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REVIEW

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Preoperative assessment of the circumferential margin in rectal cancer is more informative in treatment planning than the T stage

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Abstract Preventing local recurrence in rectal cancer means achieving a free circumferential resection margin (CRM) through an optimal combination of surgery, radiotherapy and chemotherapy. This requires a differentiation between primary resectable and locally advanced cancers. The T staging used, while being a powerful marker of prognosis, has two major downsides. First, accuracy of preoperative predictions of the T stage is unacceptably low. Second, a T3 tumor can be either primary resectable or locally advanced. A review of the literature was performed to establish the value of the CRM as the preferred preoperative staging classification, and to establish the feasibility of predicting the CRM using modern day, high-resolution imaging techniques. We advocate using the CRM as preoperative staging classification. Magnetic resonance imaging and multislice computed tomography offer an accurate pre-operative prediction of the CRM, and staging by means of predicted CRM offers the ideal combination of accuracy and clinical relevance.

Key words Rectal neoplasms • Neoplasm staging • Total mesorectal excision • Circumferential resection margin • Diagnostic imaging

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Introduction

Colorectal cancer is the second most common cause of cancer death after lung cancer in the Western world, and its incidence is increasing. In 2005, there will be an estimated number of 145 290 new cases of colorectal cancer and 54 290 deaths due to colorectal cancer in the United States [1].

Rectal cancer traditionally has a relatively poor prognosis. This prognosis is due to the risk for distant metastases on the one hand, and even more important, a high risk of local recurrence on the other hand. Although some recent articles reported good results [2, 3], in general a local recurrence causes severe disabling symptoms, is difficult to treat, and usually proves fatal for the patient [4, 5]. Curative treatment of rectal cancer involves surgery and has two major aims: maximal local control and the prevention of distant metastasis.

Free circumferential resection margin: the key element in local control

The single most important element in the realization of local control is a free circumferential resection margin (CRM) [6–8]. The elegant work of Quirke et al. [6] demonstrated that microscopically inadequate radial margins lead

Table 1 Publications relating circumferential resection margin (CRM) to treatment outcome

Reference	Patients, n		Surgery	Margin involvement	Positive margins, %	Median follow-up, months	LR, % (+vs.-)	*p*	DM, % (+vs.-)	*p*	Survival, % (+vs.-)	*p*
	Total	Curative operation										
Quirke et al. [6]	52	39	Conv	NG	27	23	80–0	<0.001	NG	NG	NG	NG
Cawthorn et al. [9]	187	122	TME	NG	7	NG	9–8	NG	NG	NG	NG	NG
Adam et al. [7]	190	141	Conv	≤1 mm	25	64	66–8	<0.001	NG	NG	24–74	<0.001
de Haas-Kock et al. [8]	325	253	Conv	<1mm	12	29	25–8	<0.001	30–6	0.20	85–84	0.38
Hall et al. [10]	218	152	TME	<1mm	13	41	15–11	0.38	35–17	0.01	NG	0.005
Nagtegaal et al. [11]	756	656	TME	≤1mm	18	35	16–6	0.0007	38–13	0.0001	70–90	0.0001
Wibe et al. [12]	686	NG	TME	≤1mm	9	29	22–5	<0.001	40–12	0.001	63–?	0.001
Birbeck et al. [13]	586	NG	NG	≤1mm	28	NG	38–10	<0.0001	NG	NG	40–79	<0.0001

NG, not given; *Conv*, conventional; *TME*, total mesorectal excision; *LR*, local recurrence; *DM*, distant metastases, *(+vs.-)*, positive margin versus negative margin

to a recurrence rate of 86%, thus identifying the main reason for local recurrence. Several studies have confirmed the importance of a free CRM (Table 1) [9–13].

Surgery aimed at achieving a free circumferential margin thus remains the key element in the treatment of rectal cancer [14]. However, adjuvant therapy in the form of radiotherapy or chemotherapy is a valuable contribution in achieving free margins. The optimal combination and sequence of these treatment modalities must be chosen. In order to do so, the clinician needs to distinguish between the primarily curatively resectable tumor and the locally advanced tumor.

Treatment of primarily curatively resectable tumors

Surgery

After the traditional blunt dissection, recurrence rates varying from 32% to 35% have been reported [15–18]. To counter this problem, a new standardized surgical technique called total mesorectal excision (TME) has been introduced. This technique involves a sharp dissection along the mesorectal fascia, thus removing the rectum and surrounding mesorectal fat, without "coning", to ensure excision of lateral tumor spread as well. Using TME, prognosis has substantially improved due to a drop in local recurrence rates, ranging from 4% to 9% [15, 19–21].

Radiotherapy

Radiotherapy has been used in primary resectable rectal cancer both pre- and postoperatively as adjuvant therapy. A systematic review by the Colorectal Cancer Collaborative Group found that the risk of local recurrence was reduced 44% by preoperative radiotherapy and 33% by postoperative radiotherapy. Survival after rectal cancer was improved by preoperative radiotherapy. This positive effect was, however, counterbalanced by deaths from other causes [22].

Both preoperative radiotherapy [22–28] and postoperative radio(chemo)therapy [29–31] have proven to be effective in a large number of trials and are therefore used in treating rectal cancer. In the Netherlands and Scandinavia, short-term preoperative radiotherapy preceding TME has now become the standard treatment for primary resectable rectal carcinoma. Standard procedure in the United States involves postoperative radiotherapy (sometimes combined with chemotherapy) if the margins are involved.

Treatment of locally advanced tumors

Locally advanced tumors are those tumors reaching to and beyond the mesorectal fascia (extensive T3 and T4 tumors) and node-positive tumors. These tumors may be extirpable but not curatively resectable using TME since achievement of a free CRM is unlikely, even with a well-performed TME. Wide en bloc resection of adjacent organs has been described, but failure rates remain high with 5-year survival rates of only 19%–33% with surgery alone [32]. Downstaging and downsizing of the tumor are therefore the key elements. Thus far, radiotherapy has been shown to make a significant contribution to achieving a free CRM [33]. A number of other strategies, such as high-dose preoperative external beam radiotherapy (EBRT) [34–38], intraoperative radiotherapy (IORT) [39–41] and chemoradiation [42–44], are employed to achieve adequate downstaging and downsizing and thus facilitate achieving a free CRM. Recent evidence indicates that the combination of both long-term preoperative radiotherapy and chemotherapy is the treatment strategy of choice [45–47].

Staging

Staging of rectal cancer is usually described using the TNM classification. This classification is based on the findings from the resected specimen and describes the depth of invasion of tumor in the bowel wall and adjacent fat. The basic principle of this classification is thus a staging "from the inside outward." While staging according to this classification is a valid marker of the prognosis, there are two major downsides to the preoperative use of this classification from a clinical point of view. First of all, it has proven difficult to determine the TNM stage of rectal cancer preoperatively. A number of studies concerning a variety of imaging techniques have been published in which an attempt at predicting the TNM stage was done. Due to limitations of endorectal ultrasound to assess local tumor extent and limitations of planar imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) to distinguish the different inner wall layers of the mesorectum (the muscular rectal wall), this has proven most difficult. Digital examination therefore remains a key element in determining the stage of the rectal cancer. Unfortunately based on data of the TME study, 25% of the patients can be considered as having advanced stage rectal cancer despite standard work-up to exclude advanced disease [25].

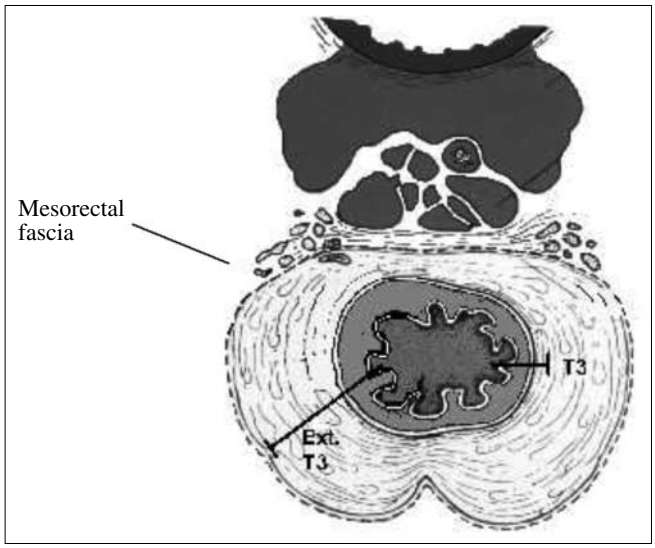

Fig. 1 T3 tumors can be primary resectable or locally advanced. In the TNM classification, the difference between primary resectable and locally advanced tumors is not clear: both can fall into the same category (*T3*)

In the second place, the clinically important question is the distinction between primary resectable tumors and locally advanced tumors. When "translated in TNM", the borderline between primary resectable and locally advanced falls within the T3 stage. Although a division into limited T3 and advanced T3 does add to the clinical relevance of the TNM staging, modern multidisciplinary treatment of rectal cancer would be greatly assisted by a adding a more accurate means of preoperative staging (Figs. 1, 2).

As stated before, the TME technique established the importance in defining the margin of the tumor in relation to the mesorectal fascia in order to obtain free circumferential margins. Since the CRM is an important prognostic factor in itself as well as the clinically most relevant parameter, we advocate the routine use of the predicted circumferential margin as well as the TNM stage as preoperative staging classification.

Imaging of the CRM

In the last couple of years, overwhelming evidence has been published that high-resolution MRI performed with dedicat-

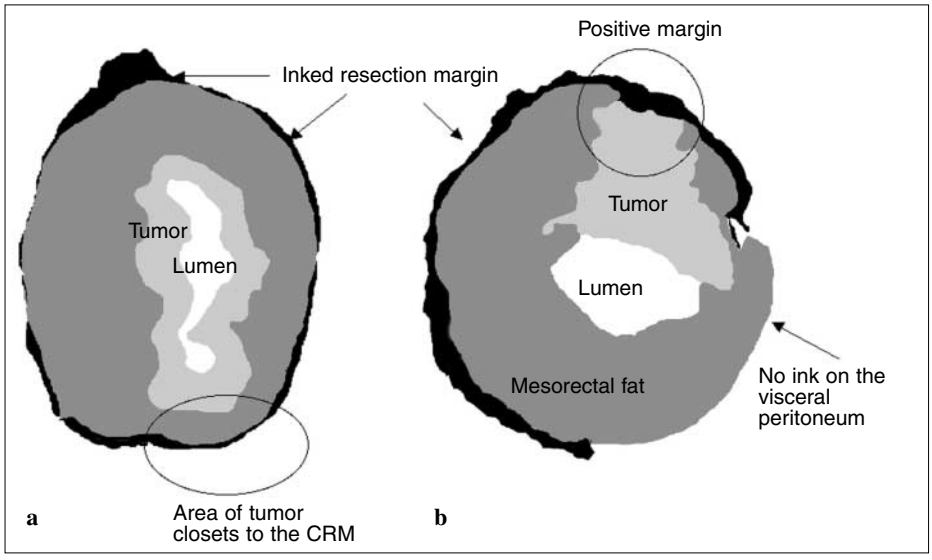

Fig. 2a, b *The circumferential margin.* Upon pathological examination of the rectal resection specimen, a well-performed TME resulted in the removal of the mesorectum in both cases. **a** Primary resectable tumor, free CRM. **b** Tumor growing into the inked resection margin (extended T3)

ed external coils (phased array coils) provides anatomical information of the mesorectum that is detailed and easy to communicate [48–50]. Initial studies have shown that high-resolution MRI can clearly visualize the mesorectal fascia. One of these studies tested the phased array technique in 76 patients and concluded that MRI is more accurate in predicting the CRM than the T stage [48]. These findings were supported by other MR studies in smaller numbers of patients [49–52]. Following these initial reports, larger European clinical trials have established MRI as an accurate imaging tool for the preoperative identification of the CRM and have proven that MRI has a beneficial effect on the outcome of treatment of rectal cancer [53–55].

Despite the potential of newer generation spiral CT, to date its role in determining the CRM has never been investigated. The first report on the identification of the mesorectal fascia by imaging dated from a CT study in 1983 [56], but since that time nothing has been published on the CT identification of the mesorectal fascia and CRM. Even the most recent publication known to us, by Mathur et al. [57] comparing high resolution MRI and CT, has focused on the CT determination of the T stage of rectal tumors. Few studies with conventional CT paid special attention to the assessment of tumor infiltration in neighboring organs [58]. A large study by Zerhouni et al. showed that conventional CT was more accurate than MRI in staging local tumor extent [59]. A comparative study between conventional CT and MRI focused on the assessment of tumor ingrowth in surrounding pelvic organs and found MRI to be superior to CT [60]. Horgan and Finlay described a study in which preoperative staging was related to clinical outcome after TME surgery [61]. Conventional CT showed promising accuracy figures for prediction of the clinical outcome, although two meta-analyses comparing conventional CT with MRI both showed results in clear favor of MRI [62, 63]. All mentioned CT studies, however, have been performed using an outdated conventional technique.

Theoretically, new-generation multislice spiral CT techniques with optimal bolus timing and reconstructions in multiple planes may perform better than conventional CT [64, 65]. It can be expected that high-resolution multislice spiral CT will compete with high-resolution MRI for the determination of the mesorectal fascia and CRM. The additional advantage of a multislice spiral CT is that, within the same breathhold, staging can be performed for distant metastases. Further research in this field is therefore called for.

Conclusions

Modern treatment of rectal cancer is based on minimizing the local recurrence rate. Since Quirke et al. [6] identified a positive resection margin as the main reason for local recurrences, the single most important goal in the curative treatment of rectal cancer is to achieve a free CRM. Surgery remains a key element in this respect, however adjuvant therapy consisting of radiotherapy or chemotherapy greatly adds to successful treatment. To determine the optimal sequence and combination of these modalities, a sharp and clear distinction between primary resectable tumors and locally advanced tumors is called for.

The TNM classification currently in use is based on samples describing depth of bowel infiltration. Although a valid marker of prognosis, this classification has two major downsides when used preoperatively. Even the most advanced imaging techniques are unable to preoperatively predict the T stage with adequate accuracy. Furthermore, the important distinction between primary resectable tumors and locally advanced tumors is not expressed clear enough in the currently TNM classification: a T3 tumor can be either primary resectable with a wide tumor-free CRM or locally advanced with a close or involved CRM. The addition of a more clinically guided classification is therefore called for. Since the relation of the tumor to the mesorectal fascia is the clinically most relevant issue, the CRM should be the main focus of pre-operative staging. Given their ability to visualize the mesorectum and mesorectal fascia, both spiral CT and MRI should be able to accurately predict the CRM. The CRM should therefore be the primary basis of preoperative staging.

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