What is the Significance of the Circumferential Margin in Locally Advanced Rectal Cancer After Neoadjuvant Chemoradiotherapy?

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ABSTRACT

Background. The circumferential resection margin (CRM) is highly prognostic for local recurrence in rectal cancer surgery without neoadjuvant treatment. However, its significance in the setting of long-course neoadjuvant chemoradiotherapy (nCRT) is not well defined.

Methods. Review of a single institution's prospectively maintained database from 1998 to 2007 identified 563 patients with locally advanced rectal cancer (T3/T4 and/or N1) receiving nCRT, followed after 6 weeks by total mesorectal excision (TME). Kaplan-Meier, Cox regression, and competing risk analysis were performed.

Results. The authors noted that 75 % of all patients had stage III disease as determined by endorectal ultrasound (ERUS) and/or magnetic resonance imaging (MRI). With median follow-up of 39 months after resection, local and distant relapse were noted in 12 (2.1 %) and 98 (17.4 %) patients, respectively. On competing risk analysis, the optimal cutoff point of CRM was 1 mm for local recurrence and 2 mm for distant metastasis. Factors independently associated with local recurrence included CRM ≤ 1 mm, and high-grade tumor ($p = 0.012$ and 0.007 , respectively). CRM ≤ 2 mm, as well as pathological, nodal, and overall tumor stage are also significant independent risk factors for distant metastasis ($p = 0.025$, 0.010 , and <0.001 , respectively).

Conclusion. In this dataset of locally advanced rectal cancer treated with nCRT followed by TME, CRM ≤ 1 mm

is an independent risk factor for local recurrence and is considered a positive margin. CRM ≤ 2 mm was associated with distant recurrence, independent of pathological tumor and nodal stage.

At the time of rectal cancer surgery, a positive circumferential radial margin (CRM) indicates incomplete resection and is associated with high rates of local and distant recurrence.^{1–4} This has been well documented in studies that do not use neoadjuvant therapy. When delivered in 25–28 fractions over 5–6 weeks, chemoradiotherapy induces tumor downsizing and downstaging, which facilitates complete resection.^{5,6} The optimal radial margin has not been well defined. For instance, in a comprehensive review of the literature, Nagtegaal and Quirke report positive CRM is associated with local recurrence; however, the definition of CRM varied between studies.⁷ The aim of this study was to further define the relationship between CRM and local and distant recurrence in the setting of long-course neoadjuvant chemoradiotherapy.

MATERIALS AND METHODS

Study Population

Following approval of this study by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center (MSKCC), we performed a review of a prospectively maintained institutional database from 1998 to 2007. We identified 563 patients diagnosed with locally advanced rectal cancer (T3/4 or N1) by endorectal ultrasonography (ERUS) and/or magnetic resonance imaging (MRI). All of these

patients received an infusional fluorouracil chemotherapy regimen concurrent with radiotherapy (50.4 Gy in 28 fractions), followed by a 6-week break. The break was followed by resection, performed according to the standard technique of total mesorectal excision. Demographic data, clinical characteristics, operative procedure, and histopathology were examined.

Pathologic Assessment

Specimens were inked and fixed. The entire tumor was sectioned perpendicularly to include the radial margin. The CRM was measured as the distance from the deepest part of the tumor in the inked soft tissue edge.

Pathologists reported the tumor response from neoadjuvant treatment by measuring the proportion of residual viable tumor mass replaced by the amount of fibrosis. Percent response was defined by the percent of lesion composed of fibrous or fibroinflammatory tissues in the primary lesion. The complete pathological response was defined as complete regression of the tumor, by means of no disease left in the specimen.

Statistical Analysis

The Pearson χ^2 -test for binary parameters was used to compare demographic data between groups. Analysis of CRM as a continuous variable was performed to identify the optimal cutoff point(s) associated with local recurrence and distant metastasis. Univariate analysis of recurrence-free survival was calculated using the Kaplan-Meier procedure-limit method and reported as median survival and estimated 5-year survival. Multivariate analysis was performed using the Cox proportional hazards regression

method. A p value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 563 patients with locally advanced rectal cancer were included in this study. Median age at diagnosis was 60 years (range, 17–88 years). The majority of patients were male (59 %). Also, 477 patients (85 %) underwent low anterior resection (LAR), and 85 (15 %) underwent abdominoperineal resection (APR). Based on ERUS and/or MRI, 75 % were clinical stage III and 25 % were clinical stage II. Of all patients, 20 % were found to have pathological complete response after multimodality treatment. The median follow-up was 39 months with an interquartile range from 27 to 55 months. There were 12 patients (2 %) who developed local recurrence and 98 (17 %) who developed distant metastasis within the follow-up period. The median interval between completion of neoadjuvant treatment and surgery was 48 days.

Optimal CRM Cutoff Point

In an attempt to identify the most prognostic cutoff point, CRM was analyzed as a continuous variable (Fig. 1). Unfortunately, no clear inflection point was noted for either local or distant recurrence. Competing risk analysis was then used to determine the association of CRM with local and distant recurrence. For local recurrence, creation of cohorts based on CRM ≤ 1 and >1 mm (1-mm cutoff point) resulted in the greatest separation of recurrence curves, compared with 2 mm and 4 mm (Fig. 2a). A total of 20 patients had CRM ≤ 1 mm (Table 1). Patients undergoing APR showed a higher incidence of CRM ≤ 1 mm

FIG. 1 Analysis of correlation between CRM as continuous variable and 5-year recurrence-free survival. **a** Local recurrence, **b** distant recurrence

FIG. 2 Competing risk analysis of **a** local recurrence and 1-, 2-, and 4-mm CRM cutoff points and **b** of distant recurrence and 1-, 2-, and 4-mm CRM cutoff points

compared with those undergoing low anterior resection (LAR) (10.3 vs 3.6 %, $p = 0.016$). In contrast, when analyzing distant recurrence, a cutoff point of 2 mm created the greatest separation of survival curves (Fig. 2b).

Local Recurrence

Univariate analyses demonstrated that low rectal cancer (≤ 5 cm from the anal verge; $p < 0.001$), advanced pathological staging (ypT3–4; $p < 0.02$), high-grade tumor (poorly differentiated to undifferentiated; $p < 0.005$), and CRM ≤ 1 mm ($p < 0.001$) were associated with local recurrence (Table 2). The 5-year local recurrence-free survivals were 66 and 98 % in CRM ≤ 1 and > 1 mm, respectively. Multivariate analysis confirmed that CRM and tumor grade are independent prognostic factors for local recurrence (Table 3).

Distant Metastasis

Univariate analysis demonstrated that low rectal cancer ($p < 0.003$), advanced pathological staging ($p < 0.001$), high-grade tumor biology ($p < 0.004$), partial tumor response ($p < 0.001$), pathological nodal (ypN) disease ($p < 0.001$), and CRM ≤ 2 mm ($p < 0.001$) were significantly associated with distant recurrence (Table 2). Multivariable analysis confirmed that CRM, as well as pathological tumor (ypT) and nodal (ypN) stage, were independent prognostic factors for distant metastasis (Table 3).

Correlation Between CRM and Other Clinicopathologic Factors

CRM was associated with distance of the lesion from the anal verge; lower tumors were more likely to have CRM

TABLE 1 Demographic data of 563 patients with locally advanced rectal cancer

	CRM ≤ 1 mm (<i>N</i> = 20)	CRM > 1 mm (<i>N</i> = 409)	<i>P</i> value ^a
Age (years)	60.2	59.2	0.993
Gender			0.649
Female	7	164	
Male	13	245	
Distance from anal verge			0.667
> 5 cm	6	145	
≤ 5 cm	13	253	
Operation			0.016
LAR	13	348	
APR	7	61	
Preoperative staging			0.995
Stage II	4	80	
Stage III	13	261	

CRM circumferential resection margin, LAR low anterior resection, APR abdominoperineal resection

^a Pearson χ^2 test for binary parameters

≤ 1 mm, consistent with the association between CRM and APR (Fig. 3a). We identified no association between CRM and primary tumor response to chemoradiotherapy (Fig. 3b).

DISCUSSION

The strong association between CRM and local recurrence was clearly demonstrated in 1986 by Quirke et al. in a series of patients undergoing rectal cancer surgery without neoadjuvant therapy. Local recurrence developed in 85 % of all patients (11 of 13) with a positive CRM (≤ 1 mm), compared with 3 % of those with a clear margin (1 of 38).¹ These results were reproduced by several investigators, again in the setting of no preoperative therapy.^{2,3,8,9} The optimal cutoff for defining positive CRM is still debated, however, and some investigators propose 2 mm rather than 1 mm.^{2,8} Nagtegaal et al. reported on a series of 656 rectal cancer patients undergoing rectal resection without neoadjuvant treatment. They found that patients with CRM ≤ 2 mm had a 16 % risk of local recurrence at 2 years, compared with 5.8 % risk for those patients with CRM > 2 mm ($p < 0.001$). The authors also noted that CRM ≤ 1 mm was associated with distant metastasis.² However, most of the literature defines a positive CRM as tumor within 1 mm of the cut surface, and this definition is currently endorsed by the NCCN Guidelines.^{1-4,10,11}

The prognostic significance of CRM status in the setting of neoadjuvant treatment is not as well defined, because the majority of studies excluded patients receiving neoadjuvant treatment. One might expect different results in patients treated neoadjuvantly, as long-course neoadjuvant chemoradiotherapy results in tumor downsizing and downstaging in a majority of cases.^{5,6} In a comprehensive review of the literature, Nagtegaal and Quirke⁷ noted that CRM was a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy (hazard ratio [HR] = 6.3; 95 % confidence interval [95 % CI], 3.7–16.7 in studies using neoadjuvant therapy vs HR = 2.0; 95 % CI, 1.4–2.9 in studies not using neoadjuvant therapy).

The current study evaluates the significance of CRM in a homogeneous cohort of locally advanced rectal cancer patients receiving standard long-course neoadjuvant chemoradiotherapy, followed by total mesorectal excision. The results suggest that CRM remains an independent prognostic factor for local recurrence. The 5-year local recurrence-free survival is significantly different in patients with CRM ≤ 1 mm than in patients with CRM > 1 mm (66 vs 98 %, respectively, $p < 0.001$). This result supports the current NCCN Guidelines.

Furthermore, CRM is also an independent prognostic factor for distant recurrence. Of note, while a wider CRM was associated with fewer recurrences, 2 mm appears to create the greatest separation of survival curves, indicating the optimal cutoff point compared with 4- and 1-mm margins. The 5-year distant recurrence-free survival is 41 % in CRM ≤ 2 mm and 78 % in CRM > 2 mm ($p = 0.001$). One could hypothesize that those tumors that do threaten the mesorectal margin and do not regress with neoadjuvant therapy represent aggressive tumor biology. Although one may expect that tumors with greater response to chemoradiation will demonstrate more regression from the mesorectal fascia, we did not identify a relationship between CRM and response to chemoradiation (percent tumor regression or tumor regression grade). This may result from the fact that not all stage II and III tumors encroach upon the mesorectal fascia at presentation. Multivariate analysis further demonstrated that CRM and pathological staging are independent prognostic factors, whereas the treatment response is not a significant factor. This result is consistent with previously published data from our institution concluding that postoperative pathological tumor and nodal staging are more important prognostic factors than treatment response.⁵ As demonstrated in our study, the association of CRM with distant recurrence is identified not only in the setting of neoadjuvant treatment but in the setting of no neoadjuvant treatment as well.^{2,9,12,13}

The higher rate of positive CRM in patients undergoing APR versus LAR is again demonstrated in this study. This

TABLE 2 Univariate analysis of clinicopathological prognostic factors associated with local and distant recurrence-free survival

Variable	Local recurrence-free survival			Distant recurrence-free survival			
	No. ^a	5-Year survival (%)	<i>P</i> value ^b	No. ^a	Median (months)	5-Year survival (%)	<i>P</i> value ^b
Gender			0.609				0.416
Female	230	95		230	95	68	
Male	333	94		333	113	77	
DTAV			<0.001				0.002
≤5 cm	153	90		153	70	59	
>5 cm	398	97		398	110	79	
Tumor response			0.289				<0.001
Partial	452	95		452	95	68	
Complete	108	98		108	NR	96	
ypT			0.020				<0.001
ypT 0–2	304	97		304	113	92	
ypT 3–4	257	92		257	70	54	
ypN			0.063				<0.001
ypN 0	435	97		435	NR	81	
ypN 1–2	128	89		128	60	49	
Tumor grade			0.005				0.003
1–2	499	97		499	110	75	
3–4	59	85		59	NR	54	
CRM							
≤1 mm	20	66	<0.001	–	–	–	–
>1 mm	409	98		–	–	–	
≤2 mm	–	–	–	45	59	41	0.001
>2 mm	–	–		384	110	78	
Distal margin			0.153				0.417
≤2 cm	238	96		238	110	72	
>2 cm	259	94		259	98	71	

DTAV distance from anal verge, *ypT* pathological tumor staging, *ypN* pathological nodal staging, CRM circumferential resection margin, NR median recurrence-free survival not reached

^a Number of patients available for analysis

^b Survival estimates calculated by Kaplan–Meier product limit method; differences analyzed by log-rank test

TABLE 3 Multivariate analysis of clinicopathological factors associated with local and distant recurrence

HR hazard ratio, 95 % CI 95 % confidence interval, CRM circumferential resection margin, *ypT* pathological tumor stage, *ypN* pathological nodal stage

^a Multivariate analysis performed by Cox proportional hazards regression method

Variable	HR	95 % CI	<i>P</i> value ^a
Local recurrence			
CRM ≤1 mm	7.39	1.55–35.24	0.012
Grade 3–4	5.82	1.62–20.90	0.007
ypT 3–4	2.05	0.37–11.25	0.407
ypN 1–2	1.44	0.39–2.67	0.581
Distant recurrence			
CRM ≤2 mm	1.80	1.08–3.03	0.025
Grade 3–4	0.93	0.42–2.04	0.858
ypT 3–4	1.91	1.17–3.11	0.010
ypN 1–2	5.11	2.49–10.48	<0.001

FIG. 3 Correlation analysis between CRM and pathological percentage of tumor response to neoadjuvant therapy

finding is consistent with the literature, which reports positive CRM in 15–30 %.^{2,8,9,14} Even with optimal cylindrical/extralevator resection, CRM positivity rates approach 15 %.^{10,15} The Polish study comparing short-course radiotherapy to long-course chemoradiotherapy noted a significant reduction in positive CRM in the long-course chemoradiation cohort.¹⁶ In this study, the rate of positive CRM was demonstrated in seven of 68 patients undergoing APR (10.3 %).

This study shares the limitations associated with any retrospective review. Although treatment protocols were standardized, there was some variability in the time from end of chemoradiation to surgery, which could affect CRM. Furthermore, the low rate of local recurrence can limit statistical analysis.

In conclusion, in the setting of neoadjuvant chemoradiotherapy, CRM ≤ 1 mm is considered to be a positive margin and remains a poor prognostic factor for local recurrence. CRM < 2 mm is a prognostic factor for distant metastasis, independent of pathological tumor (T) and nodal (N) staging.

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CONFLICT OF INTEREST The author(s) declare that they have no competing interests

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