Int J Colorectal Dis (2008) 23:1099–1107
DOI 10.1007/s00384-008-0531-z

ORIGINAL ARTICLE

Magnetic resonance imaging (MRI)-based indication for neoadjuvant treatment of rectal carcinoma and the surrogate endpoint CRM status

Joachim Strassburg · Theo Junginger · Trong Trinh · Olaf Püttcher · Katja Oberholzer · Richard J. Heald · Paul Hermanek

Accepted: 26 June 2008 / Published online: 17 July 2008
© Springer-Verlag 2008

Abstract
Aim Is it possible to reduce the frequency of neoadjuvant therapy for rectal carcinoma and nevertheless achieve a rate of more than 90% circumferential resection margin (CRM)-negative resection specimens by a novel concept of magnetic resonance imaging (MRI)-based therapy planning?
Materials and methods One hundred eighty-one patients from Berlin and Mainz, Germany, with primary rectal carcinoma, without distant metastasis, underwent radical surgery with curative intention. Surgical procedures applied were anterior resection with total mesorectal excision (TME) or partial mesorectal excision (PME; PME for tumours of the upper rectum) or abdominoperineal excision with TME.
Results With MRI selection of the highest-risk cases, neoadjuvant therapy was given to only 62 of 181 (34.3%). The rate of CRM-negative resection specimens on histology was 170 of 181 (93.9%) for all patients, and in Berlin, only 1 of 93 (1%) specimens was CRM-positive. Patients selected for primary surgery had CRM-negative specimens on histology in 114 of 119 (95.8%). Those selected for neoadjuvant therapy had a lower rate of clear margin: 56 of 62 (90%).
Conclusion By applying a MRI-based indication, the frequency of neoadjuvant treatment with its acute and late adverse effects can be reduced to 30–35% without reduction of pathologically CRM-negative resection specimens and, thus, without the danger of worsening the oncological long-term results. This concept should be confirmed in prospective multicentre observation studies with quality assurance of MRI, surgery and pathology.

Keywords Circumferential resection margin (CRM) · Indication for neoadjuvant therapy · Magnetic resonance imaging (MRI) · Rectal carcinoma · Surrogate endpoint

J. Strassburg
Department of General and Visceral Surgery,
Vivantes Klinikum im Friedrichshain,
Berlin, Germany

T. Junginger · T. Trinh
Department of General and Abdominal Surgery,
Johannes Gutenberg University,
Mainz, Germany

O. Püttcher
Department of Radiology, Vivantes Klinikum im Friedrichshain,
Berlin, Germany

K. Oberholzer
Department of Radiology, Johannes Gutenberg University,
Mainz, Germany

R. J. Heald
North Hampshire Hospital,
Basingstoke, UK

P. Hermanek
Department of Surgery, University of Erlangen,
Erlangen, Germany

P. Hermanek (✉)
Chirurgische Universitätsklinik,
Postfach 3560, 91023 Erlangen, Germany
e-mail: susanne.merkel@uk-erlangen.de

Introduction

At present, the indication for neoadjuvant treatment for rectal carcinoma usually is based on the clinical assessment of the local extent of the tumour, in particular by T and N classification (T3,4 and/or N+) [1–5]. Unfortunately, this policy inevitably is connected with undesirable overtherapy

[6–8]. An alternative is offered by pretherapeutic assessment of the relation of the carcinoma to the plane of surgical excision (mesorectal fascia) as today possible by the modern high-resolution thin-section magnetic resonance imaging (with phased-array surface coils) with high reliability [8–11]. The experience of two institutions with a magnetic resonance imaging (MRI)-based indication for neoadjuvant treatment and use of the circumferential resection margin (CRM) status as early surrogate endpoint will be reported.

Materials and methods

This study reports the pooled experience of the Department of General and Visceral Surgery, Vivantes Klinikum im Friedrichshain, Berlin, Germany, and the Department of General and Abdominal Surgery, Johannes-Gutenberg-University, Mainz, Germany, with rectal carcinoma patients, treated according to a uniform concept of MRI-based indication for neoadjuvant therapy and optimised total mesorectal excision (TME)/partial mesorectal excision (PME) surgery in Berlin between 11/2001 and 10/2005 and in Mainz between 12/2003 and 11/2007. Patients in Berlin have taken part in the MERCURY Study (Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study) evaluating the possibilities of modern magnetic resonance imaging for predicting involvement of CRM [11]. The data of Berlin have in part already been reported by Strassburg et al. [12].

Inclusion criteria were:

1) Carcinoma of the rectum (aboral margin of the tumour within 16 cm from the anal verge when measured from below with a rigid sigmoidoscope), at least invading into the submucosa
2) No emergency presentation (no need for urgent surgery within 48 h of admission)
3) No distant metastasis
4) Pretherapeutic high-resolution thin-section MRI employing pelvic phased-array coils performed
5) Indication for neoadjuvant therapy: (a) fixed or tethered tumour (cT4); (b) mobile tumour in case of CRM positivity on MRI (for definition, see below); (c) mobile low rectal carcinoma (<6 cm from anal verge) with invasion beyond the muscularis propria as assessed by ultrasonography and/or MRI (cT3)
6) Radical surgery by anterior resection with total mesorectal excision for tumours of the middle and lower rectum or partial mesorectal excision for tumours of the upper rectum or abdominoperineal excision (APE) with TME
7) Curative intention of surgery, i.e. complete tumour resection with no remaining residual tumour according to the surgeon's assessment
8) Histopathological examination with special attention paid to the relation between tumour and circumferential resection margin [13, 14]

In some patients, the indication for neoadjuvant therapy was given; however, it was not applied, e.g. in case of refusal by patient or because of extensive perirectal abscess formation. Such patients have been excluded (three patients in Berlin, seven in Mainz).

For the classification of tumour site, the rectum was subdivided into three parts according to the distance of the lower margin of the tumour from the anal verge (assessed by rigid sigmoidoscopy) [15, 16]: upper rectum, 12 to 16 cm; middle rectum, 6 to <12 cm; lower rectum, <6 cm.

The MRI technique of the MERCURY Study was used [17]. CRM-positive was defined as minimal distance between tumour and mesorectal fascia of 1 mm or less.

The surgical treatment for carcinomas of the upper rectum was high anterior resection with PME. Carcinomas of the middle and lower rectum were treated by anterior resection or APE, both with TME.

As neoadjuvant therapy, concomitant radiochemotherapy (50.4 Gy in 28 fractions through 5 weeks, 5-fluoracil either in weeks 1 and 4 or as continuous infusions on days 1–38) was applied. Surgery followed 4–6 weeks after the end of radiotherapy.

The histological classification and grading followed the rules of WHO [18]. For the assessment of anatomical extent of tumour and stage, the sixth edition of tumour–node–metastases (TNM) [16, 19] was applied.

The histological examination of the circumferential resection margin distinguishes between two categories [13, 20, 21]:

- pathological CRM (pCRM)-positive, direct carcinomatous involvement of the CRM or minimal distance between tumour and CRM of 1 mm or less
- pathological CRM-negative, minimal distance between tumour and CRM more than 1 mm

For the evaluation of the CRM status, continuous extensions of the primary tumour, discontinuous extensions (tumour deposits, satellites), lymphatic and venous invasion (tumour cells in the lumen with adherence to the vessel wall and/or vessel wall invasion), perineural invasion and lymph node metastasis were taken into account.

Tumour perforation (spontaneous, iatrogeneous) and incision into/through tumour tissue were registered by the pathologist. The assessment of the quality of mesorectal excision by the pathologist was carried out in a part of specimens only.

Differences in frequencies between categorial variables were tested for statistical significance with the chi-square test or Fisher's exact test when appropriate. For differences of

quantitative variables, the *U* test (Mann–Whitney) was used. The level for statistical significance was set at $p<0.05$. Differences with $p=0.05$–0.10 were marked as "trend".

Results

One hundred eighty-one consecutive patients met the inclusion criteria, 93 (51.4%) from Berlin and 88 (48.6%) from Mainz. Table 1 shows the patient, tumour and treatment characteristics. Significant differences between the two institutions are seen relating to pretherapeutic grading of the primary tumour, pathological stage following neoadjuvant therapy and frequency of partial mesorectal excision. Neoadjuvant treatment was given in both institutions in the same frequency (34%).

For all patients, the rate of pCRM-negative resection specimens was 170 of 181 (93.9%). This rate was significantly different between Berlin (92/93=99%) and Mainz (78/88=89%; $p=0.004$).

The rate of pathologically CRM-negative resection specimens for patients following neoadjuvant therapy and

Table 1 Patient, tumour and treatment characteristics

	Berlin ($n=93$)	Mainz ($n=88$)	Total ($n=181$)	Statistically significant differences (p)
Age (years)				
Median (range)	65 (44–87)	69 (37–85)	67 (37–87)	n.s.
Sex				
Males/females	63/30 (2.10)	55/33 (1.67)	118/63 (1.87)	n.s.
Tumour site				
Lower rectum (<6 cm)	26 (28%)	27 (31%)	53 (29.3%)	n.s.
Middle rectum (6 to <12 cm)	44 (47%)	39 (44%)	83 (45.9%)	
Upper rectum (12 to 16 cm)	23 (25%)	22 (25%)	45 (24.9%)	
Pretherapeutic grading of primary tumour				
G1	0 (0%)	3 (3%)	3 (1.7%)	0.001
G2	85 (91%)	63 (72%)	148 (81.8%)	
G3	8 (9%)	21 (24%)	29 (16.0%)	
GX	0 (0%)	1 (1%)	1 (0.6%)	
Tumour mobility				
Mobile (cT1–3)	83 (89%)	76 (86%)	159 (87.8%)	n.s.
Tethered/fixed (cT4)	10 (11%)	11 (13%)	21 (11.6%)	
NG	0 (0%)	1 (1%)	1 (0.6%)	
Pretherapeutic clinical stage				
I	18 (19%)	21 (24%)	39 (21.5%)	n.s.
II, III	75 (81%)	67 (76%)	142 (78.5%)	
Pathological stage/primary surgery	($n=61$)	($n=58$)	($n=119$)	n.s.
Is[a]	1 (2%)	–	1 (0.8%)	
I	22 (36%)	21 (36%)	43 (36.1%)	
II	20 (33%)	23 (40%)	43 (36.1%)	
III	18 (30%)	14 (24%)	32 (26.9%)	
Pathological stage/following neoadjuvant therapy	($n=32$)	($n=30$)	($n=62$)	0.013
y0	0 (0%)	0 (0%)	2 (3%)	
yis	2 (6%)	1 (3%)	1(2%)	
yI	5 (16%)	12 (40%)	17 (27%)	
yII	10 (31%)	12 (40%)	22 (35%)	
yIII	15 (47%)	5 (17%)	20 (32%)	
Neoadjuvant radiochemotherapy applied	32 (34%)	30 (34%)	62 (34.3%)	n.s.
Surgical procedure/Mesorectal excision				
TME	89 (96%)	75 (85%)	164 (90.6%)	0.021
PME	4 (4%)	13 (15%)	17 (9.4%)	
Surgical procedure/Sphinkter preservation				
AR	75 (81%)	66 (75%)	141 (77.9%)	n.s.
APE	18 (19%)	19 (22%)	37 (20.4%)	
Hartmann	–	3 (3%)	3 (1.7%)	

AR Anterior resection, *TME* total mesorectal excision, *PME* partial mesorectal excision, *APE* abdominoperineal excision
[a] One patient clinically uT2, primary surgery, pathologically pTis

for those with primary surgery were 56 of 62 (90%) and 114 of 119 (95.8%), respectively. This difference is statistically not significant (p=0.190).

Table 2 shows the results of univariate analysis of factors influencing the frequency of pCRM-positive resection specimens. For patients treated by primary surgery, significant factors were sex, surgical procedure and institution; for pT, a trend to a significant difference was seen. For patients treated by neoadjuvant radiochemotherapy, tumour mobility, pathological stage and surgical procedure influenced the frequency of pCRM-positive resection specimens significantly; pretherapeutic clinical stage, ypT and institution showed a trend to significant differences. Because of the small number of terminal events (five and six pCRM-positive resection specimens, respectively) a multivariate analysis could not be carried out.

Discussion

The present treatment of rectal carcinoma is influenced predominantly by the advances in surgical methods

Table 2 Frequency of pathologically circumferential resection margin-positive resection specimens

Influencing factor	Patients with primary surgery (n=119)		Patients with neoadjuvant RCT followed by surgery (n=62)	
	pCRM-positive	p[a]	pCRM-positive	p[a]
Sex				
Male	1/78 (1%)	0.047	4/40 (10%)	n.s.
Female	4/41 (10%)		2/22 (9%)	
Tumour site				
Low	0/18 (0%)	n.s.	4/38 (11%)	n.s.
Middle	4/65 (6%)		2/22 (9%)	
Upper	1/36 (3%)		0/2 (0%)	
Tumour mobility				
Mobile (cT1-3)	5/116 (4%)	n.s.	1/45 (2%)	0.006
Tethered/fixed (cT4)	0/3 (0%)		5/17 (29%)	
Pretherapeutic grading of primary tumour				
G1	0/3 (0%)	n.s.	–	n.s.
G2	3/96 (3%)		4/26 (15%)	
G3	2/20 (10%)		2/35 (6%)	
GX	–		0/1 (0%)	
Pretherapeutic clinical stage				
I	1/38 (3%)	n.s.	1/1 (100%)	(0.097)
II, III	4/81 (5%)		5/61 (8%)	
pT classification				
is[b]	0/1 (0%)	(0.069)	–	–
1	0/11 (0%)		–	
2	0/44 (0%)		–	
3	4/60 (7%)		–	
4	1/3 (33%)		–	
ypT classification				
0	–	–	0/6 (0%)	(0.052)
is	–	–	0/1 (0%)	
1	–		0/3 (0%)	
2	–		0/12 (0%)	
3	–		3/37 (8%)	
4	–		3/3 (100%)	
pN classification				
0	3/87 (3%)	n.s.	–	–
1,2	2/32 (6%)		–	
ypN classification				
0	–	–	6/42 (14%)	n.s.
1, 2	–		0/20 (0%)	
Pathological stage				
is[b]	0/1 (0%)	n.s.	–	–
I	0/43 (0%)		–	
II	3/43 (7%)		–	

Table 2 (continued)

Influencing factor	Patients with primary surgery (n=119)		Patients with neoadjuvant RCT followed by surgery (n=62)	
	pCRM-positive	p[a]	pCRM-positive	p[a]
III	2/32 (6%)		–	
y0	–	–	0/2 (0%)	0.047
yis	–		0/1 (0%)	
yI	–		0/17 (0%)	
yII	–		6/22 (27%)	
yIII	–		0/20 (0%)	
Mesorectal excision				
TME	3/102 (2.9%)	n.s.	6/62 (10%)	–
PME	2/17 (12%)		–	
Surgical procedure				
AR	3/104 (2.9%)	0.041	2/37 (5%)	0.038
APE	1/13 (8%)		3/24 (13%)	
Hartmann	1/2 (50%)		1/1 (100%)	
Intraoperative tumour cell dissemination				
Yes	0/6 (0%)	n.s.	1/9 (11%)	n.s.
No	5/113 (4.4%)		5/53 (9%)	
Institution				
Berlin	0/61 (0%)	0.025	1/32 (3%)	(0.099)
Mainz	5/58 (9%)		5/30 (17%)	

Dependence on selected tumour-related factors, surgical procedure and institution. Univariate analysis.
n.s. Differences not significant (p>0.100), *RCT* radiochemotherapy, *TME* total mesorectal excision, *PME* partial mesorectal excision, *AR* anterior resection, *APE* abdominoperineal excision
[a] p values in parentheses indicate a trend to significant differences (p=0.050–0.100).
[b] One patient clinically uT2, primary surgery, pathologically pTis

(optimised TME surgery) but also by the introduction of multimodal procedures, in particular by neoadjuvant radio-/radiochemotherapy and adjuvant chemotherapy for patients with regional lymph node metastasis.

The indication for the neoadjuvant treatment conventionally is based on the clinical classification of tumour extent according to T and N categories of the Union Internationale Contre le Cancer TNM system as assessed by digital rectal examination, rigid rectosigmoidoscopy, endorectal ultrasonography and sometimes pelvic computed tomography. In this way, neoadjuvant treatment is frequently recommended in case of T3,4 and/or N+ tumours, i.e. for about 70–75% of patients [1–5]. By applying such a policy, certainly a quite considerable part of patients is overtreated, especially if optimised TME surgery is performed. This is valid for the about 15–30% of patients with overstaging by imaging procedures (see review by Junginger et al. [8]). But neoadjuvant treatment has to be considered as overtreatment at least for T1,2 N+ patients [22, 23] and patients with pT3 carcinomas invading perirectal tissue in only limited extension (not more than 5 mm [24]).

As neoadjuvant radiotherapy has acute toxicity, subacute and late adverse effects [25–29] and increased occurrence of secondary malignancies [30] is observed, any unnecessary neoadjuvant therapy should be avoided. Thus, the demand for a more selective indication for neoadjuvant treatment increases [7, 8, 31–34].

One possibility to accomplish this goal has been opened by the modern high-resolution thin-section MRI with phased-array surface coils and imaging the tumour in its true transverse plane [11, 17, 35–38]. This technique allows the assessment of the relation between tumour and mesorectal fascia with high reliability (see overviews by Lahaye et al. [9] and Hermanek et al. [10]). In this way, the possibility of complete tumour resection can be predicted. In cases of potentially involved CRM and, thus, questionable complete resection, in particular if the distance between tumour and mesorectal fascia is 1 mm or less in MRI, neoadjuvant treatment with the target of tumour shrinkage and regression (downsizing, downstaging) seems indicated [8, 31, 39–42].

Up to now, there are no studies comparing T/N-based and MRI-based indication for neoadjuvant treatment. A possibility of evaluation of these two policies is the assessment of pCRM status on the resection specimens. In this respect, today [21] it should be differentiated between:

– pCRM-negative—minimal distance between tumour and CRM more than 1 mm,
– pCRM-positive—tumour minimal 1 mm or less from the CRM or directly involving the CRM.

Table 3 Prognostic relevance of the pathological CRM status

Parameter	Author(s), year, place	Recruitment period	Treatment TME surgery[a]	multimodal	Follow-up (months)	pCRM-negative	pCRM-positive	p/HR
Local recurrence						Locoregional recurrence rates		
Crude recurrence rate	Ng et al. 1993 [49], Hongkong	04/1989–01/1991	N.G.	N.G.	Median 26.6	10/59 (17%)	3/5 (60%)	(p=0.053)
	Wibe et al. 2002 [50][b], population-based registry of the Norwegian Rectal Cancer Project	11/1993–08/1997	Always	No RT, 3% adjuvant CT	Median 29, range 14–60	32/621 (5.2%)	14/65 (22%)	p<0.001
	Mawsdley et al. 2005 [51], pooled data, Mount Vernon Cancer Center, UK (9.3% T3,4 and/or N+)	1995–2002	Always	Always neoadjuvant RCT	Median 25	10/98 (10%)	15/24 (63%)	p<0.001
Actuarial 5-year local recurrence rate	Birbeck et al. 2002 [44], Leeds, UK[c]	1986–1997	Partly	4.3% neoadjuvant RT, 11.9% adjuvant CT	Minimum 12, maximum 144	15% (95% CI 10–20%)[d]	56% (95% CI 42–69%)[d]	p<0.001
	Wibe et al. 2003 [52], population-based registry of the Norwegian Rectal Cancer Project	11/1993–12/1999	78% (1994) increasing to 96% (1998)	9% RT (neoadjuvant or adjuvant), 2% adjuvant CT	Mean 39, range 1–86	~10%[e,f] (n=2912)	~33%[e] (n=286)	HR 3.1 (95% CI 2.2–4.2)
	Baik et al. 2007 [53], Seoul, Korea (path. stage II, III only)	1997–2001	Always	Always adjuvant RCT	For CRM-negative median 45, range 1.1–88.7, for CRM-positive median 35.8, range 4.8–83.4	11.3% (n=460)	35.2% (n=44)	p=0.010
	Peeters et al. 2007 [54], Dutch TME trial[b]	1996–1999	Always	No	Median 73.2, range 14.4–114	8.7% (n=717)	23.5% (n=144)	HR 4.03 (95% CI 2.82–5.76)
Distant metastasis						Rate of distant metastasis		
Crude rate	Wibe et al. 2002 [50][b]	See above				74/621 (11.9%)	26/65 (40%)	p<0.001
	Mawsdley et al. 2005 [51]	See above				28/98 (29%)	18/24 (75%)	p<0.001
Actuarial 5-year rate	Baik et al. 2007 [53]	See above				25.3% (n=460)	60.8% (n=44)	p<0.001
Survival						Survival rates		
Actuarial 3-year overall survival rate	Mawsdley et al. 2005 [51]	See above				64% (n=98)	25% (n=24)	p<0.001
Median overall survival time	Mawsdley et al. 2005 [51]	See above				59 months (n=98)	23 months (n=24)	p<0.001
Actuarial 3-year disease-free survival rate	Mawsdley et al. 2005 [51]	See above				52% (n=98)	9% (n=24)	p<0.001
Median disease-free survival time	Mawsdley et al. 2005 [51]	See above				38 months (n=98)	16 months (n=24)	p<0.001
Crude overall survival rate	Wibe et al. 2002 [50][b]	See above				540/621 (87.0%)	41/65 (53%)	p<0.001

Actuarial 5-year cancer-related survival rate	Birbeck et al. 2002 [44][b,c]	See above	79% (95% CI 74–84%)[c]	40% (95% CI 29–51%)[c]	$p<0.001$
	Baik et al. 2007 [53]	See above	72.5% ($n=460$)	26.9% ($n=44$)	$p<0.001$
Actuarial 5-year overall survival rate	Wibe et al. 2003 [52]	See above	70%[e,g] ($n=2827$)	35%[e] ($n=274$)	N.G.

Patients with radical surgery in curative intention (according to the surgeon's opinion, no remaining residual tumour) and using the ≤1 mm definition of pCRM-positive. Only publications with at least 3-year recurrence/survival rates and with $n>50$. Abstracts of oral presentations not included. Publication of Eriksen et al. [47] and Das et al. [48] excluded because only hazard ratios but no detailed figures are given.

[a] For all carcinomas of the middle and lower rectum TME, for carcinomas of the upper rectum PME or TME

[b] Only patients with TME

[c] Earlier publications from Leeds, UK [46, 55, 56] not considered because their data included in the publication by Birbeck et al. [44].

[d] Total number of patients operated in curative intention, 488; number of CRM+ and CRM− not stated.

[e] Estimation based on visual inspection of recurrence-free survival curves.

[f] Without 234 pCRM-negative patients with intraoperative tumour perforation

[g] Without 223 pCRM-negative patients with intraoperative tumour perforation

pCRM-negative Histological distance tumour/CRM minimal >1 mm, *pCRM-positive* histological distance tumour/CRM minimal ≤1 mm (including direct tumour involvement of the CRM), *N.G.* not given, *CI* confidence interval, *HR* hazard ratio, *RT* radiotherapy, *CT* chemotherapy, *RCT* radiochemotherapy

Nagtegaal et al. [43] proposed a 2-mm cutoff between pCRM-positive and pCRM-negative specimens. However, this proposal was based on data obtained after a median follow-up of 35 months and 2-year local recurrence rates only. It could not be confirmed for patients from Leeds, with a substantially longer follow-up and 5-year local recurrence rates [44]. According to a review of the literature by Glynne-Jones et al. [21], the large majority of studies dealing with the CRM status used the ≤1 mm definition of the CRM positivity (91.1%; 7,373 of 8,094 patients). This definition is accepted in a new publication from the Netherlands, too (with Nagtegaal as co-author) [45].

Quirke et al. [46] demonstrated for the first time the correlation between the pCRM status and the crude local recurrence rate after a median follow-up of 23 months and conventional surgery: pCRM-negative, 1 of 38 (3%) vs. pCRM-positive, 11 of 13 (85%; $p<0.001$). In the meantime, there are data of more than 5,000 patients published showing the correlation between pCRM status and prognosis (local recurrence, distant metastasis and survival; Table 3). In multivariate analyses, the pCRM status was the strongest predictive factor for local recurrence [44, 50].

The pCRM status has to be regarded as the most important prognosticator of recurrence and survival. Thus, it is increasingly recommended as early alternative endpoint (intermediate endpoint, surrogate endpoint) [44, 51, 57–59].

From a clinical point of view, the negative predictive value of the pCRM status relating to local recurrence is especially important. It describes the probability that, in case of pCRM-negative resection specimens in the further course, local recurrences will not be observed. According to the data of Table 3, the pooled negative predictive value for crude recurrence is 726/778=93.3%, and the estimated negative predictive value for actuarial 5-year local recurrence is 92.5% ($n=4089$). This emphasizes that a tumour resection with a negative pCRM has to be the goal of rectal carcinoma treatment.

In the reported pooled patients from Berlin and Mainz, the indication for neoadjuvant treatment has been based on the relation between carcinoma and mesorectal fascia as assessed by MRI. Following this, the frequency of neoadjuvant radiochemot-therapy could be reduced from 79% to 34%. This policy, together with optimised TME surgery, resulted in 93.5% of patients in pCRM-negative resection specimens. With this result a 5-year local recurrence rate of less than 10% and a 5-year overall survival rate of at least 80% can be expected (Table 3).

Our analysis of the pooled data from Berlin and Mainz has a limitation because a multivariate analysis could not be carried out because of the small number of terminal events (five and six pCRM-positive resection specimens, respectively). Thus, the conclusion of our analysis, namely the concept of a selective MRI-based indication of neoadjuvant

radiochemotherapy, has to be assessed as hypothesis only that should be confirmed in prospective multi-centre observation studies with quality assurance of surgery, pathology and MRI. Such a study has started recently (contact Prof. Dr. T. Junginger, e-mail junginger@uni-mainz.de).

References

1. SIGN (Scottish Intercollegiate Guidelines Network) (2003) Management of colorectal cancer. A national guideline. SIGN, Royal College of Physicians, Edinburgh
2. NHMRC (National Health and Medical Research Council, Australian Government) (2005) Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Australian Cancer Network. http://www.nhmrc.gov.au
3. Arnoletti JP, Bland KI (2006) Neoadjuvant and adjuvant therapy for rectal cancer. Surg Oncol Clin N Am 15:147–157
4. NCCN (National Comprehensive Cancer Network) (2006) Clinical practice guidelines in oncology/rectal cancer. Version 2.2006. National Comprehensive Cancer Network
5. Schmiegel W, Pox C, Adler G et al (2004) S3-Leitlinienkonferenz "Kolorektales Karzinom". Z Gastroenterol 42:1129–1177
6. Carne PWG, Nelson H (2004) Are we overtreating rectal cancer: time for another trial? Ann Surg Oncol 11:124–126
7. Pahlman L (2005) Indications for long-term radiotherapy. Recent Results Cancer Res 165:212–220
8. Junginger Th, Hermanek P, Oberholzer K, Schmidberger H (2006) Rektumkarzinom: Behandeln wir zu häufig neoadjuvant? Vorschläge zu einer selektiveren, MRT-basierten Indikation. Zentralbl Chir 131:275–284
9. Lahaye MJ, Engelen SME, Nelemans PJ et al (2005) Imaging for predicting the risk factors—the circumferential resection margin and nodal disease—of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MRI 26:259–268
10. Hermanek P, Junginger Th, Merkel S, Oberholzer K (2006) High-resolution magnetic resonance imaging (MRI) in patients with rectal carcinoma: effectiveness in selection for neoadjuvant treatment. Recent Res Devel Cancer 8:39–56
11. MERCURY Study Group (2006) Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. Br Med J 333:779–784
12. Strassburg J, Lewin A, Ludwig K et al (2007) Optimised surgery (so-called TME surgery) and high-resolution MRI in the planning of treatment of rectal carcinoma. Langenbeck's Arch Surg 392:179–188
13. Quirke P, Dixon MF (1988) The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. Int J Colorect Dis 3:127–131
14. Quirke P (1997) Limitations of existing systems of staging for rectal cancer: the forgotten margin. In: Soreide O, Norstein J (eds) Rectal cancer surgery. Optimisation–standardisation–documentation. Springer, Berlin, pp 63–81
15. Soreide O, Norstein J, Fielding LP, Silen W (1997) International standardisation and documentation of the treatment of rectal cancer. In: Soreide O, Norstein J (eds) Rectal cancer surgery. Optimisation–standardisation–documentation. Springer, Berlin, pp 405–445
16. UICC (2003) TNM Supplement. A commentary on uniform use. 3rd ed. Wittekind C, Greene FL, Henson DE, Hutter RVP, Sobin LH (eds) John Wiley & Sons, New York
17. MERCURY Study Group (2007) Extramural depth of tumour invasion at thin section MRI in patients with rectal cancer: results of the MERCURY study. Radiology 243:132–139
18. Hamilton SR, Aaltonen LA (eds) (2000) Pathology and genetics of tumours of the digestive system. WHO classification of tumours. IARC Press, Lyon
19. UICC (2002) TNM classification of malignant tumours, 6th ed. Sobin LH, Wittekind Ch (eds) John Wiley, New York
20. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP (2000) American joint committee on cancer prognostic factors consensus conference: colorectal working group. Cancer 88:1739–1757
21. Glynne-Jones R, Mawdsley S, Novell JR (2006) The clinical significance of circumferential resection margin following preoperative pelvic chemoradiotherapy in rectal cancer: why we need a common language. Colorectal Disease 8:800–807
22. Gunderson LL, Sargent DJ, Tepper JE et al (2002) Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. Int J Radiat Oncol Biol Phys 54:386–396
23. Libuti SK, Tepper JE, Saltz LB, Rustgi AK (2005) Cancer of the rectum. In: De Vita jr VT, Hellman S, Rosenberg SR (eds) Cancer. Principles & practice of oncology. 7th edn. Lippincott Williams & Wilkins, Philadelphia, pp 1110–1125
24. Merkel S, Mansmann U, Siassi M et al (2001) The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorect Dis 16:298–304
25. Glimelius B, Pahlman L (1999) Perioperative radiotherapy in rectal cancer. Acta Oncol 38:23–32
26. Birgisson H, Pahlman L, Gunnarson U, Glimelius B (2005) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish rectal cancer trial. J Clin Oncol 23:8697–8705
27. Chessin DB, Enker W, Cohen AM et al (2005) Complications after preoperative combined modality therapy and radical resection of locally advanced rectal cancer: a 14-year experience from a specialty service. J Am Coll Surg 200:876–884
28. Peeters KCMJ, van de Velde CJH, Leer JWH et al (2005) Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients—a Dutch Colorectal Cancer Group Study. J Clin Oncol 23:6199–6206
29. Petersen S, Jongen J, Petersen C, Sailer M (2007) Radiation-induced sequelae affecting the continence organ: incidence, pathogenesis and treatment. Dis Colon Rectum 50:1466–1474
30. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B (2005) Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. J Clin Oncol 23:6126–6131
31. Daniels IR, Moran BJ, Heald RJ (2004) Surgery alone: is total mesorectal excision sufficient for rectal cancer? In: Wiegel T, Höcht S, Sternemann M et al (eds) Controversies in gastrointestinal tumour therapy. Karger, Basel, pp 28–36
32. Heald RJ, Daniels IR (2005) Rectal cancer management: Europe is ahead. Recent Results Cancer Research 165:75–81
33. Burton S, Brown G, Daniels IR et al, on behalf of the Royal Marsden Hospital, Colorectal Cancer Network (2006) MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Brit J Cancer 94:351–357
34. MacKay G, Downey M, Molloy RG, O'Dwyer RJ (2006) Is preoperative radiotherapy necessary in T1–T3 rectal cancer with TME? Colorectal Disease 8:34–36
35. Brown G, Richards CJ, Newcombe RG et al (1999) Rectal carcinoma: thin-section MR imaging for staging in 28 patients. Radiology 211:215–222
36. Brown G, Radcliffe AG, Newcombe RG et al (2003) Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg 90:355–354

37. Beets-Tan RGH, Beets GL (2004) Rectal cancer: review with emphasis on MR imaging. Radiology 232:335–346
38. Brown G, Daniels IR (2005) Preoperative staging of rectal cancer: the MERCURY research project. Recent Results Cancer Research 105:58–74
39. Glimelius B, Grönberg H, Järhult J et al (2003) A systematic review of radiation therapy effects in rectal cancer. Acta Oncol 42:476–491
40. Glynne-Jones R, Grainger J, Harrison M et al (2006) Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: should we be more cautious? Brit J Cancer 94:363–371
41. Sebag-Montefiore D (2006) Developments in the use of chemotherapy in rectal cancer. Colorectal Disease 8(Suppl. 3):14–17
42. Wolberink SVRC, Beets-Tan RGH, Nagtegaal ID, Wiggers T (2006) Preoperative assessment of the circumferential margin in rectal cancer is more informative in treatment planning than the T stage. Tech Coloproctol 10:171–176
43. Nagtegaal ID, Marijnen CAM, Kranenberg EK et al (2002) Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma. Am J Surg Pathol 26:350–357
44. Birbeck KF, Macklin CP, Tiffin NJ et al (2002) Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 235:449–457
45. Gosens MJEM, van Krieken JMJM, Marijnen CAM et al (2007) Improvement of staging by combining tumor and treatment parameters: the value of prognostication in rectal cancer. Clin Gastroenterol Hepatol 50:997–1003
46. Quirke P, Dudley P, Dixon MF, Williams NS (1986) Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet ii:996–999
47. Eriksen MT, Wibe A, Haffner J, Wiig JN, on behalf of the Norwegian Rectal Cancer Group (2007) Prognostic groups in 1.676 patients with T3 rectal cancer treated without preoperative radiotherapy. Dis Colon Rect 50:156–167
48. Das P, Skibber JM, Rodriguez-Bigas MA et al (2006) Clinical and pathological predictors of loco-regional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J Clin Oncol 29:219–224
49. Ng IOL, Luk ISC, Yuen ST et al (1993) Surgical lateral clearance in resected rectal carcinoma. Cancer 71:1972–1976
50. Wibe A, Rendedal PR, Svensson E et al, on behalf of the Norwegian Rectal Cancer Group (2002) Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 89:327–334
51. Mawdsley S, Glynne-Jones R, Grainger J et al (2005) 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
52. Wibe A, Eriksen MT, Syse A et al (2003) Total mesorectum excision for rectal cancer—what can be achieved by a national audit. Colorectal Dis 5:471–477
53. Baik SH, Kim NK, Lee YC et al (2007) Prognostic significance of circumferential resection margin following total mesorectal excision and adjuvant chemoradiotherapy in patients with rectal cancer. Ann Surg Oncol 14:462–469
54. Peeters KCMC, Marijnen CAM, Nagtegaal IDI et al (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 246:693–701
55. Adam IJ, Mohamdee MO, Martin IG et al (1994) Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 344:707–711
56. Hall NR, Finan PJ, Al-Jaberi T et al (1998) Circumferential margin involvement after mesorectal excision of rectal cancer: predictor of survival but not local recurrence? Dis Colon Rect 41:979–983
57. Maughan NJ, Quirke P (2003) Modern management of colorectal cancer—a pathologist's view. Scand J Surg 92:11–19
58. Glynne-Jones R, Mawdsley S, Pearce T, Buyse M (2006) Alternative clinical end points in rectal cancer — are we getting closer? Ann Oncol 17:1239–1248
59. Bittner R, Burghardt J, Gross E et al (2007) (Arbeitsgruppe Workflow Rektumkarzinom II) Qualitätsindikatoren bei Diagnostik und Therapie des Rektumkarzinoms. Zbl Chir 132:85–94