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ORIGINAL ARTICLE – COLORECTAL CANCER

MRI-Based Use of Neoadjuvant Chemoradiotherapy in Rectal Carcinoma: Surgical Quality and Histopathological Outcome of the OCUM Trial

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ABSTRACT

Background. Preoperative magnetic resonance imaging (MRI) allows highly reliable imaging of the mesorectal fascia (mrMRF) and its relationship to the tumor. The prospective multicenter observational study OCUM uses these findings to indicate neoadjuvant chemoradiotherapy (nCRT) in rectal carcinoma.

Methods. nCRT was indicated in patients with positive mrMRF ($\leq$ 1 mm) in cT4 and cT3 carcinomas of the lower rectal third.

Results. A total of 527 patients (60.2%) underwent primary total mesorectal excision, and 348 patients (39.8%) underwent long-term nCRT followed by surgery. The mrMRF was involved in 4.6% of the primary surgery group and 80.7% of the nCRT group. Rates of resections within the mesorectal plane (90.8%), sparing of pelvic nerves on both sides (97.8%), and number of regional lymph nodes (95.3% with $\geq$ 12 lymph nodes examined) are indicative of high-quality surgery. Resection was classified as R0 in 98.3%, the pathological circumferential resection margin (pCRM) was negative in 95.1%. Patients in the nCRT group had more advanced carcinomas with a significantly higher rate of abdominoperineal excision. Independent risk factors for pCRM positivity were advanced stage (T4), metastatic lymph nodes, resection in the muscularis propria plane, and location in the lower third.

Conclusions. The risk classification of rectal cancer patients by MRI seems to be highly reliable and allows the restriction of nCRT to approximately half of the patients with clinical stage II and III rectal carcinoma, provided there is a high-quality MRI diagnostic protocol, high-

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quality surgery, and standardized examination of the resected specimen.

Total mesorectal excision (TME) reduces the local recurrence (LR) rate by approximately half compared with conventional surgery for rectal cancer.[1] With presurgical radiotherapy (nRT) or chemoradiotherapy (nCRT), the risk of LR can be reduced further,[2,3] but at the cost of an increased risk of adverse events[4–6] and loss of fertility, in addition to prolonged treatment time and increased costs. Therefore, restriction to patients who will most likely benefit has been proposed.[2,3] Until now, most guidelines have recommended presurgical treatment for stage cII and cIII rectal cancer of the middle and lower third;[7] however, the low accuracy of imaging techniques, especially in determining cN staging,[8] is unsatisfactory and carries the risk of overtreatment.[9]

The involved circumferential resection margin (pathological circumferential resection margin [pCRM]) was identified as one of the key factors in rectal cancer treatment, predicting LR, distant metastases, and survival.[10] Preoperative magnetic resonance imaging (MRI) allows imaging of the mesorectal fascia (mrMRF), the potential resection plane, and its relationship to the tumor, with high reliability.[11,12] Thus, pretherapeutic MRI should be able to distinguish between low-risk patients with uninvolved mrMRF who do not need nCRT (provided that the quality of mesorectal excision is high) and high-risk patients with threatened or involved mrMRF who need nCRT to shrink the tumor for complete resection. Based on these assumptions, the prospective, multicenter, observational OCUM trial (Optimierte Chirugie Und MRT, i.e. optimized surgery and MRI-based multimodal therapy; ClinicalTrials.gov identifier: NCT325649) was commenced in 200[7,13] recruitment was finished in 2016. The primary endpoints were 5-year LR rates and overall survival. In the present study, the secondary endpoints of quality of mesorectal excision and involvement of pCRM[14] are reported for all included patients. The hypotheses were that the quality of TME resection was high, without differences between participating centers, and that complete resection can be achieved in more than 90% of all patients by restricting nCRT to high-risk patients, based on MRI. Details of the study and preliminary results have already been published.[13,15,16]

PATIENTS AND METHODS

Study Design and Participants

Patients with solitary cancer of the rectum (aboral tumor margin $\leq$ 16 cm from the anal verge)[17] with cT2-4, any cN, or cM0 staging,[18] and elective surgery with curative intent (R0, R1), were included. Based on a 5-year LR rate of $<$ 10%, a minimum of 784 patients treated according to the protocol was necessary for proof of concept.

Preoperative diagnosis included a high-resolution MRI of the pelvis, according to a standardized protocol, on a 1.5-Tesla system with phased-array surface coils.[19] A sagittal T2-weighted turbo spin-echo sequence (TSE) was used to determine the tumor site. High-resolution T2-TSE images were acquired perpendicular to the longitudinal axis of the rectum. Coronal images were obtained for carcinomas located in the lower third of the rectum. Slice thickness for both sequences was 3 mm. The minimal distance of the tumor or lymph node suspicious for metastasis from the mesorectal fascia was determined; $\leq$ 1 mm was considered positive for involvement (mrMRF+), whereas a minimal distance $>$ 1 mm was considered to be negative (mrMRF−). cT4 tumors were classified as cT4a (tumor perforates visceral peritoneum), and cT4b (tumor directly invades other organs or structures).[7,18]Because of the thin mesorectum in the anterior compartment of the lower rectum (i.e. $<$ 6 cm from the anal verge), correctly predicting mrMRF is more difficult.[20] In addition, because of the inferior prognosis,[21] nCRT was administered for each cT3 and cT4 low rectal tumor. For tumors in the middle third of the rectum (i.e. 6 to $<$ 12 cm) nCRT was applied when mrMRF was positive ($\leq$ 1 mm) and in cT4 tumors. Patients with cancer of the upper third (i.e. 12–16 cm) were selected for primary surgery, with the exception of patients with cT4 tumors, who underwent nCRT, apart from in cases of infiltration of the urinary bladder (Fig. 1).

nCRT was performed as a long course, with 1.8 Gy fractions delivered to the pelvis five times weekly using individually shaped portals and a three- or four-field box technique up to 50.4 Gy. Concurrent chemotherapy with fluorouracil 1000 mg/m^2/day was administered daily during the first and fifth week of radiotherapy (RT). Surgery followed the principles of TME[22] and partial mesorectal excision in carcinomas of the upper third of the rectum, and was scheduled for 6 weeks after the completion of nCRT.[10] The quality of mesorectal excision[10,23] was determined by the surgeon and by pathology. Any adverse effects of nCRT were recorded according to a modified scoring system.[24,25] To determine tumor regression, we used the five-stage system suggested by Dworak et al.[26] Intraoperative local tumor cell dissemination, by cutting through the tumor or tearing the tumor, was documented by the surgeon and by pathology. The pCRM was considered positive if the shortest distance assessed microscopically between the tumor and the pCRM was $\leq$ 1 mm, and negative if $>$ 1 mm.[1] Complete resection of the tumor was classified as a distance of $>$ 1 mm between the tumor and the distal and circumferential resection lines. All intra- and postoperative surgical and general complications requiring

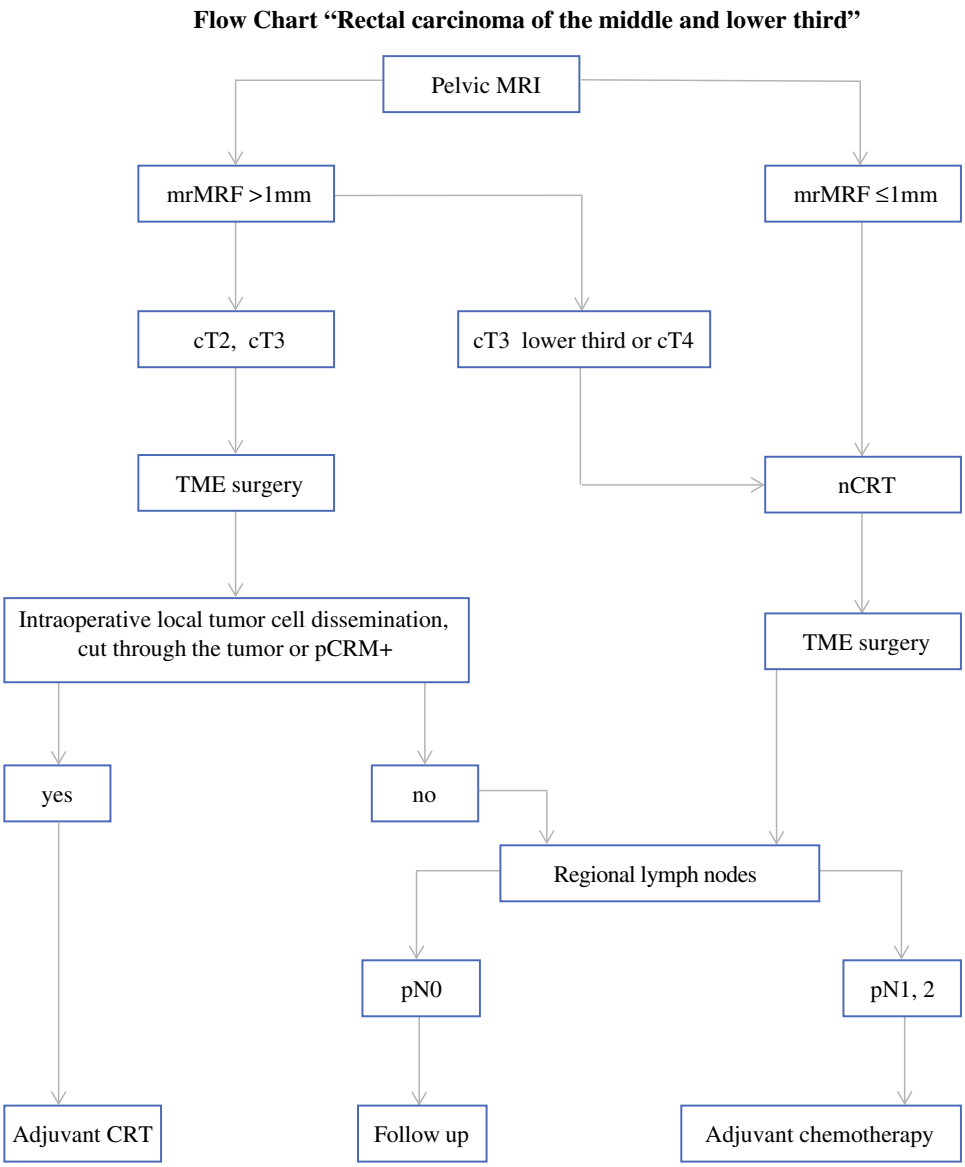

FIG. 1 Study protocol for treating middle- and lower-third rectal cancer. *MRI* magnetic resonance imaging, *mrMRF* mesorectal fascia in MRI, *TME* total mesorectal excision, *nCRT* neoadjuvant chemoradiotherapy, *pCRM* pathological circumferential resection margin, *CRT* chemoradiotherapy

treatment (grade II–IV)[27] were recorded, and 30-day, 90-day, and 6-month mortality determined.

Patients who fulfilled the inclusion criteria but were not treated according to the protocol were considered a separate group who underwent the same follow-up as patients treated according to the study protocol. After finishing recruitment on 30 September 2016, the participating centers were grouped as low-volume (10–50 patients), medium-volume (51–90 patients), or high-volume (> 90 patients) according to the number of recruited patients. Hospitals that recruited < 10 patients were excluded.

Quality and Ethics

This study was approved by the relevant Ethics Committee of each participating department. Written informed consent was obtained from all patients after providing information regarding the study. Quality assurance was performed by several pathology and radiology workshops, as well as regular meetings, to ensure the standardization of techniques and interpretation before the start of the study and during recruitment. In each center, one surgeon, one radiologist, and one pathologist were responsible for surgical therapy and assessment of the findings. The database of the cancer registry at the University of Erlangen (Germany) was utilized for data management. Quality was ensured by assessing the completeness and plausibility of the data and by comparing the original dataset with the case report forms in 10% of randomly chosen cases from each participating department.

TABLE 1 Baseline characteristics and type of surgery in 1091 patients from 14 departments

	All [n = 1091]	Primary surgery [n = 527]	nCRT followed by surgery [n = 348]	Deviations from protocol [n = 216]
Volume (centers)				
High	736 (67.5)	330 (62.6)	249 (71.6)	157 (72.7)
Middle	196 (18.0)	96 (18.2)	64 (18.4)	36 (16.7)
Low	159 (14.6)	101 (19.2)	35 (10.1)	23 (10.6)
Sex				
Male	677 (62.1)	329 (62.4)	221 (63.5)	127 (58.8)
Female	414 (37.9)	198 (37.6)	127 (36.5)	89 (41.2)
ASA				
1–2	648 (59.4)	330 (62.6)	208 (59.8)	110 (50.9)
3–4	346 (31.7)	161 (30.6)	101 (29.0)	84 (38.9)
Unknown	97 (8.9)	36 (6.8)	39 (11.2)	22 (10.2)
Tumor site (cm)				
< 6	368 (33.7)	53 (10.1)	208 (59.8)	107 (49.5)
6 to < 12	570 (52.2)	342 (64.9)	127 (36.5)	101 (46.8)
12–16	153 (14.0)	132 (25.0)	13 (3.7)	8 (3.7)
cT				
cT2	312 (28.6)	241 (45.7)	14 (4.0)	57 (26.4)
cT3	667 (61.1)	274 (52.0)	255 (73.3)	138 (63.9)
cT4	109 (10.0)	10 (1.9)	79 (22.7)	20 (9.3)
cTX	3 (0.3)	2 (0.4)	0	1 (0.5)
cN				
cN0	412 (37.8)	266 (50.5)	67 (19.3)	79 (36.6)
cN1	383 (35.1)	169 (32.1)	138 (39.7)	76 (35.2)
cN2	215 (19.7)	63 (12.0)	112 (32.2)	40 (18.5)
cN+	80 (7.3)	28 (5.3)	31 (8.9)	21 (9.7)
cNX	1 (0.1)	1 (0.2)		
Clincal stage				
I	196 (18.0)	164 (31.1)	3 (0.9)	29 (13.4)
II	217 (19.9)	103 (19.5)	64 (18.4)	50 (23.1)
III	678 (62.1)	260 (49.3)	281 (80.7)	137 (63.4)
mrMRF (mm)				
≤ 1	368 (33.7)	24 (4.6)	281 (80.7)	63 (29.2)
> 1	663 (60.8)	486 (92.2)	45 (12.9)	132 (61.1)
Uncertain	60 (5.5)	17 (3.2)	22 (6.3)	21 (9.7)

Data are expressed as n (%)

nCRT neoadjuvant chemoradiotherapy, *ASA* risk classification according to the American Society of Anesthesiologists, *mrMRF* distance of tumor from the mesorectal fascia in pretherapeutic magnetic resonance imaging

Statistical Analysis

The Chi square test and Fisher's exact test were used to compare categorical data, and the Mann–Whitney U test and Kruskal–Wallis test were utilized for comparison of continuous data. A logistic regression analysis was performed to consider factors influencing pCRM positivity. A p value ≤ 0.05 was considered significant. Statistical analyses were performed using the statistical software package SPSS® version 21 (IBM Corporation, Armonk, New York, USA).

RESULTS

A total of 1100 patients were recruited from 14 centers between January 2007 and September 2016. Nine patients were excluded from the analysis because they were lost to follow-up within 6 months postoperatively.

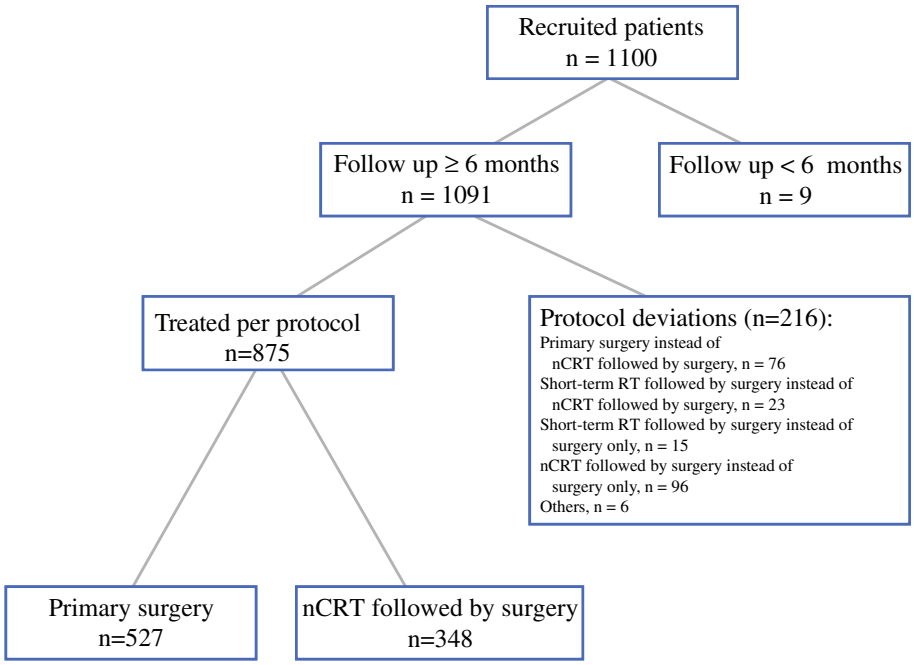

FIG. 2 Study treatment and protocol deviations. *nCRT* neoadjuvant chemoradiotherapy, *RT* radiotherapy

Three centers including 99–448 patients were classified as high volume, three as middle volume (62–71 patients), and eight as low volume (12–39 patients). The distance of the tumor to the mesorectal fascia could be determined in 1031 patients (94.5%); in 60 patients (5.5%) the result was uncertain, mostly in patients with tumors in the lower rectal third (n = 50). Of the 1091 patients, 875 (80.2%) were treated according to the protocol. A total of 216 (19.8%) patients fulfilled the inclusion criteria but were not treated according to the protocol (Table 1; Fig. 2).

Patients Treated According to the Protocol

The 527 patients who underwent primary surgery had locally less-advanced tumors than the 348 patients with nCRT followed by surgery, due to the selection criteria (Table 1). Of the 527 patients, all mrMRF-positive tumors were tumors of the upper third. RT was completed in 342 patients (98.3%) and chemotherapy was completed in 340 patients (97.7%). The median interval between pelvic MRI and primary surgery was 9 days (range 1–105), and 20 days (range 1–77) until the start of nCRT, while the interval between the end of nCRT and surgery was 51 days (range 17–98). Acute adverse effects during nCRT (grade 3 or lower) were observed in 61.3% of patients (204/333 with complete documentation), with no difference reported between participating centers.

Surgical Treatment

Of 875 patients, 769 (87.9%) underwent sphincter-saving procedures, and 106 (12.1%) underwent abdominoperineal excisions (APEs) (Table 2). The median open-to-close operative time was 182 min (range 56–684 min); however, time was significantly shorter for patients who underwent primary surgery than for patients after nCRT, and was shortest in high-volume centers. APE increased the median operating time by 30 min. The autonomic pelvic nerves were identified and preserved on both sides in 98.3% of surgeries, and only 1.1% (5/809) of patients received blood transfusions intraoperatively. Intraoperative local tumor cell dissemination was observed in 2.9% (25/875) of patients. The plane of surgery achieved in resection specimens was classified as mesorectal in 90.9% (795/875) of patients, intramesorectal in 8.0% (70/875) of patients, and muscularis propria plane in 1.1% (10/875) of patients. The values differed between patients with and without nCRT ($p < 0.001$), but there were no differences between participating centers (p = 0.156). Intra- and/or postoperative complications were observed in 245 of the 875 (28.0%) patients.

Histopathological Outcomes

Pathological tumor stages are shown in Table 3. After nCRT, 38/348 (10.9%) patients had a complete pathological response (pCR, ypT0, ypN0) without significant differences between the centers (8–13%, p = 0.545). R0 resection was confirmed in 860/875 patients (98.3%), and, in 822/870 patients (94.5%), complete resection of the

TABLE 2 Details of the surgical resections

	Primary surgery [n = 527]	nCRT followed by surgery [n = 348]	p-Value	High-volume centers [n = 579]	Middle-volume centers [n = 160]	Low-volume centers [n = 136]	p-Value
Anterior resection	54 (10.2)	2 (0.6)		18 (3.1)	21 (13.1)	17 (12.5)	
Low anterior resection	423 (80.3)	215 (61.8)		426 (73.6)	112 (70.0)	100 (73.5)	
Intersphincteric resection	6 (1.1)	41 (11.8)		40 (6.9)	7 (4.4)	0	
Abdominoperineal excision	24 (4.6)	82 (23.6)		75 (13.0)	18 (11.3)	13 (9.6)	
Hartmann procedure	20 (3.8)	8 (2.3)	< 0.001	20 (3.5)	2 (1.3)	6 (4.4)	< 0.001
Laparoscopic surgery	31 (5.9)	13 (3.7)	0.155	34 (5.9)	3 (1.9)	7 (5.1)	0.123
Multivisceral resection	7 (1.3)	41 (11.8)	< 0.001	34 (5.9)	9 (5.6)	5 (3.7)	0.597
Time of surgery, min [median (range)][a]	179 (56–570)	190.5 (78–684)	0.003	169.5 (78–443)	225 (85–600)	229.5 (56–684)	< 0.001
Blood loss > 300 ml[b]	28 (6.3)	37 (12.7)	0.003	32 (6.9)	18 (12.7)	15 (11.4)	0.058
Median, ml[b]	100	150	< 0.001	120	150	100	< 0.001
Sparing pelvic nerves on both sides[c]	522 (99.4)	334 (96.5)	0.002	570 (99.0)	152 (95.6)	134 (98.5)	0.021
Intraoperative tumor cell dissemination[d]	9 (1.7)	13 (3.8)	0.062	17 (2.9)	2 (1.3)	3 (2.2)	0.556
Mesorectal plane	496 (94.1)	299 (85.9)		531 (91.7)	141 (88.1)	123 (90.4)	
Intramesorectal plane	30 (5.7)	40 (11.5)		39 (6.7)	18 (11.3)	13 (9.6)	
Muscularis propria plane	1 (0.2)	9 (2.6)	< 0.001	9 (1.6)	1 (0.6)	0	0.156
Morbidity	154 (29.2)	91 (26.1)	0.322	169 (29.2)	36 (22.5)	40 (29.4)	0.230
Reoperation	50 (9.5)	31 (8.9)	0.772	51 (8.8)	17 (10.4)	13 (9.4)	0.775
30-day mortality	6 (1.1)	3 (0.9)	1.0	9 (1.6)	0	0	0.136
90-day mortality	11 (2.1)	3 (0.9)	0.181	13 (2.2)	1 (0.6)	0	0.137
6-month mortality	13 (2.5)	4 (1.1)	0.214	16 (2.8)	1 (0.6)	0	0.043

Data are expressed as n (%) unless otherwise specified

nCRT neoadjuvant chemoradiotherapy

[a]Unknown in 68 patients

[b]Unknown in 140 patients

[c]Unknown in 4 patients

[d]Unknown in 2 patients

tumor was achieved with free circumferential and distal resection lines > 1 mm. Significant independent factors for pCRM positivity were advanced tumor stage, especially pT4 or ypT4, metastatic lymph nodes, resection in the muscularis propria plane, and low rectal cancer (Table 4).

The median number of examined lymph nodes was higher in patients with primary surgery than after nCRT followed by surgery, as was the percentage of patients with ≥ 12 regional lymph nodes examined (Table 3). In low-volume centers, the number of harvested examined lymph nodes was lower (median 16, range 3–43, $p < 0.001$), as was the percentage of patients with ≥ 12 harvested and examined lymph nodes (91.1%, $p < 0.001$).

Patients with Clinical Stage II/III Carcinoma in the Lower or Middle Rectal Third

Of 600 patients with clinical stage II or III carcinomas in the lower or middle rectal third, 265 were mrMRF− and 3 were uncertain; these 268 (44.7%) patients did not receive nCRT. In 260 patients (97.0%), negative pCRM was diagnosed by the pathologist, whereas only 8 patients (3.0%) were found to be pCRM+ (Fig. 3). All three patients with uncertain mrMRF were diagnosed as pCRM−. A total of 332 (55.3%) high-risk patients received nCRT (Table 5).

TABLE 3 Histopathological outcomes

	Primary surgery [n = 527]	nCRT followed by surgery [n = 348]	p-Value
pT category			
–/ypT0, ypTis		45 (12.9)	
pT1/ypT1	37 (7.0)	15 (4.3)	
pT2/ypT2	204 (38.7)	93 (26.7)	
pT3/ypT3	276 (52.4)	179 (51.4)	
pT4/ypT4	9 (1.7)	16 (4.6)	
pTX/ypTX	1 (0.2)		
pN category			
pN0/ypN0	341 (64.7)	240 (69.0)	
pN1/ypN1	123 (23.3)	72 (20.7)	
pN2/ypN2	63 (12.0)	36 (10.3)	
Stage			
–/y0, yis		42 (12.1)	
I/yI	189 (35.9)	87 (25.0)	
II/yII	155 (29.4)	111 (31.9)	
III/yIII	183 (34.7)	108 (31.0)	
Regression of the primary tumor[a]			
Complete regression		42 (12.5)	
Dworak 3 (> 50%)		92 (27.3)	
Dworak 2 (> 25 to 50%)		155 (46.0)	
Dworak 1 (1–25%)		41 (12.2)	
Dworak 0 (no regression)		7 (2.1)	
R classification			
R0	523 (99.2)	337 (96.8)	
R1	4 (0.8)	11 (3.2)	0.014
pCRM			
pCRM−	514 (97.5)	318 (91.4)	
pCRM+	13 (2.5)	30 (8.6)	< 0.001
Completeness of resection[b]			
Circumferential and aboral distance > 1 mm (*n/N*)	509/523	313/347	
Circumferential and/or aboral distance ≤ 1 mm (*n/N*)	14/523	34/347	< 0.001
Regional lymph nodes examined (*n*)			
Median (range)	23 (1–79)	17 (3–56)	< 0.001
≥ 12 lymph nodes	518 (98.5)	316 (90.8)	< 0.001

Data are expressed as *n* (%) unless otherwise specified

nCRT neoadjuvant chemoradiotherapy, *pCRM* pathological circumferential resection margin

[a]Unknown in 11 patients

[b]Aboral distance unknown in 5 patients

DISCUSSION

In this prospective observational study, nCRT was restricted to approximately 40% of all included patients with high-risk rectal cancer (involved mesorectal fascia, cT3 tumor of the lower third, cT4 tumor), whereas TME surgery alone was performed in 60% of patients (uninvolved mesorectal fascia, tumors of the upper third). Complete tumor resection[28] with clear circumferential and distal resection margins > 1 mm could be achieved in 94.5% of patients treated according to the protocol.

The prerequisite for making a decision for or against nCRT based on MRI is high-quality surgery. Only, in this case, the findings of pretherapeutic MRI reflect the findings in the resected specimen. In addition, tumor recurrence and sexual and urinary sequelae are related to the quality of

TABLE 4 Risk factors for pCRM positivity in logistic regression analysis

	All	Univariate analysis		Multivariate analysis		
		pCRM + [*n* (%)]	*p*-Value	Exp(B)	95% CI	*p*-Value
All	875	43 (4.9)				
Primary surgery	527	13 (2.5)		1.0		
nCRT followed by surgery	348	30 (8.6)	< 0.001	0.2	0–1.3	0.092
High-volume centers	579	30 (5.2)				
Middle-volume centers	160	7 (4.4)				
Low-volume centers	136	6 (4.4)	0.877			
Male	550	30 (5.5)				
Female	325	13 (4.0)	0.336			
Upper third	145	4 (2.8)		1.0		
Middle third	469	17 (3.6)		2.8	0.7–12.2	0.166
Lower third	261	22 (8.4)	0.007	7.0	1.3–38.5	0.026
pT1–2, ypT0–2	670	11 (1.6)		1.0		
pT3, ypT3	179	23 (12.8)		10.2	2.4–42.9	0.002
pT4, ypT4	25	9 (36)	< 0.001	48.9	11.6–205.2	< 0.001
pN0, ypN0	581	16 (2.8)		1.0		
pN1, ypN1	195	15 (7.7)		2.5	1.1–5.8	0.032
pN2, ypN2	99	12 (12)	< 0.001	5.2	2.1–13.0	< 0.001
mrMRF−	531	12 (2.3)		1.0		
mrMRF+	305	30 (9.8)		2.1	0.5–8.8	0.297
mrMRF uncertain	39	1 (3)	< 0.001	0.5	0–6.0	0.565
(Low) anterior resection	696	26 (3.7)		1.0		
Intersphincteric resection	47	4 (9)		0.7	0.2–2.7	0.554
Abdominoperineal excision	104	8 (8)		0.7	0.2–2.4	0.618
Hartmann procedure	28	5 (18)	0.002	3.0	0.7–12.4	0.126
Mesorectal plane	795	31 (3.9)		1.0		
Intramesorectal plane	70	7 (10)		2.0	0.7–5.3	0.168
Muscularis propria plane	10	5 (50)	< 0.001	9.4	1.7–52.0	0.010
Multivisceral resection, no	827	35 (4.2)		1.0		
Multivisceral resection, yes	48	8 (17)	< 0.001	1.1	0.3–3.5	0.872

pCRM pathological circumferential resection margin, *mrMRF* mesorectal fascia in magnetic resonance imaging, *CI* confidence interval, *nCRT* neoadjuvant chemoradiotherapy

dissection.[29] The high quality of surgical resection is reflected in the high rates of resection in the mesorectal plane (90.9%), which could be achieved in all participating centers and is comparable with previous randomized studies.[30] Preoperative RT changes the perirectal tissue and lowers the quality of TME surgery. The present study confirmed this, even though the percentage of patients with a prognostically unfavorable resection plane was low after nCRT. The autonomic pelvic nerves were identified in nearly all patients with and without nCRT. The low rate of blood loss, low rates of blood transfusion during surgery, high lymph node yield equal to or exceeding that in other trials,[30–32] even in patients after nCRT,[33] and the low rate of intraoperative local tumor cell dissemination suggest a high quality of surgery.

The high rate of complete tumor resection in the whole population is in line with proposed requirements for surgical treatment of rectal cancer,[10] and justified the restricted use of nCRT. Sixty percent of included patients were classified as low risk and received TME only. The high reliability of determining uninvolved mesorectal fascia on pelvic MRI[34] was confirmed. This was the rationale for the omission of nCRT in these patients, regardless of clinical lymph node status. Due to the inclusion criteria, some patients for whom nCRT was not discussed at all were included. Most guidelines recommend nCRT in patients with rectal tumors of the middle and lower third with clinical stage II and III disease.[7] This subgroup represented 600 patients and 268 mrMRF− patients (44.7%) who received primary surgery only. In 260 patients (97.0%), the resection margin was tumor-free, and, in 8

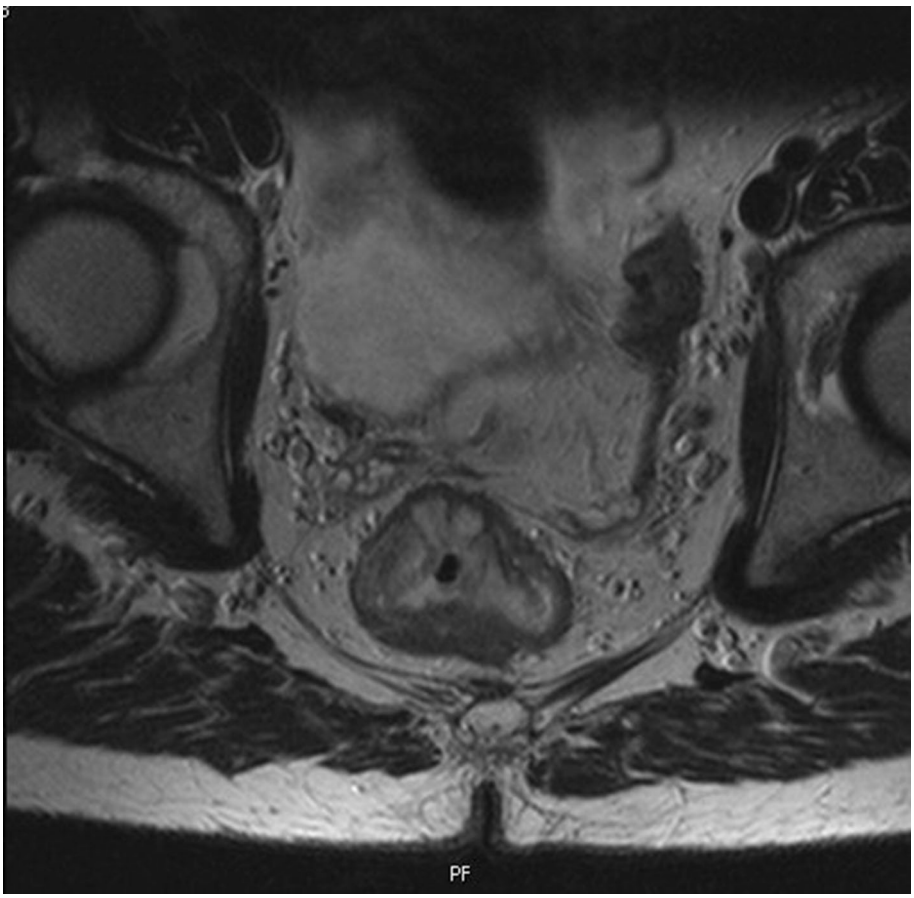

FIG. 3 High-resolution T2-weighted image of a 73-year-old male showing a cT3 tumor of the lower third of the rectum without involvement of the mesorectal fascia. Pathological examination revealed invasion of the circumferential resection margin by an adenocarcinoma

TABLE 5 mrMRF/pCRM in stages II–III in middle- and lower-third carcinomas

	mrMRF			pCRM	
	mrMRF+	mrMRF−	mrMRF uncertain	pCRM−	pCRM+
Primary surgery	0	265	3[a]	260	8
Stage II					
Middle third	0	83	1	80	4
Stage III					
Lower third	0	16	1	16	1
Middle third	0	166	1	164	3
nCRT followed by surgery	265	45[b]	22[c]	302	30
Stage II					
Lower third	18	16	8	40	2
Middle third	21	0	0	21	0
Stage III					
Lower third	121	29	14	145	19
Middle third	105	0	0	96	9

mrMRF mesorectal fascia in magnetic resonance imaging, *pCRM* pathological circumferential resection margin, *nCRT* neoadjuvant chemoradiotherapy

[a]All three patients with uncertain mrMRF were diagnosed as pCRM−

[b]42 patients were diagnosed as cT3, and 3 were diagnosed as cT4

[c]15 cT3 carcinomas and 7 cT4 carcinomas

patients (3.0%), the resection margin was involved. These eight patients may have benefited from nCRT; however, this possible undertreatment has to be balanced against the avoidance of nCRT with all adverse events in 97% of mrMRF− patients. Accepting this, the result suggests that in 45% of patients with clinical stage II/III, nCRT can be omitted; however, these results are based on the second endpoint of the study, i.e. pCRM, and the final result has to be awaited.

Forty percent of the included patients and 55% of the subgroup of patients with clinical stage II/III cancer of the middle and lower rectal third were classified as high-risk patients, receiving nCRT followed by TME. High-risk patients had more advanced tumors, and the percentage of patients with involved pCRM was higher than in patients with primary surgery. This is in line with other studies[10] and was caused mostly by the resistance of advanced tumors to nCRT, and, in a few patients, by the lower quality of mesorectal excision (data not shown). Accordingly, multivariate analysis confirmed the known independent predictive factors for pCRM positivity, i.e. advanced tumor (pT4, ypT4), metastatic lymph nodes, resection in the muscularis propria plane, and tumors of the lower rectal third.[10,21]

The rate of complete response (ypT0, ypN0) was in the lower range of observed rates (8–20%).[35] The response to RT depends on tumor size[36] and tumor stage,[37] and the more advanced tumor stage of patients selected for nCRT in this trial may explain the lower rate of a complete response.

This study has some limitations. First, the study design is that of an observational study. Second, the number of protocol deviations was high. The study protocol did not specify an age limit. Consequently, older patients who were excluded in most previous randomized studies were included. Third, our study design did not allow an examination of whether nCRT could be omitted in patients with cT3 mrMRF− low rectal cancers. Finally, data regarding the primary endpoint, i.e. the 5-year LR rate, are still incomplete. Based on the results for pCRM, a low overall LR rate can be expected,[14] as suggested by the preliminary results for the 3-year LR rates.[16]

CONCLUSIONS

Even without this final proof-of-concept for the study, the risk classification of rectal cancer patients by MRI seems to be highly reliable and allows the restriction of nCRT to approximately half of the patients with clinical stage II and III, provided there is a high-quality MRI protocol and a dedicated radiologist in rectal cancer MRI,[38] as well as high-quality surgery and standardized examination of the resected specimen.

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