

## Review Article

# Do all locally advanced rectal cancers require radiation? A review of literature in the modern era

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### ABSTRACT

Potentially curable rectal cancer is primarily treated with surgical resection. Adjuvant or neoadjuvant radiotherapy is often utilized for patients deemed to be at unacceptable risk for local recurrence. The purpose of this article is to review the pertinent literature and elucidate the role of radiotherapy in patients with an intermediate risk of local recurrence. The addition of chemoradiotherapy is recommended in the majority of patients with transmural or node positive rectal cancer. However, some patients with favorable characteristics may have only a small incremental benefit from the addition of radiotherapy. The decision to treat or not to treat should take into consideration the patient and physician tolerance of risk of recurrence and risk of treatment related toxicity. The primary factors identified for determining low risk patients are circumferential radial margin (CRM), location within the rectum, and nodal status. Patients at lowest risk have widely negative CRM (>2mm), proximal lesions (>10cm from the anal verge), and no nodal disease. Patients with all three low risk factors have an absolute reduction in local recurrence that is <5% and may be eligible to forego radiotherapy. Additional factors identified which may impact local recurrence risk are elevated serum CEA level, lymphovascular space invasion, pathologic grade, and extramural space invasion. combined modality therapy; rectal cancer; neoadjuvant chemoradiation; adjuvant therapy; radiation therapy

### KEY WORDS

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### Introduction

The addition of radiotherapy to surgery for locally advanced rectal cancer has demonstrated improvement in local control in historic randomized trials (1-3). An improvement in overall survival has not been shown in the majority of studies; only a single Swedish rectal cancer trial demonstrated an improvement in overall survival with the addition of short course neoadjuvant radiotherapy to surgery (4). This landmark trial reported a local recurrence improvement from 27% to 11% with the addition of preoperative radiotherapy. This translated into a survival benefit of 10% at 5 years (48% vs. 58%). While the majority of randomized data has not corroborated this survival benefit, the morbidity of

local recurrence and relatively poor salvage rates have been sufficient to justify radiotherapy as standard practice for stage II or III rectal cancer. Nonetheless, there are subsets of patients with stage II or III disease who are expected to have low absolute benefit from radiation therapy, and the therapeutic ratio may be insufficient to routinely recommend radiation. Furthermore, advances in surgery and chemotherapy have called into question the role of radiation in the modern treatment era. This review is to discuss factors that should be considered when determining which patients should receive adjuvant or neoadjuvant radiation therapy.

### Total mesorectal excision

The advent of the total mesorectal excision (TME), which utilizes sharp dissection through a plane between the visceral and parietal layers of the pelvic fascia to excise the tumor and mesorectum en bloc, has dramatically improved local control following surgery (5). TME mobilizes the rectum from the sacral promontory to the pelvic floor, with a 5-6 cm mesorectal margin distal to the lowest edge of the primary tumor. Prior to TME, surgery was typically performed with blunt dissection, without close attention to circumferential

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margin. Resection of the mesentery with its blood supply and lymphatics maximizes the probability of clear circumferential margins, and removes mesorectal lymph nodes at risk for harboring metastatic disease. A review of the literature encompassing more than 5000 patients reports local recurrence rates of 6.6% with TME, compared to about 15% in similarly staged patients treated without TME (6-8). The success of TME is dependent on surgeon training, and rectal cancer patients should be treated by surgeons experienced in this technique (9, 10).

While TME has decreased local recurrence, thus decreasing the absolute benefit of radiotherapy, a randomized trial by the Dutch demonstrated that the addition of radiation to TME decreases local recurrence (11). In this trial 1861 stage I to III rectal cancer patients were randomized to TME with or without short course neoadjuvant radiation therapy (25 Gy in 5 fractions). Local relapse at 2 years was 2.4% in patients who received radiation, versus 8.2% in those who did not ( $P < 0.001$ ), with equivalent 2 year overall survival rates of 82%. It should be noted, however, that this study did not include chemotherapy, and therefore the benefit of radiation added to chemotherapy remains a topic of debate. As discussed in more detail below, the absolute benefit of radiation is dependent on tumor characteristics including circumferential margin, location in the rectum, and stage.

### *Influence of circumferential radial margin*

Prior to the development of TME, it was recognized that circumferential radial margin (CRM) had a dominant influence on local relapse. In the landmark study by Quirke et al., rigorous pathologic analysis revealed 27% occult positive CRM after potentially curative surgery (12). This correlated with a 23% local failure rate. Subset analysis of Dukes' B patients revealed 5% CRM involvement and a subsequent local failure rate of 5%. A subset analysis of the Swedish rectal cancer trial examined local failure after curative or noncurative surgery (13). The authors did not differentiate noncurative resection due to proximal, distal, or radial margin status. Local failures were much more common in patients who received a noncurative resection (34% vs. 16%). The addition of preoperative radiation improved local control for patients with curative resection (24% vs. 9%) as well as noncurative resection (44% vs. 23%).

Following the advent of TME, local recurrences were reduced, in part due to wider CRM. Nonetheless, close or positive CRM remains a predictor of local recurrence. A retrospective analysis of the influence of CRM status on local control in the aforementioned Dutch preoperative radiotherapy trial was reported by Nagtegaal et al (14). In non-irradiated patients, tumor involving the surgical

margin or within 2 mm of the surgical margin resulted in 2 year local recurrence rates of 16.4% and 14.9% respectively (non-significant difference). However, a surgical margin  $> 2$  mm resulted in a 2 year local failure rate of 5.8% ( $P = 0.0007$  compared to CRM  $\leq 2$  mm). The authors further subdivided width of CRM to show that the benefit of increased margin continued beyond 2 mm. Surgical margins of 2-5 mm, 5-10 mm, and  $> 10$  mm resulted in local recurrence rates of 10.3%, 6.0%, and 2.4% respectively. In this study, location within the rectum and TNM stage strongly affected the likelihood of obtaining a negative CRM. Distal lesions ( $< 5$  cm from the anal verge) had involved margins in 25.9% of patients, compared to only 13.2% and 16.5% for lesions 5-10 cm and 10-15 cm from the anal verge, respectively ( $P = 0.009$  for trend). In regards to stage, positive margins were noted in 2.0%, 14.6%, and 33.1% of patients with stage I, II, and III disease, respectively ( $P < 0.001$  for trend). Due to the low rate of local recurrence in patients with stage I or II disease, circumferential margin was no longer of predictive value for local failure.

The Medical Research Council examined the use of short course preoperative radiotherapy versus selective adjuvant chemoradiation therapy in patients with close CRM in a prospective randomized trial, MRC CR07 (15). All patients underwent TME. One arm received neoadjuvant short course radiotherapy, consisting of 25 Gy in 5 fractions. The second arm received upfront TME, and patients who were found to have CRM closer than 1 mm were treated with chemoradiotherapy consisting of 45 Gy in 25 fractions with concurrent 5-fluorouracil. No radiation was given if CRM was  $> 1$  mm. Adjuvant chemotherapy was given to patients in either arm as per the standards of the treating institution (declared prospectively). A total of 1350 patients were enrolled. The short course of preoperative radiotherapy did not have a discernable downstaging effect on margin status (positive margin rate 10% with preoperative radiotherapy vs. 12% with upfront surgery), likely due to the short delay between starting RT and surgery (7 days), which was insufficient to allow for significant tumor shrinkage. However, preoperative radiotherapy provided a significant improvement in local recurrence (4.4% vs. 10.6% at 3 years,  $P < 0.0001$ ) and disease-free survival (77.5% vs. 71.5% at 3 years,  $P = 0.013$ ). The authors suggest that while margin status is a strong predictor of local recurrence, selective adjuvant chemoradiation therapy for close margins is inferior to preoperative radiotherapy in terms of local control and disease free survival. In other words, radiation provides a benefit even in patients with CRM  $> 1$  mm (Table 1).

In a separate analysis of 1156 in the MRC CR07 trial who had detailed pathological data available, the authors showed that the plane of surgery (mesorectal, intramesorectal, or

**Table 1 3-year local recurrence (MRC CR07)<sup>15</sup>**

	Preoperative radiotherapy	Selective postoperative chemoradiotherapy	HR (95% CI)
CRM Positive ( $\leq 1$ mm)	13.8%	20.7%	0.64 (0.25-1.64)
CRM Negative ( $>1$ mm)	3.3%	8.9%	0.36 (0.23-0.57)

CRM = Circumferential radial margin, HR = Hazard ratio, CI = Confidence interval

muscularis propria plane) influenced local control, with 3 year local recurrence rates of 4%, 7%, and 13%, respectively ( $P=0.0011$ ) (16). Although plane of surgery was an independent predictor of local recurrence, there was no evidence that the benefit of radiation was dependent on the plane of surgery ( $P=0.3$  for trend). The effects of optimal mesorectal resection and radiation were additive, with 3 year local recurrence rate of 1% in patients who had short course preoperative radiotherapy and mesorectal plane of resection. Radiation reduced local recurrence by greater than 50% regardless of plane of resection.

CRM status remains an important indicator of local control in the era of TME, as recognized in NCI consensus guidelines (17). CRM of  $>2$ mm is preferable, though the risk of recurrence is likely a continuum, with larger margins at lower risk of recurrence. The presence of close CRM is one factor influencing the decision of whether or not to employ adjuvant radiation therapy, though the MRC CR07 trial suggests that radiation decreases local recurrence even in the setting of CRM  $>1$ mm (Table 1). Part of the challenge for treating physicians is deciding on whether the degree of benefit of local control justifies the potential toxicities, and the decision to use radiation will depend on a constellation of risk factors rather than margin status alone.

MRI scan has been used as a tool to predict negative circumferential margin, with a meta-analysis reporting sensitivity of 94% and specificity of 85% (18). The use of MRI scan to identify patients more likely to benefit from radiation therapy, however, remains investigational.

### Location

The anatomic definition of the proximal extent of the rectum is debated. The rectum is extraperitoneal on its posterior surface. The upper one-third of the rectum is covered by the peritoneum on the anterior and lateral surfaces, and the inferior two-thirds of the rectum is completely extraperitoneal. The proximal extent of the rectum has classically been defined as the peritoneal reflection. The peritoneal reflection cannot be visualized by imaging studies. Rather, it is defined at the time of operation. Therefore, whether or not a tumor is in the true rectum can be challenging to determine prior to surgery. In the adjuvant setting, randomized trials demonstrating a benefit to radiation in stage II or III disease have variably

defined the rectum as below the peritoneal reflection, below the sacral promontory,  $<12$  cm from the anal verge on rigid proctoscopy, or  $<16$  cm from the anal verge (1, 2, 15, 19, 20, 21, 22). Neoadjuvant trials do not allow for intraoperative evaluation of the peritoneal reflection, and have variably included patients with tumor from  $<12$  cm to  $<16$  cm from the anal verge (15, 21). Yun et al. reported that the average length of the posterior peritoneal reflection from the anal verge at the time of surgery was 14 cm in 46 patients, and it correlated with patient height (23). Whether or not the tumor lies within the rectum influences treatment decisions as colon cancer has no proven benefit from radiation therapy, and making this determination prior to surgery remains a challenge for physicians.

Even if the tumor lies within the rectum, proximal rectal cancers have relatively lower benefit from radiation compared to distal. Prior to the advent of TME, the MRC working group identified location in the rectum as a prognostic factor in a randomized trial of preoperative radiotherapy (3). Lesions less than 8 cm from the anal verge had a 5 year local disease free survival rate of 52%, vs. 62% for lesions greater than 8 cm from the anal verge ( $P=0.008$ ). This difference translated into an overall survival difference at 5 years of 35% for distal lesions compared to 48% for more proximal lesions ( $P<0.001$ ). While distal tumors may represent a more challenging surgery, this trial showed no difference in the rate of gross total resection as assessed by the surgeon (62% with distal lesions and 65% with proximal lesions). Circumferential margins status, however, was not assessed.

Despite reductions in local recurrence in the TME era, distal lesions continue to carry a worse prognosis. The Dutch rectal cancer trial reported that increasing distance from the anal verge was associated with higher local control on multivariate analysis ( $P=0.02$ , Table 2) (11). On univariate analysis, the addition of radiation therapy to TME did not improve local control in tumors more than 10 cm from the anal verge. Multivariate tests, however, suggested that the favorable effects of radiation probably didn't differ based on location in the rectum. This trial was not adequately powered to determine whether or not radiation has a small impact on local control in the proximal rectum, but at a minimum this trial demonstrates that the absolute benefit of radiation in the proximal rectum, if present, is small.

The Dutch trial revealed an increased incidence of positive

**Table 2 Influence of location on margin status and local recurrence<sup>14,15</sup>**

Distance from anal verge	Dutch trial			MRC CR07		
	Positive CRM	2y local recurrence		Positive CRM	3y local recurrence	
		S alone	S + RT		Neoadjuvant RT	Selective adjuvant CRT
10.1–15 cm	16.5%	3.8%	1.3%	9%	1.2%	6.2%
5.1–10 cm	13.2%	10.1%	1.0%	9%	5.0%	9.8%
≤ 5 cm	25.9%	10.0%	5.8%	15%	4.8%	10.4%

CRM = Circumferential radial margin, S = Surgery, RT = Radiotherapy, CRT = Chemoradiotherapy

**Table 3 Gunderson et al. analysis of 5 trials by T and N stage<sup>25</sup>**

	Risk group	S	S + RT	S + CT	S + RT + PVI CT
5-year LR	Intermediate	12-14%	7-12%	5-11%	5%
	Moderately high	11-40%	10-13%	0-20%	9-11%
	High	24-50%	0-11%	15-43%	11-33%
5-year DFS	Intermediate	29-51%	50-61%	69-78%	75-76%
	Moderately high	0-24%	33-60%	43-50%	39-70%
	High	16-50%	0-40%	14-36%	0-47%

LR = Local recurrence, DFS = Disease free survival, S = Surgery, RT = Radiotherapy, CT = Chemotherapy (5FU/LV), PVI = Protracted venous infusion

margins in distal tumors within 5cm from the anal verge (Table 2) (14). Interestingly, lesions located between 5 and 10 cm from the anal verge had an incidence of positive margins similar to more proximal lesions but an intermediate local failure rate. This suggests that margin status alone is not sufficient for predicting local recurrence and tumor location is an important independent consideration.

Similar to the results of the Dutch trial, the MRC CR07 trial comparing preoperative radiotherapy to selective adjuvant chemoradiotherapy demonstrated that tumor location influences local recurrence and CRM positivity (Table 2) (15). CRM was positive in 15% of patients with distal extent of tumor 0-5cm from the anal verge, versus 9% of patients with distal extend of tumor >10 cm from the anal verge ( $P=0.004$ ) (16). Neoadjuvant radiotherapy was found to be superior to selective adjuvant chemoradiotherapy for all tumor locations (Table 2). Although local recurrence rates were higher with mid/distal disease compared to proximal disease, the absolute benefit in 3-yr local control with the addition of radiation was about 5%, regardless of location in the rectum.

In summary, the Dutch study suggests proximal tumors likely have a lower absolute benefit in local control from the addition of radiation to surgery, while the MRC trial does not, despite showing that distal tumors are more likely to have positive CRM. Unfortunately, both trials include stage I to

III disease, and neither trial addresses the benefit of radiation based both on T stage and location. Specifically, the benefits of radiation in T3N0 proximal disease are of interest. Further study is needed to validate or refute the role of radiation in proximal T3N0 disease.

#### *Influence of nodal status*

As one would expect, the presence of malignant disease within regional lymph nodes increases the risk of local-regional recurrence. Stocchi et al. retrospectively reviewed patients enrolled in 3 North Central Cancer Tumor Group (NCCTG) trials, and confirmed the prognostic value of nodal status on local-regional recurrence (24). Eligible patients had either T3-4 or N+ disease without distant metastases. Five-year local-regional failure rates for patients with T3 disease were 10%, 15%, and 32% for N0, N1, and N2, respectively. Gunderson et al. expanded the Stocchi analysis to include patients enrolled in NSABP R01 and R02 trials, for a total of 3791 evaluable patients (25). Again nodal involvement was predictive of local failure with recurrence rates of 9%, 11%, and 13% for N0, N1, and N2 disease, respectively ( $P=0.005$ ). These authors evaluated outcomes with surgery alone, surgery plus chemotherapy, and surgery plus chemoradiation based on T stage and N stage (Table 3). Given the relatively low number of patients in certain subsets and given the



**Table 4 Dutch trial 2-year local recurrence<sup>14</sup>**

	CRM >2mm	CRM ≤2mm	p value
Node negative	3.0%	4.4%	0.97
Node positive	12.0%	21.4%	0.03

CRM = Circumferential radial margin

**Table 5 MRC CR07 3-year local recurrence by TNM stage<sup>15</sup>**

TNM stage	Neoadjuvant RT	Selective adjuvant CRT	HR (95% CI)
II	1.9%	6.4%	0.29 (0.12-0.67)
III	7.4%	15.4%	0.46 (0.28-0.76)

RT = Radiotherapy, CRT = Chemoradiotherapy, HR = Hazard ratio, CI = Confidence interval

retrospective nature of this study, the value of the addition of radiation to surgery and chemotherapy could not be answered. Nonetheless, the authors identified an intermediate risk group (T3N0, T1-2N1), a high intermediate risk group (T1-2N2, T3N1, T4N0), and a high risk group (T3-4N2, T4N1), and suggest that the intermediate risk group is the least likely to benefit from the addition of radiation therapy to chemotherapy. The studies included in this analysis were completed prior to the advent of TME and prior to the adoption of newer chemotherapies including oxaliplatin, and irinotecan. Furthermore, some utilized bolus rather than protracted venous 5FU, the latter of which has demonstrated superiority in a randomized trial (22). Therefore, the results of this study, while intriguing, are not directly applicable to the modern era. The use of TME and modern chemotherapy may further decrease the relative benefits of radiation, particularly in the intermediate risk group.

The Dutch trial demonstrated a connection between nodal status and CRM status after TME in the 769 patients who did not receive radiation (14). Patients with stage II disease (T3-4 N0) had a 14.6% rate of positive CRM (≤1mm), compared to 33.1% for patients with Stage III disease (T1-4 N1). This increase in positive CRM is due to the correlation of nodal disease with more advanced primary tumors as well as the physical presence of malignant lymph nodes near the resection margin. Nodal disease determined the closest margin in 24.9% of patients with nodal disease. Interestingly, the predictive value of margin status was dependent upon whether the margin was determined by the primary tumor or lymph node. The 2-year local failure rate for stage III patients was reported as 22.1%, 12.4%, and 12.0% for positive margin by primary tumor, positive margin by lymph node, and >2mm negative margin, respectively. This indicates that the presence of nodal disease at the margin does not worsen the prognosis for node positive patients. Additionally, the authors identified that nodal status predicted for local failure independent of

surgical margin (Table 4). This analysis further supports the role of radiation in node positive disease, particularly in patients with positive margins. As previously discussed, this study did not include chemotherapy, and therefore the benefit of radiation added to chemotherapy remains a topic of debate. The MRC CR07 of short course preoperative radiation therapy versus selective postoperative chemoradiotherapy in patients with close CRM similarly reported that the subset of patients with node positive disease (stage III) had higher local recurrence rates compared to stage I or II on multivariate analysis ( $P<0.0001$ ), and also had a greater absolute reduction in local recurrence with the use of neoadjuvant radiation (15,16). Three year local recurrence rate was 7.4% in node positive patients treated with neoadjuvant radiotherapy versus 15.4% in node positive patients treated with selective adjuvant chemoradiotherapy. Three year local recurrence rate was 1.9% in stage II patients treated with neoadjuvant radiotherapy versus 6.4% in stage II (node negative) patients treated with selective adjuvant chemoradiotherapy (Table 5). Only 12% of patients enrolled in the selective adjuvant chemoradiation arm of the study had positive circumferential margins. Therefore, the majority of patients in this arm of the study did not receive radiotherapy, and the trial is largely comparing neoadjuvant radiation versus no radiation. The results of this study suggest that patients with clinically apparent nodal disease benefit from radiotherapy and in particular from neoadjuvant radiotherapy.

### *Influence of chemotherapy*

While local recurrence represents a morbid event, distant disease remains the primary obstacle to cure, and the majority of recurrences are distant. Systemic therapy in locally advanced disease decreases distant metastases and improves survival. Adjuvant chemotherapy in the absence of radiation has not, however, been shown to improve local control. Trials

**Table 6 NSABP R-01<sup>2</sup>**

	S	S + CT	S + RT
5y OS	43%	53% ( $P = 0.05$ )*	41% (ns)*
5y DFS	30%	42% ( $P = 0.006$ )*	34% (ns)*
5y LRR	25%	22% (ns)*	16% ( $P = 0.06$ )*

OS = Overall survival, DFS = Disease-free survival, LRR = Locoregional recurrence, S = Surgery, CT = Chemotherapy, RT = Radiotherapy, ns = non-significant, \* all  $P$  values vs. surgery alone

**Table 7 GITSG 71-75<sup>1,26,27</sup>**

	S	S + RT	S + CT	S + CRT
LRR	24%	20%	27%	11%
OS	47%	58%	56%	72%

S = Surgery, RT = Radiotherapy, CT = Chemotherapy, CRT = Chemoradiotherapy, LRR = Locoregional relapse, OS = Overall survival

addressing this issue accrued patients during the pre-TME era. The NSABP R-01 trial compared observation vs. adjuvant radiotherapy vs. adjuvant chemotherapy (fluorouracil, semustine, and vincristine) (2). The authors described an improvement in the 5-year disease-free survival and overall survival in the chemotherapy arm vs. observation arm, but not local control (Table 6).

Similarly, a prospective trial by the Gastrointestinal Tumor Study Group did not show a decrease in local control with the addition of chemotherapy alone to surgery. This trial randomized patients to surgery followed by observation, chemotherapy, radiotherapy or chemoradiotherapy (1,26,27). The trial was closed early due to inferiority of the surgery alone arm and thus the data was not sufficiently powered to distinguish outcomes all four treatment arms. At a median of 80 months, the locoregional recurrence and overall survival were improved by adjuvant chemoradiotherapy, but not by either therapy alone (Table 7).

Randomized trials showed that the addition of radiation to chemotherapy improved local control in the pre-TME era, but the benefit of adding radiation to modern chemotherapy following TME is not known (1, 19, 26). The Dutch study of TME with or without short course preoperative radiation therapy proved that the addition of radiation to TME improves local control, but this trial did not use chemotherapy. It is possible, though not proven, that the lower disease burden afforded by modern surgical techniques may be amenable to local control with chemotherapy, particularly with the use of newer, more active chemotherapy regimens. These advances may obviate the benefit of adjuvant radiotherapy in some patients.

The most notable advances in chemotherapy for rectal cancer are oxaliplatin and irinotecan. Oxaliplatin is a platinum

derivative that acts as an alkylating agent and impairs DNA replication and transcription. A randomized trial by de Gramont et al. showed improvement in response rate in advanced colorectal cancer from 22% with infusional 5FU plus leucovorin to 50.7% with infusional 5FU, leucovorin, and oxaliplatin (FOLFOX),  $P=0.0001$  (28). Irinotecan is a topoisomerase I inhibitor. A randomized trial by Douillard et al. showed improvement in response rate in advanced colorectal cancer from 22% with infusional 5FU plus leucovorin to 35% with infusional 5FU, leucovorin, and irinotecan (FOLFIRI),  $P<0.005$  (29). While response rates are higher with the addition of newer agents to 5FU, it is unknown of these agents can provide equivalent local control compared to radiation.

Biologic agents including bevacizumab, cetuximab, and panitumumab have improved response rates, though these improvements in response rates have had a relatively small impact on survival in the metastatic setting, and to date have no proven benefit in terms of survival in the adjuvant setting (30). Bevacizumab is an antiangiogenic monoclonal antibody. Cetuximab and panitumumab are monoclonal antibodies directed against EGFR. KRAS mutation status is a strong predictor of response to EGFR inhibitors, and on-going studies are evaluating the benefit of cetuximab in KRAS wild-type rectal cancer patients. These agents are not routinely used in the adjuvant setting, and therefore at this time their use does not impact radiation therapy recommendations. The early results have been reported by Schrag et al. evaluating 6 cycles of induction FOLFOX-bevacizumab chemotherapy without preoperative radiotherapy for patients with clinical response (31). All 29 patients achieved clinical response and proceeded to surgery with 8 patients (27%) achieving a pathologic complete response. These results are certainly

**Table 8 Histopathologic factors associated with local recurrence<sup>33</sup>**

	Positive CRM	Serosal involvement	Poor differentiation	LVI	EMLVI
Recurrent group	16.3%	9.9%	23.9%	40.2%	41.3%
Control group	7.6%	1.1%	13.3%	11.4%	13.0%
p value	0.036	0.001	0.041	<0.001	<0.001

CRM = Circumferential radial margin, LVI = Lymphovascular invasion, EMVI = Extramural venous invasion

intriguing and we await the maturity and validation in future trials.

#### Other considerations

Other factors influencing the decision of whether or not to utilize radiation may include CEA, lymphovascular space invasion, grade, extramural vascular invasion, and distal margin status. Nissan et al. reported on the experience at Memorial Sloan Kettering of TME without adjuvant therapy for pT2 (n=45) or early pT3 (n=49) well to moderately differentiated tumors with negative lymph nodes and a negative margins (32). The authors reported a local recurrence rate of 10% at 8 years. Within this select group of low risk patients, elevated CEA and the presence of lymphovascular space invasion were associated with increased risk of local recurrence. Patients with preoperative CEA levels of  $\geq 5$  ng/mL had local recurrence rate of 21% at 8 years vs. 0% in patients with CEA  $< 5$  ng/mL. The rate of pelvic recurrence at 5 years was 32% vs. 6% with and without LVI, respectively. No difference in local recurrence was found based upon distal margin status more or less than 2 cm. Of note, pelvic recurrence in this study was not influenced by T stage, suggesting the T3N0 disease excised with negative circumferential margins may be appropriately treated with surgery alone. This study is limited, however, by a relatively small number of patients. Furthermore, this study was a retrospective analysis of a prospective database.

An analysis by Dresen et al. of Dutch patients who developed isolated local failure also elucidates factors correlated with recurrence in the TME era (33). Patients who developed an isolated local recurrence were matched with a control group who did not fail locally. All patients were treated with TME with or without neoadjuvant therapy. The authors reported positive CRM, serosal involvement, poor differentiation, lymphovascular invasion (LVI), and extramural venous invasion (EMVI) were all found more frequently in the recurrent group, and were associated with higher risk of local recurrence on multivariate analysis (Table 8). While these findings need to be evaluated prospectively, the identified histopathologic factors may be used in conjunction with tumor stage, location, and

nodal involvement to partition patients into risk groups for consideration of adjuvant treatment.

#### Neoadjuvant versus adjuvant radiation therapy

Neoadjuvant chemoradiation therapy has been shown to be superior to adjuvant chemoradiation therapy in locally advanced rectal cancer in a randomized study by the German Rectal Cancer Group (21, 34). Compared to adjuvant chemoradiation, neoadjuvant chemotherapy decreased local recurrence and decreased anastomotic stricture rates. This improvement is in spite of the fact that patients randomized to preoperative radiotherapy were more likely to have distal lesions. This supports that for patients with clear indications for radiation therapy, it is preferable to deliver therapy prior to surgery. It is noteworthy, however, that 18% of patients in this study who were clinical stage II or III who had immediate surgery were found to be pathologic stage I, despite the use of endoscopic ultrasound. Therefore, the use of preoperative chemoradiation likely over-treats some patients. One strategy is to treat patients with intermediate risk disease (T3N0 proximal rectal cancer) with immediate surgery, and deliver adjuvant radiation therapy if high risk features are identified pathologically (T4, node positive, close/positive margin). However, such an approach may result in the need for adjuvant therapy in a significant proportion of patients. Lombardi et al reported that in 32 patients with clinical T3N0 low rectal cancer based on EUS, MRI, and PET/CT, 9 (28%) had pathologic node positive disease following neoadjuvant chemoradiation. These patients would have been under-treated with immediate surgery (35). In the absence of randomized data evaluating the impact of radiation on both disease control and quality of life specifically in the T3N0 population, clinical judgement and patient education regarding risks and benefits are essential.

Another consideration in choosing neoadjuvant versus selective adjuvant radiation therapy includes whether or not surgery will require abdominal perineal resection (APR) with permanent colostomy. The German Rectal Cancer Study group prospectively followed a subgroup of 188 patients in whom the surgeon declared prior to randomization that APR was required. In that subgroup, 19% who underwent

neoadjuvant chemoradiation and 39% who underwent adjuvant chemoradiation has sphincter sparing surgery after APR ( $P=0.004$ ). Therefore, neoadjuvant radiation therapy improved the likelihood of sphincter preservation. Despite these findings, it remains controversial if the surgical plan should be modified based on response to chemoradiation, as there remains the possibility of microscopic disease beyond the grossly visible disease. A prospective pathologic analysis from investigators at Memorial Sloan Kettering Cancer Center showed that intramural extension beyond the gross mucosal edge of the residual tumor was observed in only 2 of 109 patients (1.8%), and in both of these patients the intramucosal spread was  $<1$  cm (36). Moore et al. did not identify distal margin  $\leq 1$  cm as a predictor of local recurrence after neoadjuvant chemoradiation (37). Therefore, patients with good response to neoadjuvant chemoradiation have the possibility of enhanced sphincter preservation, and in patients in whom the requirement of APR is equivocal, it is reasonable to consider neoadjuvant therapy in an attempt to enhance rates of sphincter preservation. It should be recognized, however, that data supporting sphincter preservation following chemoradiation in patients who would otherwise require APR is based on relatively small numbers of patients, and equivalence to APR in terms of local control has not been proven in a randomized fashion. Furthermore, the fecal continence rates following low anterior resection requiring intersphincteric resection are likely inferior to conventional coloanal anastomosis, and therefore decisions regarding sphincter preserving surgery need to take into account anticipated sphincter function and its impact on quality of life (38).

### **Toxicity of radiation**

The decision of whether or not to use radiation therapy is dependent not only upon the anticipated benefits in local control, but also upon potential toxicities. The authors of the MRC CR07 completed prospective quality of life questionnaires for patients who underwent short course neoadjuvant radiation therapy versus selective postoperative chemoradiation (39). As noted previously, only 12% of patients in the selective postoperative chemoradiation group underwent chemoradiation, and therefore this trial in large part evaluates radiation versus no radiation in terms of quality of life. There was no difference in physical function, general health, or overall bowel problems between the 2 arms. However, more patients who received preoperative radiation therapy reported “unintentional release of stools” at 2 years (53% vs. 37%,  $P=0.007$ ). It is noteworthy that the bulk of patients reported only “a little” unintentional release of stools (43% vs. 29%). Only a minority of patients report

“very much” unintentional release of stool (3% vs. 2%). This analysis also demonstrated that surgery impacted mean male sexual function score by more than 30 percentage points; the addition of neoadjuvant short course radiation to surgery further worsened sexual function score by 8-10%. Therefore, radiation impacted male sexual function, though not to as great a degree as surgery. Responses from women with regards to sexual function were insufficient to analyze.

Long term follow-up of the Dutch study similarly showed higher rates of fecal incontinence in patients who received short course preoperative radiation compared to those who did not receive radiation (62% vs. 38%,  $P<0.001$ ) and higher rates of anal blood loss (11% vs. 3%,  $P<0.004$ ). There were no differences in hospitalizations or urinary function. Furthermore, overall perceived health did not differ in patients who did or did not receive radiation ( $P=0.38$ ) (40). The Swedish prospective randomized of short course preoperative radiation therapy also demonstrated a small but tangible risk of radiation induced malignancy exists (relative risk 1.8 compared to no radiation) (41).

Currently in the United States, long course chemoradiation (about 45-50 Gy in 1.8-2 Gy fractions) is typically used rather than short course radiation. Haddock et al. reported slight worsening of bowel function one year after long course chemoradiation compared to baseline (median bowel movement frequency increased from 1 to 2, with increased urgency, clustering, and continence scores persistent one year after therapy). Despite worsened continence scores, the need for protective clothing did not increase above baseline (42). Other prospective trials using long course chemoradiation report severe (grade 3 or higher) late gastrointestinal toxic effects in 2-15% of patients (21, 43). Stricture at the anastomotic site occurs in 4-12% of patients, with lower likelihood if radiation is delivered preoperatively (21). Severe late bladder toxicity occurs in less than 1-4% of patients, and femoral head fractures occur in less than 1% (21, 43).

In summary, radiation therapy is associated with increased incidence of late side effects, most commonly gastrointestinal. Further study is needed to determine the degree to which these side effects impact quality of life, and the risk of side effects needs to be balanced with the expected improvements in local control.

### **Conclusion**

Neoadjuvant chemoradiotherapy is recommended in the majority of patients with transmural or node positive rectal cancer. However, some patients are in a favorable subgroup in which the incremental benefit of radiotherapy may be small. Factors to consider are proximal location ( $>8-10$  cm from the anal verge), negative margins ( $>1-2$



mm), and absence of nodal disease. Additional factors including low preoperative CEA (<5 ng/mL) and absence of lymphovascular space invasion have been reported as risk factors for local recurrence, though their use in deciding whether or not to use radiation require validation in prospective studies. Randomized data from the MRC CR07 study and the Dutch study both show that the addition of radiation to TME improves local control. However, in patients with proximal location, negative circumferential margins, and node negative disease, the absolute reduction in local recurrence is <5%. This raises the possibility that patients with proximal, T3N0 lesions with negative CRM may represent an extremely favorable subgroup eligible to forego neoadjuvant radiotherapy and instead receive adjuvant radiation only in the setting of positive margins or surgical up-staging. Since neoadjuvant radiotherapy appears to provide some local control benefit in all subgroups of stage II and III rectal cancer, the decision to treat or not to treat should take into consideration the patient and physician tolerance of risk of recurrence and risk of treatment related toxicity. Prospective studies are warranted to determine if subgroups of patients, such as T3N0 proximal disease, do not require radiation therapy.

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