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REVIEW ARTICLE

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 *v* 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.

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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[1,2] 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[3-6]; however, there are increased adverse effects.[7] 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.[8,9]

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?

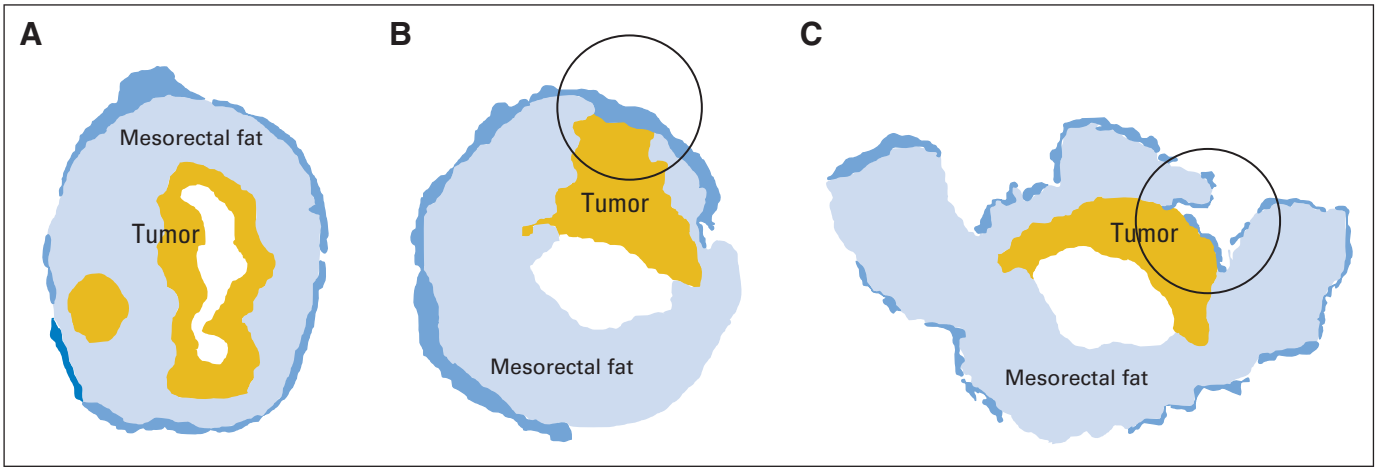

Fig 1. Schematic representation of the circumferential resection margin (CRM); the margin is marked with black ink. (A) Negative CRM. (B) Locally advanced tumor growth, directly into the circumferential margin. (C) Small tumor growing into the circumferential margin as a result of incomplete removal of the surrounding mesorectum. The plane of resection is onto the muscularis propria.

METHODS

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[10,11] 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[10] and from six to 16 patients.[11] 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"[12] are reasons for concern. Frequencies of CRM involvement in single-center studies should be treated with caution. Reports from trials[56] 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[57,58]) 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%, $P = .31$[34]; and 10% *v* 11%,[5] for radiotherapy *v* no radiotherapy, respectively), as could be expected by the lack of downstaging as a result of this regimen.[59] 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

Reference	Year	Series	Selection	Neoadjuvant Therapy	No. of Patients	TNM Stage III (% of patients)	CRM Positive (% of patients)
Single-center studies							
Chan et al[13]	1985	Single center			50	64	13
Quirke et al[10]	1986	Single center			52	48	27
Cawthorn et al[14]	1990	Single surgeon			168	43	7
Ng et al[11]	1993	Single center			80	43	20
Adam et al[15]	1994	Single center			141		25
Hall et al[16]	1998	Single surgeon			152	43	13
Hill and Rafique[17]	1998	Single surgeon			122	31	7
Marks et al[18]	2000	Single surgeon			346	48	16
Ueno et al[19]	2001	Single center*			44	100	18
Birbeck et al[20]	2002	Single center			586		28
Ueno et al[21]	2002	Single center			437	51	4
Wang et al[22]	2004	Single center			62	68	7
Macadam et al[23]	2005	Single center			168	29	19
Hermanek and Junginger[24]	2005	Single center			145		5
Das et al[25]	2006	Single center		89%	470	53	1
Chapuis et al[26]	2006	Single center			1,613	47	8
Wang et al[27]	2006	Single center			62	68	6
Population-based studies							
de Haas-Kock et al[28]	1996	Regional			253	31	12
Wibe et al[29]	2002	National			686†	36	9
Phang et al[12]	2002	Regional			481	21	12
Wibe et al[30]	2004	National			2,136†	32	8
Tekkis et al[31]	2005	National			1,036	40	13
Eriksen et al[32]	2006	National		42%	896	47	22
Randomized neoadjuvant trials							
Nagtegaal et al[33]	2002		Curative	None	656	41	18
Marijnen et al[34]			Curative	5 × 5 Gy	662	37	16
Bujko et al[35]	2004		cT3/T4	5 × 5 Gy	155	48	13
			cT3/T4	50.4 Gy + CT	157	32	4
Bosset et al[36]	2005		cT3/T4	45 Gy	505	35	9
			cT3/T4	45 Gy FU-LV	506	25	9
Sebag-Montefiore et al[5]	2006		Curative	None	676	44	10
			Curative	5 × 5 Gy	674	42	11
Other neoadjuvant studies							
Read et al[37]	2001	Single center		RT/RCT	227	57	7
Bouzourene et al[38]	2003	Phase II trial	cT3/T4	26 × 1.6 Gy	104	53	24
Wheeler et al[39]	2004	Single center	cT3/4	45-50 Gy FU	63	34	17
Luna-Perez et al[40]	2005	Single center	uT3	45 Gy FU	61	21	20
Mawdsley et al[41]	2005	Single center	LARC	45 Gy FU	122		20
Rullier et al[42]	2005	Single center	uT3/4 or N1	44 Gy	200	71	11
Box et al[43]	2005	Single center		40-50 Gy FU	100	30	17
Moore et al[44]	2005	Single center	cT3/4 or N1	RCT or RT	155	30	1
Sebag-Montefiore et al[45]	2005	Phase I/II trial	LARC	45 Gy FU-LV Ox	27	22	19
Sebag-Montefiore et al[46]	2005	Single center	LARC	45 Gy FU-LV	112†	24	26
Sebag-Montefiore et al[47]	2005	Multicenter	LARC	45-50 Gy FU	541†		21
Klaassen et al	Submitted for publication	Single center	LARC	RT or RCT	201	34	17
Rutten et al[48]	2006	Phase II trial	LARC	45 Gy Ox Cap	87		33
Laparoscopic series							
Hartley et al[49]	2001	Single center	Laparoscopy		21	29	0
			Open		22	45	0
			Conversion		21	62	10
Rullier et al[50]	2003	Single center	Laparoscopy		32	63	6
			Open		43		2

(continued on following page)

Table 1. Frequencies of CRM-Positive Patients in Single-Center Studies, Population-Based Studies, Randomized Neoadjuvant Trials, Nonrandomized Neoadjuvant Studies, and Laparoscopic Series (continued)

Reference	Year	Series	Selection	Neoadjuvant Therapy	No. of Patients	TNM Stage III (% of patients)	CRM Positive (% of patients)
Breukink et al[51]‡	2005	Case control	Laparoscopy		25	48	12
			Open		25	56	4
Breukink et al[52]‡	2005	Case control	Laparoscopy	5 × 5 Gy	41	39	7
			Open	5 × 5 Gy	41	39	12
Bretagnol et al[53]	2005	Two centers	Laparoscopy		144	53	6
			Open		83		6
Guillou et al[54]	2005	Randomized trial	Laparoscopy	17%	160	42	16
			Open	17%	40	40	14
Tsang et al[55]	2006	Single center	Laparoscopy	45 Gy FU-LV	135	35	1

Abbreviations: CRM, circumferential resection margin; CT, chemotherapy; FU, fluorouracil; LV, leucovorin; RT, radiotherapy, not specified; RCT, radiochemotherapy, not specified; LARC, locally advanced rectal cancer; Ox, oxaliplatin; Cap, capecitabine.
*Only patients with lateral node involvement were included.
†There is an overlap in the patient populations of these series.
‡≤ 2 mm is considered positive.

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 ($P < .001$).[36] 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.[60] 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.[1,61,62] As a result of the lower local recurrence rates,

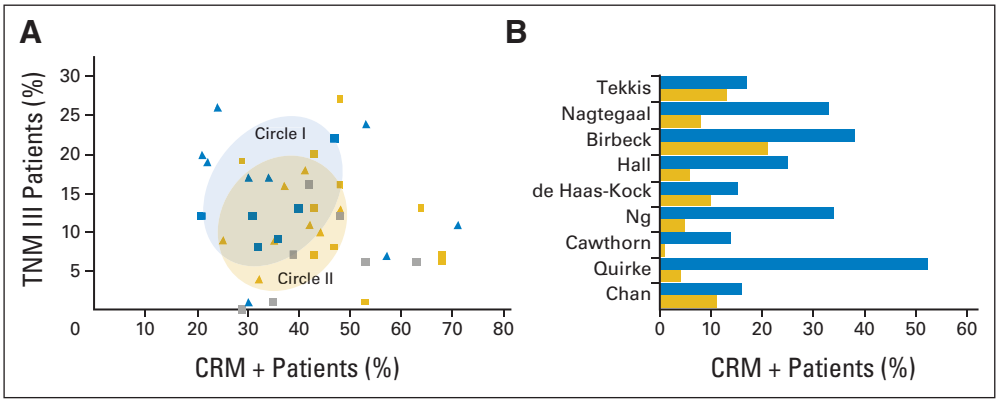

Fig 2. Incidence of circumferential resection margin (CRM) positivity. (A) Plot of the percentage of CRM-positive patients in relation to the percentage of TNM stage III patients per series. Circle I: population-based studies; circle II: randomized neoadjuvant trials. Yellow square: single-center study; blue square: population-based study; yellow triangle: randomized neoadjuvant trial; blue triangle: single-center neoadjuvant study; gray square: laparoscopic study. (B) Correlation of CRM-positive patients with TNM stage grouping. Blue bars represent TNM stage III patients; yellow bars represent TNM stage I or II patients.

both the sensitivity and the positive predictive value of circumferential margin involvement have decreased compared with our earlier publication.[10] 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.[29] 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.[63] In the series by Rullier et al,[63] 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,[36] 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[33,34] and the CR07 trials,[5] 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.[39,42,64-66] 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.[67] Despite these disadvantages, TRG has been suggested as a surrogate and early outcome parameter for neoadjuvant trials. When comparing the value of

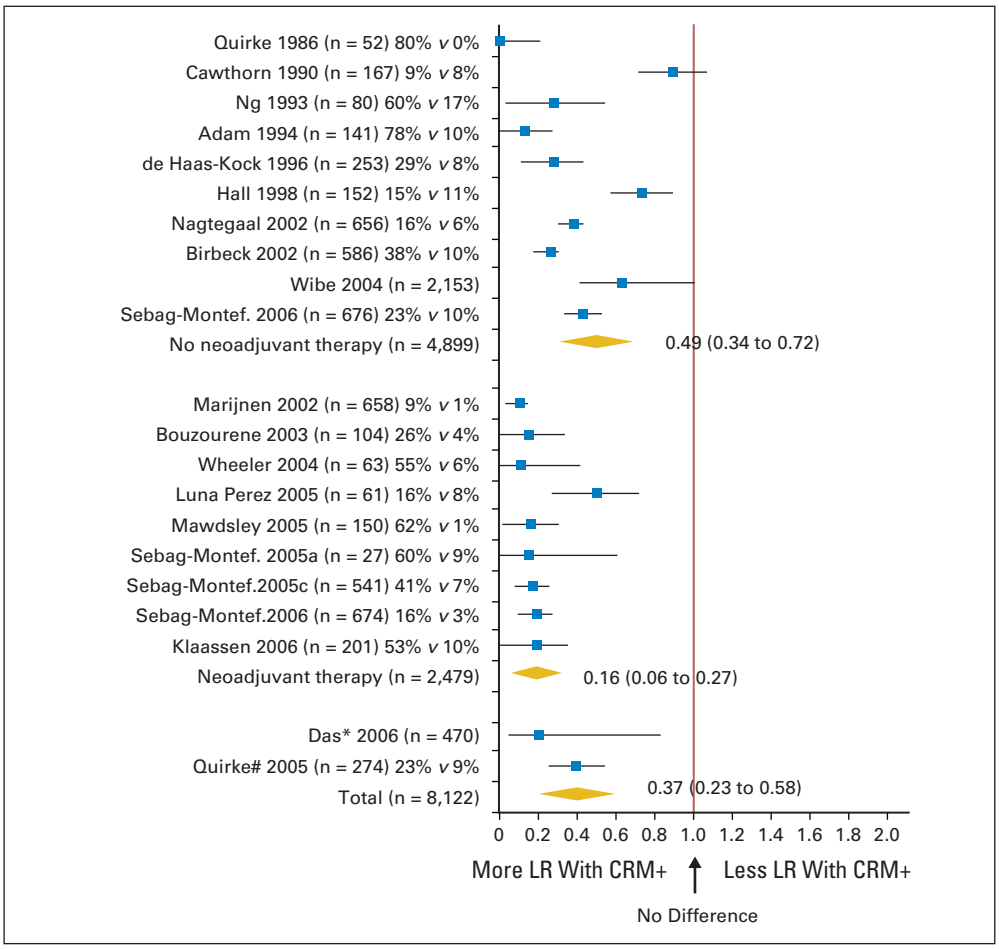

Fig 3. Local recurrence (LR) hazard ratios and 95% CIs for positive circumferential resection margin (CRM) compared with negative CRM. (*) Eighty-nine percent of patients received preoperative radiotherapy; (#) 17% of patients received preoperative radiotherapy, and 50% of patients were operated on laparoscopically.

CRM with TRG, four independent studies demonstrate superiority of CRM over TRG in a multivariate model.[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.[70,71]

LOCALLY RECURRENT DISEASE

The role of the CRM in locally recurrent disease has recently been reviewed by Caricato et al.[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 ≤ 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.[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[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[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[20,33]; however, these results were based on only 19 and 67 patients, respectively, and require further studies to establish their true importance.

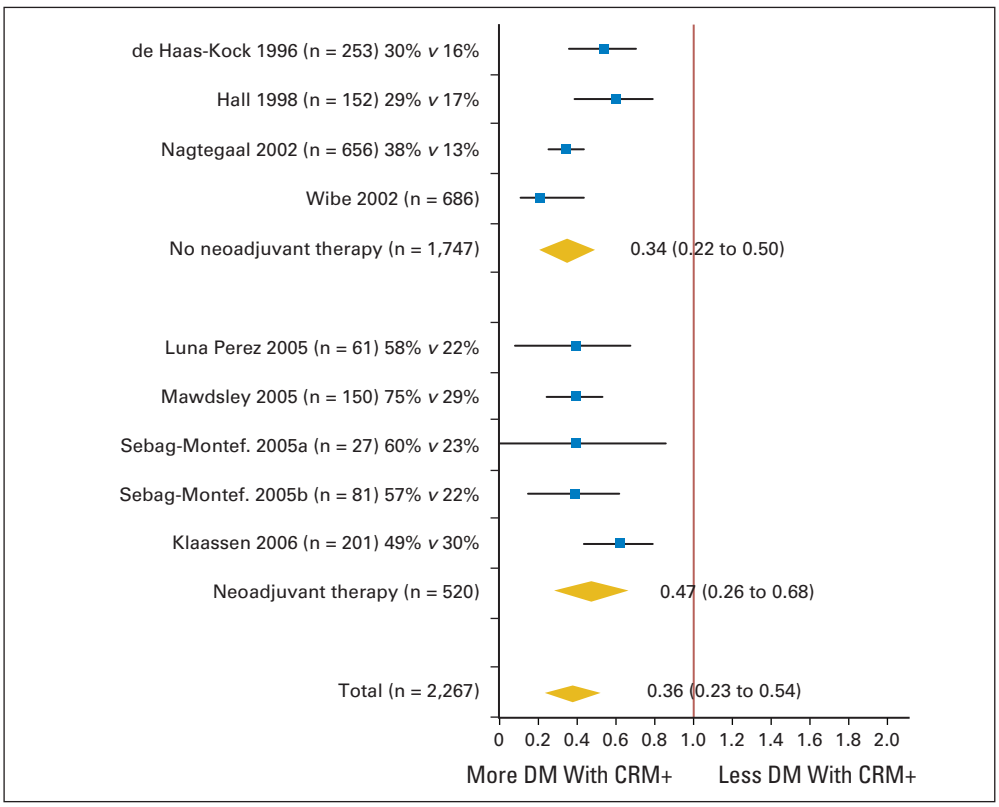

Fig 4. Distant metastases hazard ratios and 95% CIs for positive circumferential resection margin (CRM) compared with negative CRM. DM, distant metastases.

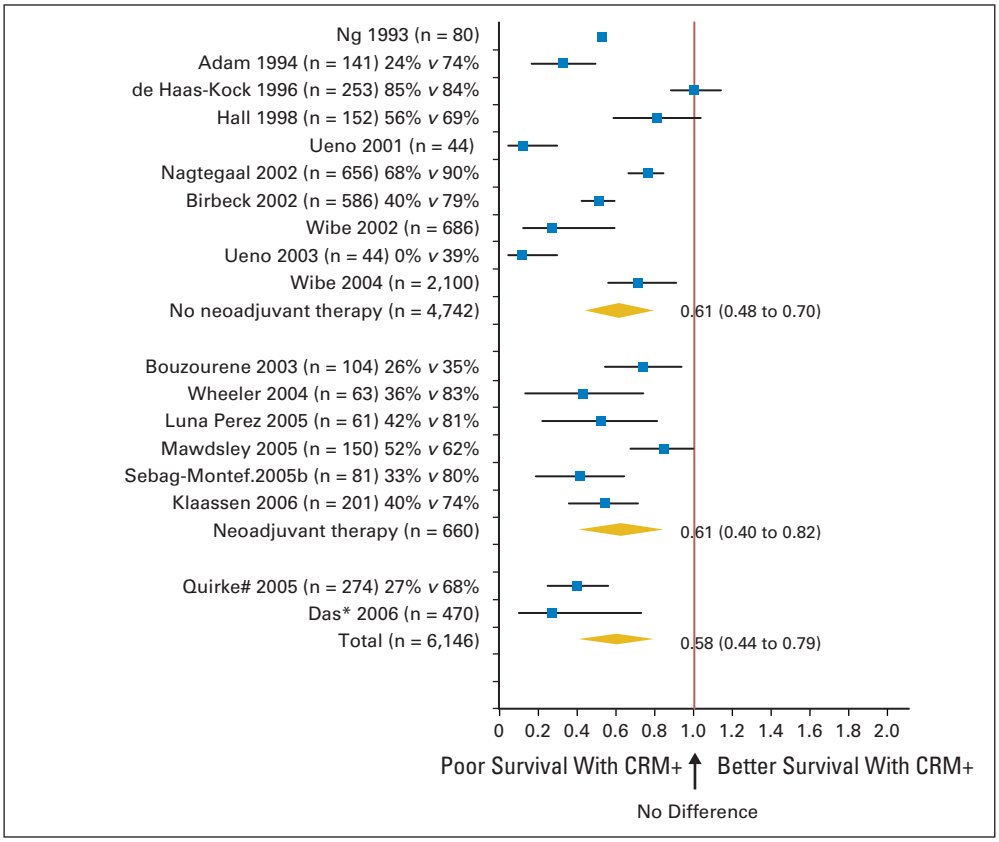

Fig 5. Survival hazard ratios and 95% CIs for positive circumferential resection margin (CRM) compared with negative CRM. (*) Eighty-nine percent of patients received preoperative radiotherapy; (#) 17% of patients received preoperative radiotherapy, and 50% of patients were operated on laparoscopically.

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.[10,11,20,23,28,31,33] 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% *v* 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[1]). This is probably a result of selection because APR is less frequently performed in women than men (26% *v* 33%, respectively; $P = .09$). No difference was found by Tekkis et al,[31] and Chapuis et al[26] found more positive margins in men than women (9% *v* 6%, respectively; $P = .023$).

In a logistic regression model, Luna-Perez et al[40] 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.[73,74] 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.[54]

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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Iris D. Nagtegaal, Phil Quirke
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REFERENCES

1. Nagtegaal ID, van de Velde CJH, Marijnen CAM, et al: Low rectal cancer: A pathologists' call for a change of approach in abdominoperineal resection. J Clin Oncol 23:9257-9264, 2005

2. Marr R, Birbeck KF, Gavircan J, et al: The modern abdominoperineal resection: The next challenge after total mesorectal excision. Ann Surg 242:74-82, 2005

3. Stockholm Rectal Cancer Study Group: Preoperative short-term radiation therapy in operable rectal carcinoma: A prospective randomised trial. Cancer 66:49-55, 1990

4. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638-646, 2001

5. Sebag-Montefiore D, Steele R, Quirke P, et al: Routine short course preoperative radiotherapy or selective postoperative chemoradiotherapy for resectable rectal cancer? Preliminary results of the MRC CR07 randomised trial. J Clin Oncol 24:148s, 2006 (suppl; abstr 3511)

6. Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731-1740, 2004

7. Marijnen CAM, Kapiteijn E, van de Velde CJH, et al: Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: Report of a multicenter trial. J Clin Oncol 20:817-825, 2002

8. Beets-Tan RGH, Beets GL, Vliegen RFA, et al: Can MRI predict the tumour free resection margin in rectal cancer surgery? Lancet 357:497-504, 2001

9. Brown G, Radcliffe AG, Newcombe RG, et al: Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg 90:355-364, 2003

10. Quirke P, Durdey P, Dixon MF, et al: Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: Histopathological study of lateral tumor spread and surgical excision. Lancet 2:996-999, 1986

11. Ng IOL, Luk ISC, Yuen ST, et al: Surgical lateral clearance in resected rectal carcinomas. Cancer 71:1972-1976, 1993

12. Phang PT, MacFarlane JK, Taylor RH, et al: Effects of positive resection margin and tumor distance from anus on rectal cancer treatment outcomes. Am J Surg 183:504-508, 2002

13. Chan KW, Boey J, Wong SKC: A method of reporting radial invasion and surgical clearance of rectal carcinoma. Histopathology 9:1319-1327, 1985

14. Cawthorn SJ, Parums DV, Gibbs NM, et al: Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. Lancet 335:1055-1059, 1990

15. Adam IJ, Mohamdee MO, Martin IG, et al: Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 344:707-711, 1994

16. Hall NR, Finan PJ, Al-Jaberi T, et al: Circumferential margin involvement after mesorectal excision of rectal cancer with curative intent: Predictor of survival but not local recurrence? Dis Colon Rectum 41:979-983, 1998

17. Hill GL, Rafique M: Extrafascial excision of the rectum for rectal cancer. Br J Surg 85:809-812, 1998

18. Marks CG, Reid FDA, Lewis CE, et al: What determines the outcome after total mesorectal excision for rectal carcinoma: 15 years experience of a specialist surgical unit. Colorectal Dis 2:270-276, 2000

19. Ueno H, Mochizuki H, Hashiguchi Y, et al: Prognostic determinants of patients with lateral nodal involvement by rectal cancer. Ann Surg 234: 190-197, 2001

20. Birbeck KF, Macklin CP, Tiffin NJ, et al: Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 235:449-457, 2002

21. Ueno H, Mochizuki H, Shinto E, et al: Histologic indices in biopsy specimens for estimating the probability of extended local spread in patients with rectal carcinoma. Cancer 94:2882-2891, 2002

22. Wang Z, Zhou ZG, Wang C, et al: Microscopic spread of low rectal cancer in regions of mesorectum: Pathologic assessment with whole-mount sections. World J Gastroenterol 10:2949-2953, 2004

23. Macadam R, Yeomans N, Wilson J, et al: Factors affecting morbidity, mortality and survival in patients undergoing surgery for rectal cancer in a district general hospital. Ann R Coll Surg Engl 87: 334-338, 2005

24. Hermanek P, Junginger T: The circumferential resection margin in rectal carcinoma surgery. Tech Coloproctol 9:193-199, 2005

25. Das P, Skibber JM, Rodriguez-Bigas MA, et al: Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J Clin Oncol 29:219-224, 2006

26. Chapuis PH, Lin BP, Chan C, et al: Risk factors for tumour present in a circumferential line of resection after excision of rectal cancer. Br J Surg 93:860-865, 2006

27. Wang Z, Zhou ZG, Wang C, et al: Regional micrometastasis of low rectal cancer in mesorectum: A study utilizing HE stain on whole-mount section and ISH analyses on tissue microarray. Cancer Invest 24:374-381, 2006

28. de Haas-Kock DFM, Baeten CGMI, Jager JJ, et al: Prognostic significance of radial margins of clearance in rectal cancer. Br J Surg 83:781-785, 1996

29. Wibe A, Rendedal PR, Svensson E, et al: Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 89:327-334, 2002

30. Wibe A, Syse A, Andersen E, et al: Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: Anterior vs. abdominoperineal resection. Dis Colon Rectum 47: 48-58, 2004

31. Tekkis PP, Heriot AG, Smith J, et al: Comparison of circumferential margin involvement between restorative and nonrestorative resections for rectal cancer. Colorectal Dis 7:369-374, 2005

32. Eriksen MT, Wibe A, Hestvik UE, et al: Surgical treatment of primary locally advanced rectal cancer in Norway. Eur J Surg Oncol 32:174-180, 2006

33. Nagtegaal ID, Marijnen CAM, Klein Kranenbarg E, et al: Circumferential margin is still an important predictor of local recurrence in rectal carcinoma: Not one millimeter but two millimeters is the limit. Am J Surg Pathol 26:350-357, 2002

34. Marijnen CAM, Nagtegaal ID, Kapiteijn E, et al: Radiotherapy does not compensate for positive resection margins in rectal cancer patients. Int J Radiat Oncol Biol Phys 55:1311-1320, 2003

35. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al: Sphincter preservation following preoperative radiotherapy for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 72:15-24, 2004

36. Bosset JF, Calais G, Mineur L, et al: Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results—EORTC 22921. J Clin Oncol 23:5620-5627, 2005

37. Read TE, McNevin MS, Gross EK, et al: Neoadjuvant therapy for adenocarcinoma of the rectum: Tumor response and acute toxicity. Dis Colon Rectum 44:513-522, 2001

38. Bouzourene H, Bosman FT, Matter M, et al: Predictive factors in locally advanced rectal cancer treated with preoperative hyperfractionated and accelerated radiotherapy. Hum Pathol 34:541-548, 2003

39. Wheeler JM, Dodds E, Warren BF, et al: Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: Correlation with rectal cancer regression grade. Dis Colon Rectum 47:2025-2031, 2004

40. Luna-Perez P, Bustos-Cholico E, Alvarado I, et al: Prognostic significance of circumferential margin involvement in rectal adenocarcinoma treated with preoperative chemoradiotherapy and low anterior resection. J Surg Oncol 90:20-25, 2005

41. Mawdsley S, Glynne-Jones R, Grainger J, et al: Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for 3-year disease-free survival? Int J Radiat Oncol Biol Phys 63:745-752, 2005

42. Rullier A, Laurent C, Vendrely V, et al: Impact of colloid response on survival after preoperative radiotherapy in locally advanced rectal carcinoma. Am J Surg Pathol 29:602-606, 2005

43. Box B, Lindsey I, Wheeler JM, et al: Neoadjuvant therapy for rectal cancer: Improved tumor response, local recurrence, and overall survival in nonanemic patients. Dis Colon Rectum 48:1153-1160, 2005

44. Moore HG, Gittleman AE, Minsky BD, et al: Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 47:279-286, 2004

45. Sebag-Montefiore D, Glynne-Jones R, Falk S, et al: A phase I/II study of oxaliplatin when added to 5-fluorouracil and leucovorin and pelvic radiation in locally advanced rectal cancer: A Colorectal Clinical Oncology Group (CCOG) study. Br J Cancer 93:993-998, 2005

46. Sebag-Montefiore D, Hingorani M, Cooper R, et al: Circumferential resection margin status predicts outcome after pre-operative chemoradiation for locally advanced rectal cancer. 2005 Gastrointestinal Cancers Symposium (abstr 193)

47. Sebag-Montefiore D, Glynne-Jones R, Mortensen N, et al: Pooled analysis of outcome measures including the histopathological R0 resection rate after preoperative chemoradiation for locally advanced rectal cancer. Colorectal Dis 7:7, 2005 (abstr)

48. Rutten H, Sebag-Montefiore D, Glynne-Jones R, et al: Capecitabine, oxaliplatin, radiotherapy, and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: Results of an international multicenter phase II study. J Clin Oncol 24:153s, 2006 (suppl; abstr 3528)

49. Hartley JE, Mehigan BJ, Qureshi AE, et al: Total mesorectal excision: Assessment of the laparoscopic approach. Dis Colon Rectum 44:315-321, 2001

50. Rullier E, Sa Cunha A, Couderc P, et al: Laparoscopic intersphincteric resection with coloplasty and coloanal anastomosis for mid and low rectal cancer. Br J Surg 90:445-451, 2003

51. Breukink SO, Pierie JP, Grond AJ, et al: Laparoscopic versus open total mesorectal excision: A case-control study. Int J Colorectal Dis 20:428-433, 2005

52. Breukink SO, Grond AJ, Pierie JP, et al: Laparoscopic vs open total mesorectal excision for rectal cancer: An evaluation of the mesorectum's macroscopic quality. Surg Endosc 19:307-310, 2005

53. Bretagnol F, Lelong B, Laurent C, et al: The oncological safety of laparoscopic total mesorectal excision with sphincter preservation for rectal carcinoma. Surg Endosc 19:892-896, 2005

54. Guillou PJ, Quirke P, Thorpe H, et al: Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): Multicentre, randomised controlled trial. Lancet 365:1718-1726, 2005

55. Tsang WW, Chung CC, Kwok SY, et al: Laparoscopic sphincter-preserving total mesorectal excision with colonic J-pouch reconstruction: Five-year results. Ann Surg 243:353-358, 2006

56. Stocchi L, Nelson H, Sargent DJ, et al: Impact of surgical and pathologic variables in rectal cancer: A United States community and cooperative group report. J Clin Oncol 19:3895-3902, 2001

57. Tepper JE, O'Connell MJ, Niedzwiecki D, et al: Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 19:157-163, 2001

58. Morris EJ, Maughan NJ, Forman D, et al: Identifying stage III colorectal cancer patients: The influence of the patient, surgeon, and pathologist. J Clin Oncol 25:2573-2579, 2007

59. Marijnen CAM, Nagtegaal ID, Klein Kranenbarg E, et al: No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 19:1976-1984, 2001

60. Quirke P, Guillou PJ, Thorpe H, et al: CLASICC trial (Conventional Versus Laparoscopic-Assisted Surgery in Colorectal Cancer): First release of 3-year results. J Pathol 207:47A, 2005 (abstr)

61. Nagtegaal ID, van de Velde CJH, van der Worp E, et al: Macroscopic evaluation of rectal cancer resection specimen: Clinical significance of the pathologist in quality control. J Clin Oncol 20: 1729-1734, 2002

62. Quirke P, Sebag-Montefiore D, Steele R, et al: Local recurrence after rectal cancer resection is strongly related to the plane of surgical dissection and is further reduced by preoperative short course radiotherapy: Preliminary results of the MRC CR07 trial. J Clin Oncol 24:149s, 2006 (suppl; abstr 3512)

63. Rullier E, Goffre B, Bonnel C, et al: Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum. Ann Surg 234:633-640, 2001

64. Dworak O, Keilholz L, Hoffmann A: Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 12:19-23, 1997

65. Bouzourene H, Bosman FT, Seelentag W, et al: Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 94:1121-1130, 2002

66. Rodel C, Martus P, Papadoupolos T, et al: Prognostic significance of tumour regression after preoperative chemoradiation for rectal cancer. J Clin Oncol 24:8688-8696, 2006

67. Ryan R, Gibbons D, Hyland JM, et al: Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 47:141-146, 2005

68. Machiels JP, Aydin S, Bonny MA, et al: What is the best way to predict disease-free survival after preoperative radiochemotherapy for rectal cancer patients: Tumor regression grading, nodal status, or circumferential resection margin invasion? J Clin Oncol 24:1319, 2006

69. Gosens MJEM, Van Krieken JH, Rutten H, et al: A critical appraisal of therapy induced tumor regression in rectal carcinoma. Ann Oncol 17:P62, 2006

70. Nagtegaal ID, Gosens MJ, Marijnen CA, et al: Combinations of tumor and treatment parameters are more discriminative for prognosis than the present TNM system in rectal cancer. J Clin Oncol 25:1647-1650, 2007

71. Gosens MJ, Van Krieken JH, Marijnen CA, et al: Improvement of staging by combining tumor and treatment parameters: The value for prognostication in rectal cancer. Clin Gastroenterol Hepatol 5:997-1003, 2007

72. Caricato M, Borzomati D, Ausania F, et al: Prognostic factors after surgery for locally recurrent rectal cancer: An overview. Eur J Surg Oncol 32: 126-132, 2006

73. Glynne-Jones R, Mawdsley S, Pearce T, et al: Alternative clinical end points in rectal cancer: Are we getting closer? Ann Oncol 17:1239-1248, 2006

74. Glynne-Jones R, Anyamene N: Just how useful an endpoint is complete pathological response after neoadjuvant chemoradiation in rectal cancer? Int J Radiat Oncol Biol Phys 66:319-320, 2006