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Novel Radiation Approaches for the Treatment of Rectal Cancer: Where Are We Now?

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Abstract Over the past decade, significant strides have been made in improving local control for stage II and III rectal cancer, including the use of neoadjuvant chemoradiation and total mesorectal excision. These advancements have led to a remarkable 10-year local failure rate of just 7.1 %. This has come, however, at the cost of moderate treatment-related morbidity, emphasizing a need for further refinement of management strategies. This article will explore recent innovations and novel approaches involving radiation therapy to address these issues, including the use of intensity-modulated radiation therapy, avoidance of radical resection with the use of chemoradiation alone, total neoadjuvant chemotherapy with the selective use of chemoradiation, and the use of local excision approaches following neoadjuvant treatment. Although many of these novel strategies appear promising, data from prospective randomized trials will be necessary before implementation into standard practice.

Keywords Intensity-modulated radiation therapy · Chemoradiation alone · Watchful waiting · Local excision · Total neoadjuvant therapy · Selective use of radiation

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Introduction

Surgical resection is the primary treatment for localized rectal cancer. While surgical resection alone leads to high cure rates for early-stage disease (T1–T2N0), there is a high rate of both local and distant recurrence for locally advanced cancers (T3–T4 and/or N+) of up to 50 %. This high risk of recurrence was overcome with the use of adjuvant chemoradiation therapy [1–3]. In 1990, the National Cancer Institute Consensus Conference recommended postoperative chemoradiation utilizing 5-fluorouracil (5-FU)-based chemotherapy as the standard of care for patients with pathologic T3–T4 and/or node-positive rectal cancer [4].

With the advent of improved methods of pretreatment clinical staging including endoscopic ultrasonography, preoperative chemoradiation was evaluated in the treatment of stage II/III rectal cancer. In 2004, the results of the German Rectal Cancer trial established preoperative chemoradiation as the new standard of care for the treatment of stage II/III rectal cancer with improved local control as well as decreased toxicity when compared to patients treated in the adjuvant setting [5].

Formerly, low anterior resections (LAR) for high rectal cancers or abdominoperineal resection (APR) for low rectal cancers involved blunt dissection of the mesorectal fascia, which was associated with high rates of local recurrence and necessitated the use of adjuvant radiation therapy. Currently, total mesorectal excision (TME) involves the sharp dissection of the mesorectum, resulting in lower rates of local recurrence [6]. TME has been shown, on its own, to improve pelvic control over non-TME surgeries in rectal cancer [7, 8]; however, the addition of radiation still significantly enhances local-regional control even with TME [9–11]. The German Cancer Rectal trial included TME for all patients with quality control. Surgery is performed 6–8 weeks following

completion of preoperative chemoradiation to allow for maximum tumor regression.

In this study, the addition of preoperative chemoradiation improved the rates of 5-year cumulative local relapse from 13 % (postoperative arm) to 6 % (preoperative arm). Preoperative chemoradiation resulted in better sphincter preservation in low-lying tumors, which were deemed upfront by the surgeon to require an APR (39 vs. 19 %, $p = 0.004$). Acute grade 3 or 4 toxicities were also improved in the preoperative group (27 %) when compared to the postoperative group (40 %, $p = 0.006$) [5]. This benefit persisted with long-term follow-up, with 10-year cumulative incidence of local relapse of 7.1 % in the preoperative group vs. 10.1 % in the postoperative group ($p = 0.048$). Late toxicity rates were lower for the preoperative group, 14 vs. 24 % ($p = 0.01$) [12].

Based on the German Rectal Study, when all three modalities (neoadjuvant chemotherapy with concurrent radiation and TME) are applied, the 10-year local failure rate is only 7.1 % [12]. Therefore, preoperative chemoradiation followed by TME and then additional chemotherapy is considered the standard of care in the treatment of stage II/III rectal cancer.

Problem of Enhanced Toxicity with Adjuvant Chemoradiation

It is important to note that administering adjuvant therapy for stage II and III rectal cancer comes with a price: increased treatment-related deaths and enhanced toxicity including radiation enteritis, diarrhea, ileus, bowel obstruction, and hematologic toxicities [2, 3, 12–14]. Furthermore, patients who receive preoperative radiotherapy have a slower recovery from defecation problems ($p = 0.006$), higher negative effect on sexual functioning in both males ($p = 0.004$) and females ($p < 0.001$), and more ejaculation disorders in males ($p = 0.002$), with higher deterioration of erectile functioning over time ($p < 0.001$) when compared to patients who received surgery alone [15]. A long-term questionnaire analysis from patients in a prospective randomized TME trial revealed significantly lower rates of satisfaction with bowel function in those who received preoperative radiation compared to those who received surgery only. Irradiated patients had increased rates of fecal incontinence (62 vs. 38 %, $p < 0.001$), pad wearing as a result of incontinence (56 vs. 33 %, $p < 0.001$), anal blood loss (11 vs. 3 %, $p = 0.004$), and mucus loss (27 vs. 15 %, $p = 0.005$) [16]. Although the combination of surgery and adjuvant therapies results in excellent local control, the increased risk of acute and late morbidity is also significant.

Should Chemoradiation Be Employed for All Stage II and III Disease?

Before preoperative chemoradiotherapy and TME emerged as the new standard of care, investigators evaluated whether there was a select group of patients in which adjuvant chemoradiotherapy could be safely omitted. Retrospective data from the pre-TME era suggest that there may be a favorable subset of patients with pathologic T3N0 disease (well to moderately differentiated histology, extending 2 mm or less into the perirectal fat, without lymphatic or vascular invasion, upper rectal location, and adequate node dissection) who may not benefit from adjuvant treatment [17–21]. Furthermore, Gunderson and colleagues performed subset analyses of the largest postoperative Intergroup trials evaluating adjuvant chemoradiotherapy and found significantly improved local control and survival outcomes for patients with T3N0 or T1/2N1 disease, suggesting that selected stage II disease may warrant evaluation of more selective treatment approaches [22].

The location of the cancer is also important in determining the local recurrence risk. The rectum is divided into the upper, middle, and lower third by the valves of Houston. The upper third of the rectum is covered by peritoneum anteriorly and posteriorly, whereas the middle third has peritoneum only anteriorly, and the lower third has no peritoneal covering. Therefore, when tumors in the mid or lower rectum invade anteriorly, they can have direct invasion into anterior structures such as the prostate, cervix, or vagina (T4b), whereas the same tumor in the upper rectum will penetrate only the visceral peritoneum (T4a) [23]. Therefore, treatment recommendations could vary by the exact anatomic location of the tumor. Of note is that while digital rectal examination can accurately determine the distance of a low rectal tumor from the anorectal ring, endoscopic measurements are often less reliable in determining the distance from the anal verge to the tumor for mid and high rectal cancers. Radiographic modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or PET scans are therefore used in conjunction with endoscopic ultrasound and physical examination to localize the tumor in relation to pelvic landmarks.

The Dutch TME trial, which randomized patients to either preoperative radiotherapy plus TME or to TME alone, found that preoperative radiotherapy reduced the 10-year local recurrence from 11 to 5 % ($p < 0.0001$) [9]. However, on univariate subgroup analysis, patients with upper rectal tumors had no improvement in local recurrence with the addition of neoadjuvant radiation alone compared to surgery alone [10]. Although there are no randomized trials of cancers of the upper rectum, subset analyses of large studies indicate a 4 % risk of local recurrence in patients who have undergone TME with at least 12 negative nodes. Several small retrospective studies have also shown that high rectal cancers treated with

surgery alone have very low recurrence rates [17, 18, 24, 25]. As the risk of local recurrence decreases with distance from the anal verge, and sphincter preservation is possible due to the location, one may consider upfront surgery in this group of patients to allow for more accurate pathologic staging. In the German Rectal Study, 18 % of patients who were clinically staged as T3N0M0 and randomized to the initial surgery arm were found to have T1/2N0M0 disease at the time of pathologic review [5]. As such, in patients with pathologically staged T3N0M0 disease of the upper rectum, accurate pathologic staging may spare the need for adjuvant chemoradiation [26]. The more standard use of staging pelvic MRI in the USA may also help in this regard.

Induction Chemotherapy Followed by Selective Use of Chemoradiation

Given the availability of more active systemic agents, upfront chemotherapy followed by selective use of chemoradiation is under investigation. In a phase II study conducted at Memorial Sloan Kettering Cancer Center, 32 patients with stage II/III rectal cancer completed six cycles of neoadjuvant infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX)/Bevacizumab [27•]. All patients underwent LAR. The pathologic complete response (pCR) rate was 25 % and the 4-year local recurrence rate was 0 %. This pilot data led to the design of the current Intergroup randomized phase II/III study undertaken to validate its results. The PROSPECT (Preoperative Radiation Or Selective Preoperative Radiation and Evaluation before Chemotherapy and Total Mesorectal Excision) trial (NCT01515787) is an ongoing randomized phase II/III trial randomizing patients to either standard of care neoadjuvant chemoradiation followed by surgery and then adjuvant FOLFOX or to the experimental arm which begins with induction FOLFOX followed by restaging. Responders go on to surgery alone and complete adjuvant chemotherapy, while non-responders complete neoadjuvant chemoradiation followed by surgery and then chemotherapy.

Total Neoadjuvant Therapy

The current standard approach to stage II/III rectal cancer involves chemoradiation using radiation to 50.4 Gy in 28 fractions over 5–6 weeks followed by definitive surgery (LAR or APR) and then adjuvant chemotherapy. However, nearly 30 % of eligible patients never start postoperative chemotherapy, and less than 50 % receive the full prescribed course [28, 29]. As systemic therapy for metastatic rectal cancer has advanced with the addition of oxaliplatin, it is hypothesized that improvements in survival in this locally advanced setting may be achieved if all of the planned systemic treatment is delivered upfront. Therefore, a new treatment paradigm that moves systemic and radiation therapy before surgery—total neoadjuvant therapy (TNT)—has been proposed.

Several institutions have begun to evaluate this TNT approach. A phase II randomized trial from Spain demonstrated that TNT was well tolerated, with a lower toxicity profile and significant improvement in chemotherapy compliance when compared to conventional treatment [30•]. Additionally, long-term outcomes were not compromised, with a 5-year disease-free survival (DFS) of 64 % in the TNT arm vs. 62 % in the conventional treatment arm ($p = 0.85$), 5-year overall survival (OS) of 78 vs. 75 % ($p = 0.79$), 5-year cumulative incidence of local recurrence (LR) of 2 vs. 5 % ($p = 0.61$), and 5-year cumulative incidence of distant metastases of 21 vs. 23 % ($p = 0.79$).

Garcia-Aguilar and investigators from Memorial Sloan Kettering recently published [31•] their results of adding mFOLFOX6 between preoperative chemoradiation and TME. In this study, there were a total of 259 patients with stage II/III cancer treated among four nonrandomized sequential groups at several institutions. The primary endpoint was pCR rate. Group 1 (control) received standard chemoradiation (albeit with a total radiation dose of 54 Gy) and TME 6–8 weeks later; the proportion of patients achieving pCR in this group represented the baseline pCR rate. Patients in groups 2–4 received chemoradiation followed by two, four, or six cycles, respectively, of mFOLFOX6 and then TME. The pCR rates were 18 % in group 1 [95 % confidence interval (CI) = 10–30], 25 % in group 2 (95% CI = 16–37), 30 % in group 3 (95% CI = 19–42), and 38 % in group 4 (95% CI = 27–51, $p = 0.0036$). Patients in group 4 were significantly more likely to achieve a pCR than the control group 1 (odds ratio = 3.49, 95% CI = 1.39–8.75, $p = 0.011$). While this TNT approach with six cycles of upfront chemotherapy has yielded an impressive pCR rate without a reported increase in tumor progression or surgical complications, this study has a number of limitations. Due to its nonrandomized nature, this study may be associated with selection bias. Second, longer follow-up is necessary to assess the important endpoint of disease-free survival. As such, the findings of this study should be interpreted with caution and a larger prospective multicenter trial is warranted.

Another utility of this total TNT approach is that it allows us to readily evaluate novel systemic, biologic, and radiosensitizing agents. An excellent example of this is the NRG Oncology GI-002 trial which is a randomized phase II trial for high-risk locally advanced rectal cancer designed to test novel drugs using parallel, noncomparative experimental arms and a control arm of FOLFOX x 8, capecitabine with concurrent radiation, followed by TME. This trial should be opened for accrual in late 2016 (Thomas George, personal communication).

Table 1 Select studies evaluating surgery vs. watchful waiting following chemoradiation

Study	Method	Preoperative regimen	Results
Renehan et al. [37]	Propensity score-matched cohort	45 Gy in 25 fractions with concurrent fluoropyrimidine-based chemotherapy	3-year non-regrowth DFS[a]: 88 % in WW vs. 78 % in surgery, $p = 0.043$
	$N = 129$ (watchful waiting/cCR)		3-year OS: 96 % in WW vs. 87 % in surgery, $p = 0.024$
	$N = 228$ (surgery/pCR)		3-year colostomy-free survival: 96 % WW vs. 87 % surgery, $p = 0.024$
Habr-Gama et al. [38]	Retrospective cohort study	50.4 Gy in 28 fractions with concurrent 5-FU (425 mg m^{-2} day^{-1}) and folinic acid (20 mg m^{-2} day^{-1}) administered intravenously for 3 consecutive days on the first and last 3 days of radiation therapy	2 LR in WW at median 57.3-month follow-up
	$N = 71$ (watchful waiting/cCR)		No LRs in the surgery group
	$N = 22$ (surgery/pCR)		Surgery: 5-year OS of 88 % and DFS of 83 %
			WW: 5-year OS of 100 % and DFS of 92 %
Maas et al. [39]	Prospective cohort study	50.4 Gy in 28 fractions with concurrent capecitabine (2×825 mg/m^2)	1 LR (surgically salvaged) in WW and rest alive without disease at median 25-month follow-up
	$N = 21$ (watchful waiting/cCR)		No LRs in the surgery group
	$N = 20$ (surgery/pCR)		2-year DFS is 89 % and 2-year OS is 100 % in the WW group
			2-year DFS of 93 % and 2-year OS of 91 % in the surgery group
Smith et al. [40]	Retrospective cohort study	5–6 weeks of EBRT with concurrent 5-FU or capecitabine	6 LRs in WW at median 28-month follow-up, treated with salvage rectal resection with no further LRs
	$N = 32$ (watchful waiting/cCR)		No LRs in the surgery group
	$N = 7$ (surgery/pCR)		2-year distant DFS: 88 % in WW vs. 98 % in surgery, $p = 0.27$
			2-year OS: 96 % in WW vs. 100 % in surgery, $p = 0.56$
Appelt et al. [41]	Prospective observational trial	60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective LNs, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil (300 mg/m^2) every weekday for 6 weeks	Of 51 eligible patients, 40 had cCR (78 %) and allocated to the WW group
	$N = 40$ (watchful waiting/cCR)		9 LRs at median 23.9-month follow-up; all salvaged with APR
			1-year LR: 15.5 % (95% CI = 3.3–26.3); 2-year LR: 25.9 % (9.3–42.8)
			2-year OS: 100 %

WW watchful waiting, *cCR* clinical complete response, *pCR* pathologic complete response, *N* number of patients, *LR* local recurrence, *DFS* disease-free survival, *OS* overall survival, *EBRT* external beam radiation therapy

[a] Non-regrowth DFS defined as the length of time after treatment until death (any cause), local pelvic recurrence, and distant metastases, not including local regrowth

Chemoradiation Alone Followed by Watchful Waiting

Surgical resection is currently the standard of care after neoadjuvant chemoradiation. However, surgical resection can also be associated with significant morbidity, especially in patients with distal tumors requiring APR, which entails permanent colostomy and is associated with diminished body image perception and sexual/urinary dysfunction [32, 33].

Meta-analyses have shown that patients who achieve a pCR after neoadjuvant chemoradiation have excellent long-term outcomes as compared to patients without a pCR [34–36]. These favorable outcomes have raised the question as to whether radical surgery may be avoided or postponed in patients with a clinical complete response (cCR) via a watchful waiting approach following primary chemoradiation.

Retrospective and early prospective data suggest watchful waiting is a reasonable alternative to surgery in patients who achieve a cCR after chemoradiation [37–41]

(see Table 1). The concept of watchful waiting was first explored by a study in Brazil by Habr-Gama et al. [38]. In this study, 265 patients with resectable distal rectal adenocarcinoma were treated with neoadjuvant chemoradiation to a dose of 50.4 Gy (with 5-FU/leucovorin on the first 3 days and last 3 days of radiotherapy). Patients were evaluated 8 weeks after completion of chemoradiation for tumor response, which included proctoscopy and biopsies. Patients who were found to have residual disease or a positive biopsy were treated with surgery, whereas patients with a cCR were observed with monthly follow-up visits with repeat physical and digital rectal examination, proctoscopy, biopsies (when feasible), and serum carcinoembryonic antigen (CEA) levels. Patients must have had a sustained complete response for 12 months in order to be considered "stage 0" and were placed in the watchful waiting group. Seventy-one patients had a cCR (26.8 %) and were included in this group. Of the incomplete responders (194 patients), those who had a pCR (22 patients, 8.3 %) were considered "stage 0" and included in the resection group for comparison. The 10-year overall and disease-free survival rates were 100 and 86 %, respectively. Only two patients in the watchful waiting group experienced a local recurrence, which was managed with salvage local therapy. There was no difference in recurrence rates or mortality between these two groups ($p = 0.2$). Therefore, the authors concluded that surgery (and its associated morbidities) may be avoided in this select cohort of patients who achieve a cCR after chemoradiation. These patients must be willing to return for serial follow-ups as active monitoring is an essential component of watchful waiting. This study, however, has been criticized for its retrospective nature, lack of modern imaging, and that outcomes may have been favorably skewed by the inclusion of 20 % T2N0 patients.

A subsequent prospective cohort study was performed in the Netherlands to evaluate the watchful waiting approach, with strict selection criteria and incorporation of MRI [39]. Locally advanced rectal cancer patients (defined as a T4 tumor or a T3 tumor with involved mesorectal fascia and/or more than three involved nodes and/or a distal tumor with one to three involved nodes) were evaluated with MRI before neoadjuvant chemoradiation and after completion of treatment. Additionally, an endoscopy was performed on all patients who had a negative posttreatment MRI. The study defined cCR as having substantial downsizing with no residual tumor or residual fibrosis only, no suspicious lymph nodes on MRI, no residual tumor at endoscopy or only a small residual erythematous ulcer or scar, negative biopsies, and no palpable tumor, when initially palpable with digital rectal examination. If patients did not meet all of the above criteria, they were regarded as non-complete responders and went on to surgery. The follow-up protocol for the watchful waiting policy consisted of serial digital rectal examination, MRI, endoscopy (with biopsy), CT scan of the chest and abdomen, and CEA measurements. Of the 192 patients treated, 21 had a cCR and were included in the watchful waiting group. The control group consisted of 20 patients who had a pCR after neoadjuvant chemoradiation and TME. With a 2-year median follow-up, only one patient developed a local recurrence in the watchful waiting group, which was managed with salvage transanal endoscopic microsurgery. The cumulative probability for 2-year DFS was 89 % (95% CI = 43–98), and the cumulative probability for 2-year OS was 100 % in the watchful waiting group. Cumulative probability in the resection group for 2-year DFS was 93 % (95% CI = 59–99), and cumulative probability for 2-year OS was 91 % (95% CI = 59–99). Cumulative probabilities for DFS and OS were not significantly different between the watchful waiting patients and the patients who had surgery ($p = 0.770$ and $p = 0.228$ for DFS and OS, respectively). This study is limited by its small sample size and short follow-up. Nevertheless, the watchful waiting approach with MRI imaging appears safe and feasible for this highly select group of patients.

It is important to note that salvage therapy may be employed for local failures to this watchful waiting approach. Habr-Gama found that up to 31 % of patients locally failed, with more than half of the recurrences developing within the first 12 months of follow-up. Local salvage therapy was possible in >90 % of recurrences, leading to 94 % pelvic disease control and 78 % organ preservation [42]. A more recent prospective trial by Habr-Gama showed improvement in the cCR rates (68 %) and sustained "stage 0" rate (57 %) by increasing the dose of radiotherapy to 54 Gy, using concurrent/consolidative chemotherapy (5-FU and leucovorin q21 days × six cycles), and prolonging the time interval (10 weeks) from completion of radiotherapy to assessment of response [43•]. Although these results are promising, prospective validation in multi-institutional trials is warranted before the widespread adoption of "watchful waiting" is recommended.

Local Excision Strategies

The standard of care for patients with stage I rectal cancers (T1N0 and T2N0) remains definitive surgery alone, which is either an LAR for upper rectal cancers or APR for low rectal cancers. However, both of these procedures are associated with significant risks of complications including urinary dysfunction, sexual dysfunction, anastomotic leaks, and death [44–47]. In addition, an APR would require a permanent colostomy. Therefore, there has been growing interest in using local excision to minimize morbidity in stage I rectal cancer patients. CALGB 8984 enrolled 59 patients with T1 lesions who were treated with local excision alone and 51 patients

Table 2 Select studies of outcomes and toxicities with 3D-CRT vs. IMRT

Study	Method	Preoperative regimen	Results
Zhu et al. [57]	Prospective phase II study *N* = 78 (IMRT)	All treated with IMRT and concurrent oxaliplatin (50 mg/m^2 day 1 weekly) and capecitabine (625 mg/m^2, b.i.d. days 1–5 weekly) 50 Gy in 25 fractions to the pelvis. SIB of 55 Gy in 25 fractions to gross tumor	pCR: 23.7 % Acute grade 3 hematologic toxicity, 3.8 %; diarrhea, 10.3 %; and radiation dermatitis, 17.9 %
		One cycle of Xelox (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily days 1–14) was given 2 weeks after the completion of chemoradiation	No grade 4–5 toxicities 3-year LR, 14.6 %; DFS, 63.8 %; and OS, 77.4 %
Parekh et al. [53]	Retrospective analysis	All received 3D-CRT or IMRT with concurrent 5-FU or capecitabine chemotherapy	No significant difference in pCR (21.4 % IMRT vs. 16.7 % 3D-CRT, p = 1)
	N = 20 (IMRT)	3D-CRT prescription was 45 Gy in 25 fractions to the PTVr (rectal primary) and PTVn (elective nodal: mesorectum, presacrum, and b/l internal iliac, with b/l external iliac for T4 lesions), plus a sequential tumor boost of 5.4 Gy in 3 fractions to the PTVr using three-field technique	Grade ≥2 GI toxicity: 30 % IMRT vs. 60.7 % 3D-CRT, $p = 0.036$ Grade ≥2 diarrhea: 10 % IMRT vs. 42.8 % 3D-CRT, $p = 0.014$
	N = 28 (3D-CRT)	IMRT was 45 Gy in 25 fractions to the PTVn, and the PTVr concurrently received 50 Gy in 25 fractions using SIB technique	Acute grade 3 GI toxicity only: 10 % IMRT and 10.71 3D-CRT, $p = 1$
Engels et al. [54•]	Prospective phase II study	All treated with IMRT (no concurrent chemotherapy) 46 Gy in 23 fractions to the tumor and draining lymph nodes (mesorectum, inferior mesenteric, obturator, and internal iliac)	pCR: 8 % Grade ≥3 late GI of 9 % and urinary toxicity of 4 %
	N = 108 (IMRT)		Any grade ≥3 late toxicity of 13 %
		Patients ($n = 57$) with anticipated CRM of <2 mm (based on MRI) received SIB to the tumor for a total dose of 55.2 Gy	5-year LC, 97 %; PFS, 57 %; and OS, 68 % R1 resection and pN2 disease associated with significantly impaired OS
Jabbour et al. [55]	Retrospective analysis	All received 3D-CRT or IMRT with concurrent chemotherapy	No significant difference in pCR (20 % IMRT vs. 21 % 3D-CRT, $p = 0.55$) Fewer hospitalizations, ED visits with IMRT vs. 3D, $p = 0.005$
	N = 30 (IMRT)	IMRT was 45 Gy in 25 fractions to the rectum and at-risk lymph nodes (internal iliac, external iliac for T4 lesions, perirectal, mesorectal, presacral). Sequential boost of 5.4 Gy in 3 fractions to GTV and a minimum 2 cm uniform margin including all of the presacral space	No treatment breaks with IMRT vs. 20 % with 3D-CRT, $p = 0.0002$ Significant reduction in grade ≥3 toxicities vs. grade ≤2 toxicities ($p = 0.016$) with IMRT vs. 3D
	N = 56 (3D-CRT)	3D-CRT median total dose was 50.4 Gy	Grade ≥3 diarrhea: 9 % 3D-CRT vs. 3 % IMRT, $p = 0.31$ LR: 6.7 % IMRT vs. 7 % 3D, $p = 0.65$
Arbea et al. [58]	Prospective phase II study *N* = 100 (IMRT)	All received IMRT (47.5 Gy in 19 fractions) with concurrent capecitabine (825 mg/m^2, b.i.d., Monday to Friday) and oxaliplatin (60 mg/m^2 on days 1, 8, and 15)	pCR: 13 % Grade 1–2 proctitis, 73 %; grade 3, diarrhea 9 % LC of 100 %, DFS of 84 %, and OS of 87 % at median 55-month follow-up

IMRT intensity-modulated radiation therapy, *3D-CRT* three-dimensional conformal radiation therapy, *N* number of patients, *LN* lymph node, *SIB* simultaneous integrated boost, *GTV* gross tumor volume, *PTV* planning target volume, *pCR* pathologic complete response, *OS* overall survival, *DFS* disease-free survival, *LR* local recurrence, *LC* local control, *PFS* progression-free survival, *GI* gastrointestinal, *GU* genitourinary, *CRM* circumferential resection margin, *ED* emergency department

with T2 lesions who received external beam irradiation (54 Gy) and 5-fluorouracil (500 mg/m^2 intravenously days 1–3 and days 29–31) after local excision. The local recurrence rates for patients with T1 and T2 lesions were 8 and 18 %, respectively [48]. Therefore, for the carefully selected patient with a T1N0 tumor, transanal excision alone may be

considered. Selection would include tumors involving less than 30 % circumferential involvement, negative margins, no lymphovascular invasion, and no perineural invasion. It is important that the patient understands the risk of local recurrence and the need for careful follow-up to allow for salvage surgery if recurrence should develop. Currently, for T1N0 tumors with poor histopathologic features and all T2N0 tumors, LAR or APR is recommended in the USA.

The role of local excision in reducing long-term surgical morbidity is also being explored for more advanced rectal cancer patients following neoadjuvant therapy. A prospective randomized trial compared transanal endoscopic microsurgery (TEM) vs. TME in 100 patients with low-lying cT2N0 rectal cancer following neoadjuvant chemoradiation. With a median follow-up of 9.6 years, four patients developed a LR in the TEM arm and three patients developed a local recurrence in the TME arm. There was no significant difference in DFS ($p = 0.686$), nor in OS ($p = 0.609$) [49]. Recently, ACOSOG Z6041, a multi-institutional single-arm phase II trial, evaluated local excision after neoadjuvant chemoradiotherapy for cT2N0 rectal cancer patients. This study reported a 3-year DFS of 88.2 % (95% CI = 81.3–95.8) in the intention-to-treat group and 86.9 % (79.3–95.3) in the per-protocol group [50•]. Although the 3-year DFS rates were not as high as expected, the data suggest that neoadjuvant chemoradiation followed by local excision can be considered in carefully selected cT2N0 patients who refuse, or are not candidates for, radical surgery. In a recent multicenter phase II trial, 42 patients with T3 disease and 21 patients with low-lying T2 disease were treated with neoadjuvant chemoradiation followed by full-thickness transanal local excision. After surgery, patients who had a ypT0-1 ($n = 43$) were observed, while the remaining patients were recommended to undergo a subsequent TME. This study showed a promising cumulative 3-year OS of 91.5 % (95% CI = 75.9–97.2), DFS of 91.0 % (95% CI = 77.0–96.6), and local DFS of 96.9 % (95% CI = 80.3–99.5) [51•].

The Role of Intensity-Modulated Radiation Therapy

Considering the excellent local control afforded by chemoradiation therapy, there has been growing interest in reducing radiation-related toxicity, including enteritis, with new radiation delivery techniques. The use of a bowel displacement device (belly board) and the prone position allows for bowel sparing and has become the standard of care at most centers. Using 3D conformal radiation therapy (3D-CRT), bowel displacement, and a three-field delivery approach with posterior and two opposed laterals fields may spare the small bowel while allowing for treatment of the primary and adjacent lymph nodes at risk, including mesorectal, presacral, and internal iliacs. For patients who have T4 disease with invasion into the prostate, cervix, or vagina, a four-field box technique (AP-PA and two opposed lateral fields) is often used to include the external iliac nodes. In this situation, despite bowel displacement, small bowel doses may be high and there may be benefit from newer radiation delivery techniques.

Improvement in computing power has allowed for further conformality of radiation dose using intensity-modulated radiation therapy (IMRT). This technique uses many different beam angles with varied intensity of radiation, which allows shaping the radiation dose to the tumor or delineated target volume while simultaneously sparing radiation dose to adjacent organs, including the small bowel and femoral heads. A more advanced form of IMRT that allows for greater conformality and shorter treatment time is volumetric arc therapy (VMAT), which modulates radiation in continuous arcs instead of using multiple beam angles. Additionally, multiple areas within the target volume are able to be treated to different dose levels by varying the radiation dose administered within each beam or arc. This allows the tumor to receive a higher dose of radiation using a simultaneous integrated boost (SIB), also known as "dose painting."

In anal cancer, a prospective multi-institutional trial, Radiation Therapy Oncology Group (RTOG 0529), has shown that IMRT can reduce gastrointestinal (GI), skin, and hematologic toxicities in anal cancer compared to conventional treatment [52]. In rectal cancer, there are several reports that suggest lower GI toxicity may be achieved with preoperative IMRT [53, 54•, 55–58] (see Table 2). Dosimetric analysis confirms decreased dose to organs at risk, including the bladder, small bowel, and femoral heads [59, 60] (see Fig. 1). Parekh et al. found that despite maximal bowel displacement

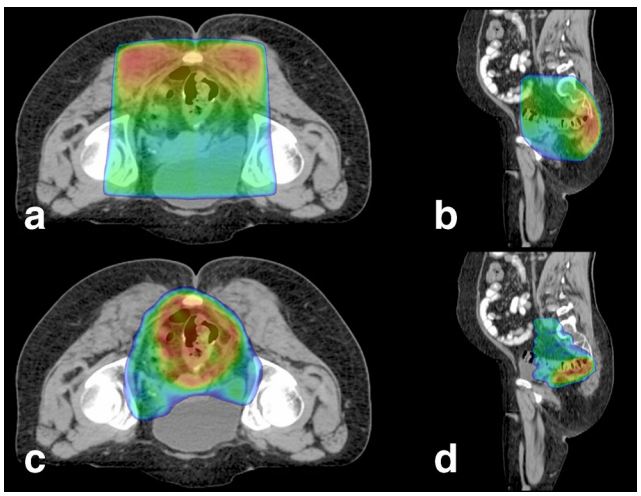

Fig. 1 3D-CRT vs. IMRT. Axial and sagittal views of the dose distribution of a typical 3D-CRT rectal plan (**a** and **b**, respectively) compared to both axial and sagittal views of the dose distribution of an IMRT plan within the same representative patient (**c** and **d**, respectively). The *green* color wash (elective nodal volume) represents 45 Gy and the *orange* color wash (gross tumor volume) 50 Gy. Note that the IMRT plan completely eliminates the small bowel from the 45-Gy dose distribution

and prone positioning with preoperative 5-FU and radiation for locally advanced rectal cancer, there was a significant reduction in grade ≥2 GI toxicity between 3D-CRT (60.7 %) and IMRT (30 %, $p = 0.036$) and in grade ≥2 diarrhea: 3D-CRT of 42.8 % and IMRT of 10 % ($p = 0.014$) [53]. Radiation duration was also significantly less with IMRT, 35 vs. 39 days using 3D-CRT ($p \leq 0.0001$). Interestingly, the pCR rates were similar between the two cohorts: 16.7 % for 3D-CRT and 21.4 % for IMRT (NS). However, the pCR plus microscopic residual rates were higher with IMRT 57.1 % vs. 27.8 % using 3D-CRT ($p = 0.093$).

The results of a prospective phase II trial, RTOG 0822, evaluating whether IMRT improved the toxicity profile of neoadjuvant chemoradiation with concurrent capecitabine 825 mg/m^2 twice daily and oxaliplatin 50 mg/m^2 weekly, have been recently reported [61•]. The goal of this study was to reduce the grade ≥2 GI toxicity rate as compared to a similar patient cohort treated with 3D-CRT on the RTOG 0247 trial [62]. Seventy-nine patients were accrued, of whom 68 were evaluable. The grade ≥2 GI toxicity rate with IMRT was 51.5 %, which was not significantly lower than that reported in the conventional radiation capecitabine/oxaliplatin arm of RTOG 0247. It is possible that the benefit of IMRT on RTOG 0822 was obscured by the higher acute toxicity of concurrent oxaliplatin [63••]. These results are also difficult to interpret as patients were not required to have maximal bowel displacement, there were heterogeneous methods of contouring small bowel, and a sequential IMRT approach (IMRT delivered 45 Gy in 25 fractions to the pelvis with a subsequent 3D-CRT boost to the mesorectum and tumor) was employed.

Despite the lack of level III data, we believe that the optimization and further analysis of this approach in the combined modality management of locally advanced rectal cancer is warranted. Many centers have now adopted IMRT and VMAT as their preferred treatment options for these patients, and current prospective trials allow for such radiation delivery techniques. IMRT/VMAT may be most beneficial in T4 tumors where external iliac nodes need to be included in the elective nodal target volume or very distal rectal cancers that involve the anal canal, where inguinal lymph nodes are treated. Similarly, this treatment approach should be strongly considered for patients on whom it is paramount to significantly limit small bowel or femoral head dosing, including those with prior pelvic radiation, hip replacements, or active inflammatory bowel disease.

Conclusions

With neoadjuvant chemoradiation and TME, the 10-year local failure rate for stage II and III rectal cancer has been reduced to 7.1 %. However, there continues to be a need for optimizing outcomes while improving the treatment-related toxicities associated with current management strategies. Novel techniques and innovations such as IMRT/VMAT, watchful waiting, total neoadjuvant therapy, and the selective use of radiation and local excision may potentially address these issues. However, many open questions remain, including proper patient selection, the sequence, timing, and selection of neoadjuvant management, and the role of MRI and biomarkers to guide personalized treatments. In the next decade, data from prospective randomized trials addressing these novel approaches may further refine the standard of care for locally advanced rectal cancer.

Compliance with Ethical Standards

Conflict of Interest Nitesh Rana, A. Bapsi Chakravarthy, and Lisa A. Kachnic declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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