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The circumferential resection margin in rectal carcinoma surgery

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Abstract After radical resection of rectal carcinoma, the circumferential resection margin (CRM) on the non-peritonealized surface of the resected specimen is of critical importance. Histopathological examination of resected specimens must include careful assessment of the CRM. There is a need to distinguish between CRM-positive (CRM directly involved by tumor or minimal distance between tumor and CRM 1 mm or less) and CRM-negative (distance between tumor and CRM more than 1 mm) situations. Optimized surgery (so-called TME surgery) and an experienced surgeon decrease the frequency of CRM-positive specimens. The CRM status is an important predictor of local and distant recurrence as well as survival. The CRM status can be reliably predicted by pre-operative thin-slice high-resolution magnetic resonance imaging (MRI). In the event of predicted CRM-positivity, neoadjuvant radiochemotherapy is indicated.

Key words Circumferential resection margin · Local recurrence · Neoadjuvant therapy · Rectal carcinoma · Survival · Total mesorectal excision

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Introduction

In recent years, the so-called CRM status, that is the histological findings at the circumferential resection margin (CRM), has gained enormously in importance for the assessment of the prognosis and the indication for multimodal treatment. The main reason for this is the fact that, with the aid of high-resolution magnetic resonance imaging (MRI), it has become possible pre-operatively to predict the CRM status after resection with a high degree of probability. Unfortunately, the full significance of the CRM is still not sufficiently recognized among surgeons, and in the pathological work-up of resected tumor specimens, relevant deficits remain to be corrected. Against this background, we review the importance of CRM in clinical and pathological settings. For rectal carcinoma resection specimens, one has to distinguish between oral (proximal), aboral (distal) and circumferential (radial, lateral) resection margins.

Definitions

The circumferential resection margin (CRM) corresponds to the non-peritonealized surface of the resection specimen created by dissection of the subperitoneal aspect at surgery. In locally incomplete resection, tumor is found on the CRM in more than 90% of cases [1]. As early as the 1970s, the CRM was examined histologically as a general principle at least in specialized European centers [2]. As a result of the activities of pathologists from Leeds, UK [3–5], the pathological examination of the CRM has become more widespread. However, it has not yet become routine practice, in particular not in the USA [6–8]. Even in controlled clinical trials on rectal cancer, the pathological examination of the CRM is not carried out [9]. This is despite the fact that almost all current recommendations for pathological examination of rectal cancer resection specimens [6–8, 10–22] include an obligatory histological assessment of the CRM.

In Leeds, UK, with regard to CRM, two categories are distinguished:

- CRM-positive (CRM+): tumor at the CRM or minimal distance between tumor and CRM 1 mm or less;
- CRM-negative (CRM-): minimal distance between tumor and CRM more than 1 mm.

In the histological assessment of the minimal distance between tumor and CRM, not only continuous spread of the primary tumor but also discontinuous spread in the form of satellites (satellite deposits), lymphatic and venous invasion and lymph node metastases are considered [3, 4, 23]. With regard to the statistics of treatment outcome, it has to be emphasized that the categories CRM+ and CRM- cannot be directly compared with the UICC residual tumor (R) classification [24]. CRM+ corresponds in part to R1 (if tumor is found directly at the CRM), and in part to R0 (if the CRM is tumor-free, but the tumor is only 1 mm or less from the CRM). Between the two CRM+ subgroups there is a significant prognostic difference, as the data reported by Birbeck et al. [25] and Nagtegaal et al. [26] demonstrate: local recurrence for cases with tumor at the CRM was 55% (n=66) versus 28% (n=97) for cases with tumor 1 mm or less from the CRM [25]. The respective figures in the publication by Nagtegaal et al. [26] are 31% (n=65) and 8% (n=55) ($p < 0.001$).

Methods for histopathological assessment of CRM status

Conventionally, resected specimens are opened anteriorly and pinned to a corkboard for fixation in formalin. After fixation, the area of the tumor is sliced transversally (5 mm) and may be photographed. Slices in which the tumor is close to the CRM and slices with areas marked by the surgeon as suggestive of incomplete tumor removal are embedded after marking the CRM with India ink or Tipp-Ex (BIC Deutschland, Liederbach, Germany). Whenever possible, the slices are embedded as large-area (giant) blocks, otherwise as conventional small blocks (Fig. 1) [23]. For studies, all slices with macroscopically recognizable tumor including slices up to 2 cm below and above the tumor are embedded [4]. For more reliable assessment of the anterior CRM and for comparison with preoperative MRI findings, the specimens are not opened in the area of the tumor and the adjacent 2 cm below and above [27, 28]. These parts of the specimen are fixed for a minimum of 48–72 hours. Gauze soaked in formalin may be pushed through the tumor to enhance fixation. In this way, transverse slices show the original situation and allow direct comparisons with MRI findings (Fig. 2).

How frequent is CRM positivity?

The frequency of CRM+ resection specimens is influenced in the first place by the intention of surgery, i.e. curative or pal-

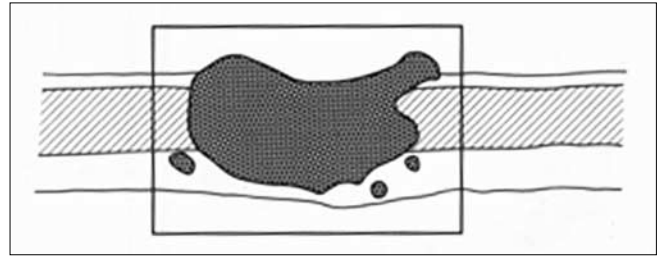


Fig. 1 Histological examination of the circumferential resection margin (CRM) by transverse slicing after fixation of the opened tumor area. Whenever possible, large-area (giant) blocks should be embedded. (Modified from [23])

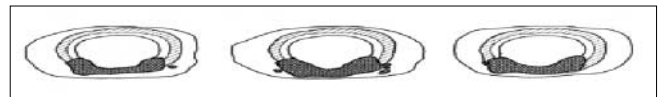


Fig. 2 Histological examination of the CRM that allows direct comparison with MRI findings. Transverse slicing after fixation of the non-opened tumor area

liative, and the type of surgery, i.e. conventional or so-called optimized or total mesorectal excision (TME) surgery. The latter is defined by TME for tumors of the middle and lower thirds of the rectum (≤ 12 cm) and partial mesorectal excision (PME) for tumors of the upper third (> 12 – 16 cm) [14]. In a pooled analysis of 10 studies (Table 1), CRM+ specimens were found in 17% of cases (190 of 1113) after conventional surgery in curative intent (6 studies) and in 7.3% (178 of 2450) after optimized surgery in curative intent (4 studies).

Birbeck et al. [25] noted the great impact of the experience of the individual surgeon on the frequency of CRM+ resection specimens: respective data varied between 15% and 48%. The frequency of CRM+ resection specimens correlates with the pathologic assessment of mesorectal excision [10, 27, 35, 36]. Nagtegaal et al. [37] reported CRM+ resection specimens in 10.8% (n=102) of complete, 34% (n=35) of nearly complete (moderate), and 42% (n=43) of incomplete mesorectal excisions. Furthermore, the frequency of CRM+ specimens is higher in abdominoperineal resection than in (low) anterior resection (Table 2). In addition, tumor-related factors also influence the frequency of CRM+ specimens (Tables 3, 4), which is higher in low rectal tumors, in higher stage (pT, pN) tumors, in high-grade tumors and in tumors with infiltrative borders.

CRM status and prognosis

CRM status is the single most critical factor in predicting local recurrence, and is also important in predicting distant metastasis and survival [25, 34, 36]. In CRM+ patients, local and distant recurrence rates as well as survival rates are worse than in CRM- patients (Table 5).

Nagtegaal et al. [26] proposed a modification of the definition of CRM involvement, namely 2 mm or less.

Table 1 Frequency of CRM+ resection specimens, by type of surgery

References	Year	Surgery in curative intention	Any surgery (curative and palliative)
Conventional surgery			
Quirke et al. [3]	1986	5/39 (13%)	14/52 (27%)
Ng et al. [29]	1993	6/65 (9%)	16/80 (20%)
Adam et al. [30]	1994	35/141 (24.8%)	–
de Haas-Kock et al. [31] ^a	1996	24/212 (11.3%)	–
Birbeck et al. [25]	2002	–	165/586 (28.2%)
Nagtegaal et al. [26]	2002	120/656 (18.3%)	–
Total		190/1113 (17.0%)	195/718 (27.2%)
Optimized surgery			
Cawthorn et al. [32]	1990	6/122 (4.9%)	11/167 (6.6%)
Bernstein et al. [33]	1998	2/47 (4.0%)	–
Wibe et al. [34]	2004	163/2136 (7.6%)	–
Hermanek, Junginger ^b	–	7/145 (4.8%)	–
Total		178/2450 (7.3%)	11/167 (6.6%)

^a Rectosigmoid carcinomas (15–25 cm from the anal verge) excluded; ^b Unpublished observations

Table 2 Frequency of CRM+ resection specimens in abdominoperineal resection and in (low) anterior resection

Reference	Year	Abdominoperineal resection	(Low) anterior resection
Conventional surgery			
Quirke et al. [3]	1986	9/23 (39%)	5/29 (17%)
de Haas-Kock et al. [31] ^a	1996	17/80 (21%)	13/161 (8.1%)
Nagtegaal et al. [26]	2002	59/205 (28.8%)	61/451 (13.5%)
Total		85/308 (27.6%)	79/641 (12.3%)
Optimized surgery			
Wibe et al. [34]	2004	95/821 (11.6%)	68/1315 (5.2%)
Total		180/1129 (15.9%)	147/1956 (7.5%)

^a 212 patients with rectal tumor (within 15 cm from the anal verge) and 40 patients with rectosigmoid tumor (15–20 cm)

This proposal was based on data obtained after a median follow-up of 35 months and 2-year local recurrence rates. It cannot be confirmed for patients from Leeds [25] with a substantially longer follow-up and 5-year local recurrence rates (Table 6). Thus, CRM+ should continue to be defined as 1 mm or less as before.

Preoperative assessment of CRM status by MRI

Knowledge of the prognostic significance of CRM status has acquired enormous clinical importance since it became possible to assess preoperatively the distance between tumor and mesorectal fascia, which was first demonstrated

in 1983 [41] but, except for a pilot study in Japan [42], it has not been pursued further. Preoperative demonstration of the mesorectal fascia was revisited by Brown et al. [43] in 1999 using thin slice high-resolution MRI with a pelvic phased-array surface coil. In the following years, this method was used in several institutions [44–50] and was also investigated in a European multicenter study [28]. With modern MRI, it is now preoperatively possible to predict the distance between the tumor and the mesorectal fascia, i.e. CRM of more than 1 mm with a high grade of certainty. The negative predictive value of modern MRI prior to primary surgery was 91.1% (265/291) in the multicentre MERCURY study (to be published) and 93.2% (247/265) in a pooled analysis of 5 single-center studies [45, 49, 51–53] (to be published in 2005 by Junginger et al.).

Table 3 Frequency of CRM+ resection specimens, by tumor-related factors

Reference	Frequency	
Tumor site (distance between distal tumor margin and anal verge)		
Nagtegaal et al. [26]		
<5 cm	55/2112	(25.9%)
5–10 cm	34/257	(13.2%)
10–15 cm	30/182	(16.5%)
Wibe et al. [34]		
≤5 cm	84/791	(10.6%)
6–8 cm	29/558	(5.2%)
9–12 cm	50/787	(6.4%)
Local spread (de Haas-Kock et al. [31])		
pT1	1/25	(4%)
pT2	3/75	(4%)
pT3	23/144	(16.0%)
pT4	4/7	(57%)
Regional lymph node metastasis (de Haas-Kock et al. [31] ^a)		
No metastasis	17/167	(10.2%)
Metastasis	12/80	(15%)
Grading (Quirke et al. [3])		
G1	0/1	(0%)
G2	5/36	(14%)
G3	9/15	(60%)
Tumor border (Quirke et al. [3])		
Pushing	2/24	(8%)
Infiltrating	10/28	(36%)

^a 212 patients with rectal tumor (within 15 cm from the anal verge) and 40 patients with rectosigmoid tumor (15–25 cm)

Table 4 Frequency of CRM+ resection specimens by UICC stage

Reference	Year	Stage I		Stage II		Stage III	
Quirke et al. [3]	1986	0/5	(0%)	1/22	(5%)	13/25	(52%)
Ng et al. [29]	1993	0/9	(0%)	2/29	(7%)	8/33	(21%)
Hall et al. [38]	1998	0/30	(0%)	6/66	(9%)	14/54	(26%)
Nagtegaal et al. [26]	2002	4/203	(2.0%)	27/184	(14.7%)	89/269	(33.1%)
Total		4/247	(1.6%)	36/301	(12.0%)	124/381	(32.5%)
Range		0%–2%		5%–15%		21%–52%	

CRM and the indication for neoadjuvant therapy

Without prejudice to the discussions on neoadjuvant therapy [16, 21, 54–60], the pre-operative MRI evaluation of CRM status to be expected after radical resection has become a decisive factor for the selection of patients for neoadjuvant therapy [36, 44, 45, 48, 49]. When the distance between tumor and mesorectal fascia is 1 mm or less, as described by pre-operative MRI, complete resection of the tumor, even with optimal surgery, is questionable. In such a situation, therefore, long-course neoadjuvant radiochemotherapy is indicated, since in many cases, this leads to downsizing and downstaging of the tumor [54–56, 61, 62], thus enabling reliable complete resection of the tumor. With this approach involving neoadjuvant therapy followed by optimized (TME) surgery, local recurrence rates of around 5% and cancer-related 5-year survival rates of up to 80% can be expected (pooled analysis of 13 publications [61, 63–74], to be published by Junginger et al. 2005).

Conclusions

Today, the pathological evaluation of resected specimens bearing rectal carcinoma must include a careful histological work-up of the CRM. The CRM status is a major factor in assessing the quality of the surgery, and is a powerful prognostic factor. When the pathological evaluation following primary surgery reveals a CRM+ status, adjuvant radiochemotherapy is indicated. Modern high-resolution MRI enables a highly accurate prediction of the CRM status that may be expected after resection. The pre-operative MRI assessment of CRM positivity represents a major indication for long-course neoadjuvant radiochemotherapy.

Table 5 Clinical course after resection with curative intention (no gross residual tumor), and relation to CRM status. CRM+; tumor 1 mm or less from the CRM (including direct involvement); CRM-, tumor more than 1 mm from the CRM

References	Year	Follow-up, months	CRM+	CRM-
Crude local recurrence rate				
Ng et al. [29] ^a	1993	Median, 26.6	3/5 (60%)	19/59 (17%)
de Haas-Kock et al. [31]	1996	Median, 35	9/31 (29%)	17/217 (8%)
Wibe et al. [39] ^b	2002	Median, 29	14/65 (22%)	32/621 (5%)
2-year actuarial local recurrence rate				
de Haas-Kock et al. [31]	1996	Median, 35	25% (n=31)	8% (n=217)
Birbeck et al. [25] ^c	2002	Minimum, 12 Maximum, 144	~35% ^e	~7% ^e
Nagtegaal et al. [26] ^d	2002	Median, 35	16.4% (n=120)	NS (n=436)
Flor et al. [40]	2004	NG	28% ^f	3.3% ^f
5-year actuarial local recurrence rate				
Birbeck et al. [25] ^c	2002	Minimum, 12 Maximum, 144	56%	15%
2-year actuarial rate of distant metastasis				
de Haas-Kock et al. [31]	1996	Median, 35	30% (n=31)	16% (n=217)
Nagtegaal et al. [26] ^d	2002	Median, 35	37.6% (n=120)	12.7% (n=536)
Wibe et al. [39] ^b	2002	Median, 29	40% (n=65)	12% (n=621)
5-year actuarial cancer-related survival rate				
Birbeck et al. [25] ^c	2002	Minimum, 12 Maximum, 144	40%	79%

NG, not given

^a 6 patients who died postoperatively were excluded

^b Multicenter observation study of the Norwegian Rectal Cancer Project

^c Total number of patients operated on in curative intention was 488, number of CRM+ and CRM- patients not stated. Earlier publications from Leeds, UK [3, 30, 38] not considered

^d Non-irradiated patients of the Dutch Radiotherapy + TNM Trial

^e Estimation based on visual inspection of survival curves

^f Total number of patients was 255, number of CRM+ and CRM- patients not stated

Table 6 Local recurrence rate according to the minimum distance between tumor and CRM

Minimum distance between tumor and CRM	Local recurrence rate	
	Nagtegaal et al. [26] ^a	Birbeck et al. [25] ^b
≤1 mm	16.4% (n=120)	38.2% (n=163)
1.1–2.0 mm	14.9% (n=53)	~3% (n=36) ^c
≥2 mm	5.8% (n=483)	~10% (n=385) ^c

^a Two-year actuarial values at median 35 months follow-up

^b Crude values; 61% of patients had a 5-year follow-up

^c Estimate based on visual inspection (columnar diagram)

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Invited comment

This review article is timely and important on a variety of levels, especially because it emphasizes the real value of close clinicopathological correlation in our clinical practice.

As mentioned in the article, resection margins are divided into longitudinal resection margin (LRM) and circumferential resection margin (CRM). The discussion on the critical length of the free distal margin in LRM should not be forgotten. The first publication to challenge the arbitrary 5 cm rule has shown that it is not necessary to have 5 cm free margin, as most tumors will not spread longitudinally such a distance [1]. This work has stimulated Kirwan and colleagues who demonstrated that a 1 cm clear margin is sufficient; this has helped to decrease the abdominoperineal operation in favor of anterior resection [2, 3].

The position with CRM although on the surface has been settled, the finer details require attention on 2 points. The first point regards the methods of sectioning. The Guilford group, who were one of the first to emphasize the importance of CRM [4], have used a longitudinal section

through the tumor parallel to the fecal stream. Quirke et al. [5], however, have adopted and popularized Chan et al.'s [6] technique of sectioning through the tumor perpendicular to the fecal stream; this has become the standard technique. So, to compare the various studies, one may need to consider this technical difference. Second, and perhaps more important, is validation of the various figures mentioned in the literature as what constitutes in biological terms an involved CRM? Is it 1 mm or less as suggested by Quirke et al. [5], 2 mm as intimated by Nagtegaal et al. [7], or only when we see the neoplastic cells at the cut end of the section (which is what Newland et al. [8] referred to as the "plane of section")? While this review is accepting Quirke et al.'s original suggestion, a subsequent paper from the same group (Birbeck et al.) [9] showed that the worst results in terms of survival or recurrence come when the tumor extends to the plane of section, i.e. zero distance. Indeed, the figures from Marks et al. [10] show the same, thus agreeing with what the Sydney group suggested earlier.

We think that the jury is still out as to what is the appropriate distance in the CRM to prognosticate patients as suggested by the Dutch study, but we strongly recommend that pathologists must document the distance between the tumor and the resection margin and any report devoid of this observation is doomed significantly deficient.

On a totally different note, we would like to emphasize that the potential benefits of using MRI-based selection criteria have been stressed in a review by Brown and Daniels, in introducing the MERCURY research project [11]. However, there is no consensus on the role of diagnostic imaging (e.g. endorectal ultrasonography, computed tomography and magnetic resonance imaging) in the choice of treatment for patients with rectal cancer [12].

Nevertheless, in cases of rectal cancer treated with neoadjuvant radiochemotherapy and total mesorectal excision, CRM involvement is correlated with high incidences of distant recurrence and cancer-related death, but a low incidence of local relapse [13].

According to Pucciarelli et al. [14], disease-free and overall survival rates are related to preoperative T stage and not to tumor response to preoperative radiochemotherapy.

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