What Is the Role for the Circumferential Margin in the Modern Treatment of Rectal Cancer?

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ABSTRACT

Purpose

Treatment of rectal cancer has changed dramatically over the last decade. The worldwide introduction of total mesorectal excision in combination with the increasing use of radio(chemo)therapy has led to an improved prognosis. One of the main prognostic factors in rectal cancer is the circumferential resection margin (CRM). Since the initial description of its clinical importance in 1986, the involvement of this margin (also called lateral or radial resection margin) has been associated with a poor prognosis.

Methods

In the current review, the evidence for the importance of the CRM in more than 17,500 patients is reviewed, and the relevance of this assessment to modern treatment is assessed.

Results

We demonstrate that, after neoadjuvant therapy (both radiotherapy and radiochemotherapy), the predictive value of the CRM for local recurrence is significantly higher than when no preoperative therapy has been applied (hazard ratio [HR] = 6.3 vs 2.0, respectively; \( P < .05 \)). Furthermore, involvement of the CRM is a powerful predictor of both development of distant metastases (HR = 2.8; 95% CI, 1.9 to 4.3) and survival (HR = 1.7; 95% CI, 1.3 to 2.3). In addition to the prognostic data, this review describes different modes of margin involvement, exact definitions, and factors influencing its presence.

Conclusion

CRM involvement is one of the key factors in rectal cancer treatment.

INTRODUCTION

Twenty years ago, the circumferential resection margin (CRM), also known as the radial, lateral, or mesorectal resection margin (Fig 1), was introduced as a powerful prognostic factor for rectal cancer resection specimens. Since then, many series have been published establishing the value of CRM involvement not only for local recurrence, but also for the development of distant metastases and patient survival. Initial series were relatively small, single-center studies, but in recent years, population studies and randomized trials have been added to the literature.

During the last 20 years, the treatment of rectal cancer has changed dramatically. The introduction of total mesorectal excision (TME) and the reinforcement of its value by our understanding of the mesorectum and CRM led to fewer positive margins and consequently fewer local recurrences. Recent changes in surgical approach are the introduction of laparoscopic TME and more radical cylindrical excisions for both low-lying carcinomas and locally advanced rectal cancer.

Short-term preoperative radiotherapy (5 × 5 Gy) has been introduced as neoadjuvant therapy for resectable rectal cancer. For locally advanced rectal cancer, various long-term radiotherapy schedules have been proposed (45 to 50 Gy), with or without chemotherapy. All treatment modalities result in improved prognosis and decreased local recurrence rates; however, there are increased adverse effects. In addition, the improvement of diagnostic imaging allowing the accurate prediction of a potentially involved margin will result in more adequate treatment planning and, thus, further decrease the number of positive resection margins at surgery.

Despite these changes in treatment, local recurrence and mortality are still major problems in rectal cancer management, and thus, the search for potential prognostic markers is important. What is the current importance of CRM involvement in 2008?
In the current study, we evaluated the prognostic value of the CRM in relation to the changes in treatment by reviewing the published data of 17,568 rectal cancer patients who have been described in the literature. A search on the Medline database was performed (January 1985 to July 2006) using the following keywords: circumferential margin, lateral margin, and radial margin. A manual cross reference of the eligible articles was performed to identify additional articles. In addition, published meeting abstracts were used.

Articles were included in the prognostic analyses if sufficient data were given (number of patients with a positive margin, number of patients with a negative margin, and prognostic information for the separate groups). Only articles and abstracts in the English language were used.

### STANDARDIZED METHOD OF CRM EVALUATION

Accurate reporting of the CRM requires serial cross sectioning of the tumor, a visual inspection of the tumor slices, and adequate histologic sampling of areas suspicious of tumor. In the Medical Research Council CR07 and Conventional Versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (CLASICC) trials, the Dutch TME trial, and the Mercury study, pathologists were trained before the start of the trial and filled in standardized proformas at the time of pathology reporting. The frequency of margin involvement is related to the interest of the pathologist, and series with high lymph node yields, a good indicator of high-quality pathology, are more likely to reflect the true incidence of CRM involvement in a given study.

### INCIDENCE

Large differences exist between centers with regard to the number of CRM-positive patients (Table 1, Fig 2), with percentages ranging from 1% to 28% in curatively operated patients. Various factors should be taken into account when reviewing these percentages (see Factors of Influence). The percentage of CRM-positive patients is dependent on patient selection, performance of preoperative imaging, preoperative long course therapy, surgical technique, and skill of the pathologist. In several studies, patients with locally advanced rectal cancer are included; however, the term locally advanced has no consistent definition and varies from one positive lymph node to a cT4 tumor. Percentages of CRM-positive patients in these series vary accordingly so that such studies cannot be compared with each other.

Effort of the pathologist may be one of the key factors. Two early studies showed that margin involvement is not always present in the macroscopically most suspect area but might be present in other areas, requiring more extensive sampling. The examination of additional microscopic slides has led to an increase in CRM-positive patients from 6% to 27% of patients and from six to 16 patients.

Statements such as “We found that pathology reports contained an assessment of radial margins in only 50% of rectal cancer specimens. We assumed that lack of comment of the radial margin implied a negative margin are reasons for concern. Frequencies of CRM involvement in single-center studies should be treated with caution. Reports from trials in which “both tumor spread and tumor-free radial margins are reported suboptimally” (ie, missing in 79% and 68% of patients, respectively) are still being published.

However, less variability is present in the population-based studies, with the percentage of CRM-positive patients ranging from 8% to 13% (Table 1). In these studies, there is a difference in patient selection as well, reflected by differences in the percentage of node-positive patients, which ranges from 21% to 40%. In unpublished data from Yorkshire, United Kingdom, the frequency of CRM positivity is associated with the median number of lymph nodes found at individual hospitals; thus, the CRM rate can be interpreted in the light of the median lymph node yield from any individual study. Good quality of pathology (as indicated by high median lymph node yields) results in increased frequencies of margin involvement.

### Neoadjuvant Therapy

Randomized neoadjuvant trials give insight to mechanisms by which negative CRMs can be obtained (Table 1). Short-course 5 × 5 Gy radiotherapy does not influence the percentage of positive margins (16% v 18%, P = .3144; and 10% v 11%, for radiotherapy v no radiotherapy, respectively), as could be expected by the lack of downstaging as a result of this regimen. When comparing short-course
### Table 1. Frequencies of CRM-Positive Patients in Single-Center Studies, Population-Based Studies, Randomized Neoadjuvant Trials, Nonrandomized Neoadjuvant Studies, and Laparoscopic Series

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Series</th>
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<th>No. of Patients</th>
<th>TNM Stage III (% of patients)</th>
<th>CRM Positive (% of patients)</th>
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radiotherapy with long-course chemoradiotherapy, there is a difference (13% v 4% involved margins, respectively; $P = .017^{35}$); in this study, downstaging is observed as well (48% v 32% TNM stage III, respectively; $P = .007$). The addition of fluorouracil/folinic acid to long-term radiotherapy did not decrease the number of positive margins, although there was more downstaging in the radiochemotherapy arm ($P < .001$). From the frequencies in the nonrandomized neoadjuvant studies (Table 1), no conclusions can be drawn about the efficiency of regimens to reduce positive margins because of the variability in inclusion criteria and treatment schemes and lack of pathology quality control. However, these studies give useful prognostic information.

### Laparoscopy

Frequencies of CRM-positive patients observed in laparoscopic series (Table 1) seem low compared with other series; however, this is the case in the open arm of the studies as well. This may be a result of patient selection and of the increased likelihood that the operating surgeon is an experienced specialist surgeon because all such trials have rigorous entry criteria for participants. Thus, such studies may reflect specialist practice more so than other trials and population studies in which a wider range of surgical skills may be represented. Converted patients have a higher risk of margin involvement. There is no follow-up described from these series, but there is no reason to assume that the prognostic value of the CRM in these series is different from open surgery series. Preliminary results from the rectal cancers in the CLASICC trial show a major increase in local recurrence at 3 years (22.8% v 8.6%, respectively) and reduction in 3-year disease-free survival (27.1% v 68.2%, respectively) in patients with a positive CRM. In this study, the pathologists were trained, and 93% of the histology was centrally reviewed.

### LOCAL RECURRENCE

High local recurrence rates, ranging from 25% to 50% in the past, have markedly decreased in recent years as a result of changes in surgical approach combined with neoadjuvant therapy. The recognition of CRM involvement as one of the main causes of local recurrence has led to the global introduction of TME, resulting in fewer positive margins and less residual disease. Because predictive values depend strongly on the prevalence of local recurrence, the role of CRM was expected to be less prominent after the introduction of the TME procedure. However, this does not seem to be the case because of the variability of the quality of TME. As a result of the lower local recurrence rates,

![Fig 2](https://example.com/fig2.png)
both the sensitivity and the positive predictive value of circumferential margin involvement have decreased compared with our earlier publication. However, after TME treatment, local recurrence can be predicted with a high specificity (92%) and a high negative predictive value (95%), which are both clinically relevant. Moreover, the addition of neoadjuvant therapy (varying from short-course radiotherapy to long-course radiochemotherapy, depending on national guidelines and patient selection based on diagnostic imaging) was expected to compensate for poor surgical performance and to diminish the role of the CRM.

**Neoadjuvant Therapy**

Most studies involving CRM focus on local recurrence. Of the single-center studies, all but one show a significant relationship with local recurrence (Fig 3). When comparing neoadjuvant studies with non-neoadjuvant studies, a significant difference in hazard ratio (HR) is observed (HR = 6.3; 95% CI, 3.7 to 16.7 v HR = 2.0; 95% CI, 1.4 to 2.9, respectively). In other words, in contrast to the expectations, a positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. One could argue that this might be a result of the fact that patients treated with neoadjuvant therapy are usually patients with locally advanced tumors. CRM involvement can be seen as tumor resistance to therapy and indicate a lack of downstaging. Indeed, when downstaging occurs, the distance of tumor to the CRM increases.

In the series by Rullier et al, CT3 tumors with downstaging (pT0-2, N0) showed a mean margin of 10 mm compared with a mean margin of 6 mm in the CT3 tumors without downstaging (P = .02). However, in the European Organisation for Research and Treatment of Cancer trial, more downstaging was present in the radiochemotherapy arm compared with the radiotherapy arm, but the CRM positivity was not different.

However, in both the TME and the CR07 trials, in patients with primary resectable rectal carcinomas, the HR values for local recurrence in CRM-positive patients are 3.8 and 2.3 (no neoadjuvant therapy, 95% CI, 3.3 to 5.6 and 1.9 to 3.0) v 10.0 and 5.3 (5 × 5 Gy, 95% CI, 6.7 to 25.0 and 3.6 to 10.0), which is significantly different. In these studies, no downstaging was present, but still the effect of CRM involvement was more pronounced in the patients who were treated with neoadjuvant therapy.

**Tumor Regression**

To monitor the effects of neoadjuvant treatment on the histology of the tumor, various tumor regression grading (TRG) systems have been used over the years. These pathologic evaluations are based on the relative amount of tumor cells present and the desmoplastic reaction. The definitions used in the different studies vary, and reproducibility is poor. Despite these disadvantages, TRG has been suggested as a surrogate and early outcome parameter for neoadjuvant trials. When comparing the value of

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![Diagram](https://example.com/diagram.png)

**Fig 3.** Local recurrence (LR) hazard ratios and 95% CIs for positive circumferential resection margin (CRM) compared with negative CRM. (*) Eighty-nine percent of patients received preoperative radiotherapy; (#) 17% of patients received preoperative radiotherapy, and 50% of patients were operated on laparoscopically.
CRM with TRG, four independent studies demonstrate superiority of CRM over TRG in a multivariate model.\textsuperscript{38,41,68,69}

**DISTANT METASTASES AND SURVIVAL**

All studies that included the development of distant metastases as a separate outcome variable show a significant difference in prognosis between the CRM-positive and the CRM-negative patients (HR = 2.8; 95% CI, 1.9 to 4.3; Fig 4). No difference is observed between the patients treated with or without neoadjuvant therapy.

The relationship between CRM involvement and patient survival is not clear from all studies, probably because of the lack of statistical power. However, when all studies are summarized, there is a clear and significant relationship with CRM, both in the neoadjuvant setting as well as in the patients treated with surgery alone (HR = 1.7; 95% CI, 1.3 to 2.3; Fig 5).

A recent study investigated the value of CRM for survival in a multivariate model and found that CRM is more important than T stage. In combination with lymph node status, CRM status provides a better prognostic model than the current TNM system.\textsuperscript{70,71}

**LOCALLY RECURRENT DISEASE**

The role of the CRM in locally recurrent disease has recently been reviewed by Caricato et al.\textsuperscript{72} In their systematic review, they included 24 observational studies in which a total of 2,206 patients were investigated. They conclude that “the only reliable prognostic marker is microscopically negative margins after surgery.”

**WHEN IS THE MARGIN POSITIVE?**

There has been an ongoing debate about when to call the CRM positive. The TNM definition of a positive margin (R1) is 0 mm; in most cases, CRM is considered positive when \(\leq 1\) mm. On the basis of prognostic value for local recurrence, 2 mm has also been considered as a cutoff point. In six studies, prognosis has been described in relation to the distance to the CRM.\textsuperscript{18,20,29,33,34,56} In general, it can be stated that the larger the distance of the tumor from the CRM is, the better the prognosis. When tumor cells are reaching into the resection margin (0 mm), prognosis is worst. In only one of the studies was preoperative therapy applied\textsuperscript{34}; there are few local recurrences when the margin is more than 1 mm (0.4%).

**MODE OF MARGIN INVOLVEMENT**

The following six distinct types of margin involvement have been described\textsuperscript{10,20}: direct tumor spread (28% to 29%), discontinuous tumor spread (14% to 67%), lymph node metastases (12% to 14%), venous invasion (14% to 57%), lymphatic invasion (9%), and perineural tumor spread (7% to 14%). In approximately 30% of patients, the tumor showed more than one method of margin involvement. Lymph node metastases in the CRM were associated with a lower than expected local recurrence rate in two independent studies\textsuperscript{20,33}; however, these results were based on only 19 and 67 patients, respectively, and require further studies to establish their true importance.
FACTORS OF INFLUENCE

**Tumor-Related Factors**

There is an obvious correlation of CRM positivity with TNM stage (Fig 2). The more advanced the stage is, the greater the chance of CRM involvement, which has been observed by many authors.\(^ {10,11,20,23,31,33}\) Both increasing depth of tumor invasion and the presence of tumor deposits and involved lymph nodes contribute to this correlation.

More positive margins are present in tumors that have an ulcerative growth pattern\(^ {11,26}\) and in tumors that show a stenosing growth pattern.\(^ {26}\) Bigger tumors more often have a positive CRM.\(^ {26}\) Histologic factors that are associated with positive CRM are an infiltrating margin,\(^ {10}\) poor differentiation,\(^ {10,21,26}\) and vascular invasion.\(^ {21,26}\) No significant relationship with tumor budding was observed.\(^ {21}\) Moreover, poor differentiation in submucosal transanal biopsies is predictive of CRM involvement (odds ratio = 10.8, 95% CI, 1.7 to 67.1), as is vascular invasion (odds ratio = 16.1; 95% CI, 1.9 to 139.2).\(^ {21}\)

**Surgical Factors**

Variation between surgeons is also reflected by the difference in incidence of positive margins in the single-center studies (Table 1). In the study by Birbeck et al.,\(^ {20}\) the variability between surgeons and their improvement over time have been demonstrated. The decrease in positive margins is accompanied by a decreased local recurrence rate and an improved survival. In a multicenter study, Tekkis et al.\(^ {31}\) show between-center variability ranging from 1% to 33% (\(P = .001\)). They did not observe any influence of timing of surgery (day or night), but there were fewer positive margins in emergency operations (2.7% vs 13% in elective cases); the reasons for this are unclear.

By judging the quality of the surgery performed by evaluating the completeness of mesorectal excision, we proved the direct relationship between CRM positivity and quality of surgery (Fig 1). In two large randomized multicenter trials,\(^ {1,61,62}\) we demonstrated that, if the mesorectum is removed as a whole (ie, the resection margin is on the mesorectal plane), few positive margins are present, and local recurrence rates are low.\(^ {1,61,62}\) In contrast, when the plane of resection is on the muscularis propria (Fig 1C), CRM involvement is common, and local recurrence rates are high. The plane of resection can explain why, in a few cases (1.1%\(^ {20}\) and 2.0%\(^ {33}\)), positive CRMs are present in TNM stage I tumors.

There are more positive margins in tumors located in the lower rectum than in the middle and upper rectum.\(^ {1,2,30}\) We believe the main cause of this is the difference in surgical technique applied and the different local anatomy. Many studies observed higher CRM positivity in patients who underwent abdominoperineal resection (APR) compared with patients who underwent low anterior resection.\(^ {1,2,28,30,31,54}\) Perforations are more common in APR\(^ {1}\) and are associated with an increased CRM positivity.\(^ {26}\) The mesorectal excision plane is more often on the muscularis propria,\(^ {1}\) and in the sphincter area, the plane of resection is often in the lumen, submucosa, or sphincters.

**Patient-Related Factors**

Surprisingly few studies have investigated patient-related factors for CRM involvement. Sex of patients seems important in APR...
patients, with CRM involvement in 39% of female and 24% of male patients (P = .003), but not in low anterior resection—operated patients (CRM involvement in 12% of female and 12% of male patients)3. This is probably a result of selection because APR is less frequently performed in women than men (26% vs 33%, respectively; P = .09). No difference was found by Tekkis et al31 and Chapuis et al36 found more positive margins in men than women (9% vs 6%, respectively; P = .023).

In a logistic regression model, Luna-Perez et al40 demonstrated a relationship between CRM involvement and age. However, this is not confirmed in other studies.26,31

## CONCLUSION

Throughout the years, measurement of CRM involvement in rectal cancer has gained a large following: a total of 17,568 patients have been described in the literature to date. The treatment of rectal cancer has changed over the years, with the introduction of newer surgical techniques (TME and laparoscopy) and neoadjuvant therapy (short-course radiotherapy, long-course radiotherapy, and combination with different types of chemotherapy). Some of these changes have caused a decrease in the incidence of positive CRMs; well-performed TMEs with a resection margin on the mesorectal plane show margin positivity in less than 10%,61,62 and in most laparoscopic series, margin positivity is also less than 10%. Although short-course radiotherapy does not decrease the number of positive margins, in patients treated with radiochemotherapy, margin positivity was decreased by 9% compared with short-course radiotherapy in a randomized trial.35

In 2008, the power of the CRM to predict local recurrence and, to a lesser extent, development of distant metastases and survival is still high. In multivariate analyses, CRM involvement is one of the strongest prognosticators.

When comparing the HRs for local recurrence, it becomes clear that CRM involvement is even more important in the neoadjuvant setting than it was in the era before the introduction of this kind of therapy. If, in advanced tumors with a positive margin on preoperative imaging, the margin becomes free after treatment, prognosis is good. If, in contrast, the margin remains positive, the prognosis is worse than in cases without neoadjuvant therapy because the remaining tumor consists of a selected population of tumor cells resistant to therapy. Therefore, CRM might function as a marker of tumor regression. Indeed, several studies demonstrate the superiority of CRM compared with the various tumor regression classifications. Measurement of tumor response has been suggested as an alternative, immediate end point for neoadjuvant trials.72,73 However, the marked differences in the definitions used in the various studies as well as the outcomes of multivariate analyses make this increasingly unlikely unless there is standardization of the method. The CRM is a much better candidate; not only can the CRM be predicted reliably before treatment starts,8,9 but also the different treatment modalities (surgery, chemotherapy, and radiotherapy) can be monitored by the CRM, combining pathology and imaging (magnetic resonance imaging). Moreover, a strong correlation with outcome parameters (local recurrence, distant metastases, and disease-free survival) has long since been established. The question remains as to whether CRM can act as an early end point in rectal cancer neoadjuvant studies in a similar way to its use in a surgical study.74

In the current review, we have demonstrated that CRM is still one of the most important factors in rectal cancer management, not only for prediction of prognosis, but also for evaluation of the various steps during treatment. In the current era, when evidence-based medicine and quality control are keywords, we believe that best practice demands the reporting of CRM by radiologists and pathologists alike and that the use of CRM as an immediate end point in neoadjuvant studies should be further explored.

## REFERENCES


## AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

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