



Which Patients With Rectal Cancer Do Not Need Radiotherapy?

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According to current guidelines, the standard treatment for locally advanced rectal cancer patients is preoperative (chemo)radiotherapy followed by total mesorectal excision surgery and adjuvant chemotherapy. Improvements in surgical techniques, imaging modalities, chemotherapy regimens, and radiotherapy delivery have reduced local recurrence rates to less than 10%. The current challenge in rectal cancer treatment lies in the prevention of distant metastases, which still occur in more than 25% of the patients. The decrease in local recurrence rates, the need for more effective systemic treatments, and the increased awareness of treatment-induced toxicity raise the question as to whether a more selective use of radiotherapy is advocated.

Semin Radiat Oncol 26:199-204 © 2016 Elsevier Inc. All rights reserved.

Background

With the implementation of total mesorectal excision (TME) surgery and the administration of preoperative (chemo)radiotherapy, local recurrence rates of locally advanced rectal cancer have decreased from 30%-50% to less than 10%.¹⁻¹⁰ Despite the clear reduction in local recurrences, the benefit of radiotherapy in terms of overall survival is limited. The gains in outcome have to be balanced against the early and late adverse effects of radiotherapy. Preoperative radiotherapy increases surgical morbidity, consequently delaying the administration of adjuvant chemotherapy.^{11,12} Radiotherapy also affects on sexual, anorectal, and urinary function and is associated with an increased risk of secondary malignancies.^{13,14} A more selective use of radiotherapy in patients with low-risk rectal cancer avoids radiation-induced morbidity and can improve patients' quality of life.¹⁵

A more selective use of radiotherapy can also be considered for patients at high risk for distant metastases. With the current treatment paradigm, full-dose systemic therapy is delayed until 4 months after diagnosis, which is disadvantageous regarding the risk of distant tumor spread. Early administration of

full-dose systemic therapy is likely to have a beneficial effect on distant metastases rates and is currently being investigated in several trials.

Which Patients can be Candidates for Upfront Surgery?

Risk Factors for Local Recurrence

As its major merit is to reduce local recurrence rates, the standard use of radiotherapy in low-risk rectal cancer patients can be questioned. Various clinicopathological features have been associated with an increased risk of local recurrences.

The most important risk factor for a local recurrence after rectal cancer surgery is the plane of surgery achieved. In patients included in the CR07 and NCIC-CTG CO16 trials, Quirke et al¹⁶ demonstrated that both an uninvolved circumferential resection margin (CRM) (defined as tumor at a minimum distance of 1 mm from the CRM on pathology) and a superior plane of surgery achieved, were associated with low local recurrence rates. The prognostic effect of CRM involvement has also been demonstrated outside clinical trials. In a population-based study with 3196 patients who were mostly treated with surgery alone, Bernstein et al¹⁷ found a 5-year local recurrence rate of 23.7% in patients with a CRM of 0-2 mm, compared with 8.9% in those with wider margins. The importance of an uninvolved mesorectal fascia (MRF) was demonstrated by Frasson et al who found that T3N0/N+ or T2N+ rectal cancer patients treated with upfront TME had a

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Conflict of interest: none.

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5-year local recurrence rate of 19.4% and 5.4% with and without threatened MRF as assessed on preoperative magnetic resonance imaging (MRI), respectively.¹⁸

Upper rectal tumors have a lower risk for local recurrence because their location above the peritoneal reflection facilitates the ability to obtain clear resection margins. Some of the landmark phase III trials that reported on local recurrences with and without preoperative radiotherapy, stratified local recurrence data according to tumor location (Table 1). After a median follow-up of 13 years, the Swedish rectal cancer trial demonstrated that a short-course regimen of preoperative radiotherapy reduced local recurrences (9% vs 26%, $P = 0.008$) and improved survival (38% vs 30%, $P < 0.001$) among patients with rectal cancer.⁵ A lower local recurrence rate was seen at all tumor heights, although this was not statistically significant for tumors located more than 10 cm from the anal verge.

The Dutch TME trial randomly assigned 1861 patients with resectable rectal cancer either to preoperative radiotherapy (5 × 5 Gy) followed by TME surgery or to TME surgery alone.⁶ Local recurrence rates at 2 years decreased from 8% with TME alone to 2% when radiotherapy was added ($P < 0.001$). This statistically significant difference in local recurrence rate was shown for mid-rectal and low-rectal cancer, but it could not be demonstrated for tumors located above 10 cm from the anal verge ($P < 0.17$). Surprisingly, the 12-year follow-up results showed that the effect of radiotherapy became stronger as the distance from the anal verge increased.⁷ However, when patients with positive margins were excluded from the analysis, the effect on the reduction in local recurrences was independent of the distance of the tumor from the anal verge. This observation can be explained by the fact that radiotherapy cannot compensate for a positive CRM, which was present in a substantial proportion of patients with distal tumors.¹⁹

The MRC CR07/NCIC-CTG C016 trial randomized 1350 rectal cancer patients to preoperative short-course radiotherapy and to selective postoperative chemoradiotherapy in case of involved CRMs.⁸ At 3 years of follow-up, there was a reduction of 61% in the relative risk of local recurrence for patients receiving preoperative radiotherapy ($P < 0.0001$). Unfortunately, no evidence of an effect of tumor location on local recurrences could be detected, perhaps because of the low number of events.

Another factor influencing the risk on local recurrences is the tumor extension. Although it is beyond question that T1-2 tumors rarely need preoperative radiotherapy and that T4 tumors benefit from preoperative (chemo)radiotherapy, T3 rectal cancers constitute a heterogeneous group and the indication for radiotherapy in these tumors is less clear. The outcome of patients with T3 tumors depends on the depth of extramural spread: patients with more than 5 mm of extramural spread have a markedly worse prognosis than patients who have T3 tumors with 5 mm or less of spread. Merkel et al suggested a subdivision of T3 tumors according to the histological measurement of the maximal tumor invasion beyond the outer border of the muscularis propria as follows: pT3a (up to 5 mm) and pT3b (more than 5 mm).²⁰ This subclassification identified 2 groups of rectal cancer patients with a distinct outcome as follows: locoregional recurrence rates were 10.4% and 26.3% for pT3a and pT3b tumors, respectively ($P < 0.0001$). The cancer-related 5-year survival rates were 85.4% for pT3a and 54.1% for pT3b lesions ($P < 0.0001$). The Mercury study group further extended this subclassification into the following 4 groups: "T3a" (<1 mm), "T3b" (1-5 mm), "T3c" (5-15 mm), "T3d" (> 15 mm) and demonstrated that MRI and histopathologic assessments of tumor spread were equivalent to within

Table 1 Local Recurrences With and Without Preoperative Radiotherapy

Trial	References	Treatment	Number at Risk	Median Follow-Up	Patient Group	LR (RT vs no RT)	p Value
Swedish rectal cancer trial	4	5 × 5 Gy + surgery vs surgery alone	553 vs 557	5 Years	All	11% vs 27%	< 0.001
	5		454 vs 454	13 Years	All	9% vs 26%	< 0.001
			136 vs 146		≤ 5 cm	10% vs 27%	0.003
			185 vs 198		6-10 cm	9% vs 26%	< 0.001
			133 vs 110		≥ 11 cm	8% vs 12%	0.3
Dutch TME trial	6	5 × 5 Gy +TME vs TME alone	924 vs 937	2 Years	All	2% vs 8%	< 0.001
	7		237 vs 253	10 Years	≤ 5 cm	6% vs 10%	0.05
			372 vs 350		5.1-10 cm	1% vs 10%	< 0.001
			262 vs 271		10.1-15 cm	1% vs 4%	0.17
			1748*		All	5% vs 11%	< 0.0001
MRC CR07 NCIC-CTG C016	8	5 × 5 Gy + surgery vs surgery with selective postoperative CRT in CRM+ patients	691 vs 691	10 Years	CRM-, M0	3% vs 9%	< 0.0001
	674 vs 676		3 Years	All	4% vs 11%	< 0.0001	
	229 vs 217		0-5 cm	5% vs 10%	NA		
	345 vs 337			> 5-10 cm	5.0% vs 9.8%	NA	
	95 vs 112			> 10-15 cm	1.2% vs 6.2%	NA	

Abbreviations: CRT, chemoradiotherapy; LR, local recurrence; Ref, reference; TME = total mesorectal excision.

*A total of 1748 patients with macroscopically complete resection. Significant values are depicted in bold.

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