td>
<td>Oral UFT 150–300 mg/m² 5 days per week + 7.5 mg Leucovorin</td>
<td>Eval with CT and DRE 4 weeks post CRT. Resection 6 weeks post CRT</td>
<td>pCR: 11% (2/18)</td>
<td>39% (7/18) diarrhea</td>
<td>Primary unresectable and local recurrent rectal cancer</td>
<td>18</td>
</tr>
<tr>
<td>Movsas 2006</td>
<td>EBRT 3D-CRT: 45.6 Gy to pelvis with 61.8 Gy to GTV</td>
<td>Pretreatment evaluation by CT, MRI, transrectal ultrasound</td>
<td>5 FU 1 g/m² per 24 hours ×4 d in 1st and 6th week of RT</td>
<td>Surgery 4–6 weeks post CRT with pathologic evaluation</td>
<td>pCR: 0%. Downstaging in 50% (10/20) of evaluated patients</td>
<td>14%</td>
<td>T3 and T4</td>
<td>22</td>
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<tr>
<td>Vestermark 2012</td>
<td>EBRT 3D-CRT: 48.6 Gy to CTV in 27 fractions, 60 Gy to GTV in 30 fractions</td>
<td>GTV determined by MRI</td>
<td>Oral UFT 300 mg/m² + 22.5 mg Leucovorin and 10 mg/m² per week of Oxaliplatin escalated to 60 mg/m² over the treatment course</td>
<td>Surgery 6 weeks post CRT with pathologic evaluation</td>
<td>pCR: 33% (5/15)</td>
<td>17%</td>
<td>Primary or recurrent unresectable rectal cancer</td>
<td>18</td>
</tr>
<tr>
<td>Mohiuddin 2013</td>
<td>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</td>
<td>Optional MRI for TNM staging</td>
<td>Arm 1: CVI of 5-FU 225 mg/m² per day; Arm 2: CVI 5-FU M-F (120 hr/wk) + Infusen 50 mg/m² once per week</td>
<td>Surgery 4–10 weeks post-CRT</td>
<td>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</td>
<td>42% in Arm 1; 51% in Arm 2; consisting mostly of dermatological, gastrointestinal and bone marrow/blood toxicity</td>
<td>T3 and T4</td>
<td>103</td>
</tr>
<tr>
<td>Engineer 2013</td>
<td>EBRT 3D-CRT: Arm 1: 45 Gy to pelvis; Arm 2: (radiation only) 45 Gy to pelvis with 20 Gy boost to tumor</td>
<td>CT or MRI for treatment planning</td>
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<td>Clinical evaluation with CT 6–8 weeks post CRT, followed by surgery and pathologic evaluation</td>
<td>pCR—Arm 1: 7%; Arm 2: 11%</td>
<td>Arm 1: 8.8% (4/45); Arm 2: 4.8% (2/42)</td>
<td>&quot;clinically unresectable rectal cancer&quot;</td>
<td>90</td>
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<tr>
<td>Freedman 2007</td>
<td>IMRT 45 Gy boosted to 55 Gy by SIB</td>
<td>CT and/or MRI</td>
<td>Capecitabine PO 825 mg/m² 7 days per week</td>
<td>PET SUV pre and post RT</td>
<td>pCR =0%</td>
<td>Acute GI 13%, anemia 13%, fatigue 13%, pain 13%, ileus 13%, dehydration 13%</td>
<td>cT3–T4/N+</td>
<td>8</td>
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<td>Ballanoff et al. 2008</td>
<td>SIB IMRT: 55 Gy</td>
<td>CT, EUS, MRI and/or PET</td>
<td>Capecitabine (825 mg/m²) 5 days per week with RT</td>
<td>6 weeks post-chemoradiation; TME and pathologic evaluation</td>
<td>pCR =38%</td>
<td>Grade 4 diarrhea in 1 of 8 patients (13%)</td>
<td>Locally advanced</td>
<td>8</td>
</tr>
<tr>
<td>Zhu 2013</td>
<td>IMRT 55 Gy</td>
<td>Planning: CT, MRI, some PET-CT</td>
<td>Capecitabine 625 mg/m² 5 days per week + oxaliplatin 50 mg/m² weekly</td>
<td>Evaluation with MRI at the conclusion or CRT, and every 2 mo until 6 mo, CT to confirm</td>
<td>cCR 4/32; pCR 5/14</td>
<td>Grade 3: Radiation dermatitis 18.8%, GI toxicity 15.6%</td>
<td>cT3–T4 cN+</td>
<td>32 total; 14 underwent surgery</td>
</tr>
<tr>
<td>Hernando 2014</td>
<td>IMRT 46 Gy boosted to 57.5 Gy by SIB</td>
<td>CT, PET-CT in all but 4 patients, MRI for staging, and CT image-guided delivery</td>
<td>Capecitabine 825 mg/m² BID</td>
<td>Blood count, tumor markers, CT, PET-CT, MRI, echoendoscopy. surgery 8 weeks post treatment. Median 67.6 days.</td>
<td>Downstaging in 55/72 (76.28%); ypCR in 22/72 (30.6%)</td>
<td>Acute: GI 10%, GU 5%</td>
<td>cT2-4 N+</td>
<td>74</td>
</tr>
<tr>
<td>Cubillo 2014</td>
<td>IMRT 46 Gy boosted to 57.5 Gy by SIB</td>
<td>ERUS, MR, CT, PET with SUV</td>
<td>Capecitabine 625 to 825 mg/m², Alone or with 50 mg/m² irinotecan, oxaliplatin, cetuximab, or bevacizumab depending on tumor genotype</td>
<td>EUS, PET SUV change, TNM staging. surgery 6-8 weeks post CRT</td>
<td>50% pCR</td>
<td></td>
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<tr>
<td>Picardi 2016</td>
<td>VMAT-SIB: 45 Gy, boost to 57.5 Gy (2.3 Gy/fraction)</td>
<td>MRI</td>
<td>Oxaliplatin and capecitabine</td>
<td>Clinical restaging 5-6 weeks after CRT by physical exam and pelvic MRI, surgery 8 weeks after CRT</td>
<td>pCR: 4 of 16 patients who underwent surgery (25%); CR =4 of total 18 (22%)</td>
<td>Leukopenia =1; skin =1; GU =1; GI =5; overall 44.4%</td>
<td>T2–T4; NO–N2</td>
<td>18</td>
</tr>
<tr>
<td>Alongi et al. 2016</td>
<td>VMAT: 60 Gy in 30 fractions to PTV-SIB; 5.4 Gy to remaining PTV</td>
<td>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</td>
<td>Capecitabine 825 mg/m² BID 5 days per week during RT</td>
<td>Restaging after 8–10 weeks, just prior to surgery</td>
<td>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</td>
<td>No Grade 3 or greater toxicity noted</td>
<td>T2–T4; NO–N1</td>
<td>40</td>
</tr>
<tr>
<td>Appelt et al. 2015</td>
<td>60 Gy in 30 fractions by IMRT, 15 Gy brachytherapy dose on final day of RT</td>
<td>CT with MRI to aid in target planning</td>
<td>Oral tegafur-uracil 300 mg/m²</td>
<td>6 weeks post treatment determined by clinical exam, endoscopy with negative biopsy from primary tumor site, plus pelvic MRI</td>
<td>cCR 40 (78.4%)</td>
<td>Nausea 2 (4%); Diarrhea 4 (8%); Anemia 1 (2%); Leukopenia 1 (2%); Other 2 (4%)</td>
<td>Primary, resectable</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 1 (continued)
<table>
<thead>
<tr>
<th>First author</th>
<th>Radiation/modality</th>
<th>Imaging used in planning/delivery</th>
<th>Chemotherapy</th>
<th>Response assessment</th>
<th>pCR or cCR</th>
<th>&gt; or = G3 toxicity</th>
<th>Tumor grade</th>
<th># of patients</th>
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<tbody>
<tr>
<td>Jakobsen 2006</td>
<td>EBRT 27 fractions, total dose of 54 Gy to CTV1, and CTV2 boosted to 60 Gy + 5 Gy brachytherapy</td>
<td>Staging with endorectal ultrasound and MRI</td>
<td>Uracl-tegafur 300 mg/m² per day</td>
<td>Histopathologic assessment with tumor regression grade system</td>
<td>27%</td>
<td>Diarrhea (6%)</td>
<td>T3; N0-N2</td>
<td>50</td>
</tr>
<tr>
<td>Jakobsen 2008</td>
<td>EBRT 27 fractions, total dose of 54 Gy to CTV1, and CTV2 boosted to 60 Gy + 5 Gy brachytherapy</td>
<td>endorectal ultrasound and MRI</td>
<td>Uracl-tegafur 300 mg/m² per day + celecoxib 400 mg BID</td>
<td>Surgery 8 weeks post CRT, evaluated with tumor regression grade system</td>
<td>7/33 (21%) pCR</td>
<td>Diarrhea (2.9%); leucopenia (2.9%)</td>
<td>T3–T4</td>
<td>35</td>
</tr>
<tr>
<td>Sun Myint 2010</td>
<td>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</td>
<td>Tumor staged with CT, MRI</td>
<td>5-FU 750 g/m² &gt;4 days in weeks 1 and 5; or oral capcitabine 625–825 mg/m² M-F with RT</td>
<td>MRI and endoscopy. Surgery 6–8 weeks post CRT</td>
<td>&gt;80% regression in 12 (35%). pCR in 9 patients (31%)</td>
<td>2 (5.8%) delayed wound healing; 2 (5.8%) anastomotic leakage; 1 (3.4%) small bowel obstruction; 1 (3.4%) stricture</td>
<td>T2–T4; NO–N2</td>
<td>34</td>
</tr>
<tr>
<td>Appelt 2014 /Jakobsen 2012</td>
<td>Arm A: 50.4 Gy EBRT; Arm B: 50.4 Gy EBRT + 2 fractions of 5 Gy Brachy</td>
<td>Tumor staged with MRI, CT, rectal US and rectoscopy. Treatment planning with CT</td>
<td>Oral tegafur-uracil 3× 100 mg/m², and oral l-leucovorin 3× 7.5 mg with RT</td>
<td>Surgery 8 weeks post-treatment, with histological evaluation</td>
<td>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</td>
<td>Reported, but not itemized</td>
<td>T3–T4; NO–N2</td>
<td>248; 111 in EBRT arm 110 in brachytherapy boost arm</td>
</tr>
<tr>
<td>Appelt 2015</td>
<td>60 Gy to tumor via EBRT in 30 fractions, with 1 dose of 5 Gy via Brachytherapy</td>
<td>Dx confirmed with transrectal US, MRI, whole-body PET-CT. Treatment planning with CT, with MRI as an aid</td>
<td>UFT 300 mg/m² on RT days (daily for 6 weeks)</td>
<td>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.</td>
<td>40/51 cCR 78%</td>
<td>Nausea: 4%; diarrhea: 8%; anemia: 2%; leucopenia: 2%; other: 4%</td>
<td>T2–T3; NO–N1</td>
<td>51</td>
</tr>
</tbody>
</table>

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

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

Table 2 Ongoing trials related to rectal dose escalation

Acknowledgements

Funding: This publication was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1TR001436.

Footnote

Conflicts of Interest: Elekta Inc. provides research support to the Medical College of Wisconsin Department of Radiation Oncology. In addition, WA Hall, MD reports research support from the American Cancer Society and the National Institutes of Health.

Disclaimer: Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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70. Grupo de Investigación Clínica en Oncología Radioterapia. Dose-escalation trial of preoperative radiotherapy and
concurrent chemotherapy in locally advanced rectal cancer. Available online: https://clinicaltrials.gov/show/NCT02964468: NCT02964468 (This study is currently recruiting participants).


