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Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge

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Abstract ***Aim:*** The purpose of this multicenter cohort study was to evaluate whether a differentiated treatment of primary rectal cancer based on magnetic resonance imaging (MRI) can reduce the number of incomplete resections and local recurrences and improve recurrence-free and overall survival.

Methods: From February 2003 until January 2008, 296 patients with rectal cancer underwent preoperative MRI using a lymph node specific contrast agent to predict circumferential resection margin (CRM), T- and N-stage. Based on expert reading of the MRI, patients were stratified in: (a) low risk for local recurrence (CRM > 2 mm and N0 status), (b) intermediate risk and (c) high risk (close/involved CRM, N2 status or distal tumours). Mainly based on this MRI risk assessment patients were treated with (a) surgery only (TME or local excision), (b) preoperative 5 × 5 Gy + TME and (c) a long course of chemoradiation therapy followed by surgery after a 6–8 week interval.

Results: Overall 228 patients underwent treatment with curative intent: 49 with surgery only, 86 with 5 × 5 Gy and surgery and 93 with chemoradiation and surgery. The number of complete resections (margin > 1 mm) was 218 (95.6%). At a median follow-up of 41 months the

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three-year local recurrence rate, disease-free survival rate and overall survival rate is 2.2%, 80% and 84.5%, respectively.

Conclusion: With a differentiated multimodality treatment based on dedicated preoperative MR imaging, local recurrence is no longer the main problem in rectal cancer treatment. The new challenges are early diagnosis and treatment, reducing morbidity of treatment and preferably prevention of metastatic disease.

1. Introduction

In the past decades studies have shown that the risk for recurrence after resection of rectal cancer is substantially reduced with the surgical technique of the total mesorectal excision (TME). In this technique, popularised by Heald, the tumour is removed as a complete package including the surrounding mesorectal fat and lymph nodes.[1] Additionally, neoadjuvant (chemo)radiation has improved local control and, in some studies, survival.[2–5] Intensifying treatment of rectal cancer however is at the expense of treatment-induced morbidity and even mortality. Therefore, individualisation of treatment taking into account characteristics such as age, co-morbidity, stage and location of the tumour might provide an optimal balance between minimising treatment related morbidity and best oncological outcome. Until now, there is however no definite evidence that the outcome is better than applying a single standard treatment for all patients. Subgroup analyses within the large randomised trials can provide clues as to what factors can be used to guide treatment decisions for individual patients. In most of the trials patients with stage I disease (T1-2N0) have a negligible risk for local recurrence, and therefore do not need preoperative irradiation.[6] On the other hand, in patients with a combination of unfavourable characteristics like a tumour extending into the mesorectal fascia, positive lymph nodes and a very distal location, a short course of preoperative radiation and immediate surgery does not provide enough protection against local recurrence, and a long course of preoperative chemoradiation (CRT) is required.[2,3,6]

Reliable preoperative imaging is essential for a differentiated treatment according to risk factors for local recurrence. Although endorectal ultrasound is good in assessing the extent of the primary tumour in small lesions,[7] magnetic resonance imaging (MRI) has repeatedly shown to provide the best information on the relation of the tumour to the mesorectal fascia.[8–12] Assessing nodal involvement however has been suboptimal, and until now all three imaging modalities (endoscopic ultrasound, computed tomography (CT) and MRI) lack sufficient accuracy for clinical decision-making.[13] MRI studies with lymph node-specific contrast agents have shown promising results for the prediction of nodal involvement.[14,15] This would enable MRI to assess the two most important risk factors for local recurrence: relation of the tumour to the mesorectal fascia and nodal stage.

The primary aim of our prospective cohort study was to assess the outcome as defined by the number of complete resections of a differentiated treatment protocol for rectal cancer, based on MRI. The secondary aim was the assessment of long-term outcome as defined by three-year local recurrence, disease-free and overall survival, compared to the data of the Dutch TME trial.

2. Patients and methods

2.1. Patients

Between February 2003 and January 2008, a prospective multicentre cohort study was performed in patients with primary rectal cancer in whom a differentiated treatment protocol was primarily based on MRI. In February 2003 the study started as a single centre pilot study at the Maastricht University Medical Centre, and was continued as a multicentre study from December 2005 onwards ($n = 117$). Three regional hospitals joined the study: Laurentius Hospital Roermond (start of inclusion: 12–2005, $n = 38$), St. Jans Hospital Weert (start of inclusion: 12–2005, $n = 17$) and VieCuri Medical Center Venlo (start of inclusion: 02–2006, $n = 58$). Institutional review board approval was obtained for all hospitals. All patients gave a written informed consent.

2.1.1. Inclusion criteria

Histologically proven adenocarcinoma of the rectum.

2.1.2. Exclusion criteria

Patients were excluded from the study if they had locally recurrent rectal cancer, were pregnant, were younger than 18 years, had a contra-indication for MR imaging (pacemaker, neurostimulator, insulin pump and certain vascular clips (e.g. used in brain surgery), cochlear implants, metal fragments in the eye or any other metal implant not securely fixed or electronic device), or did not give informed consent for participation. For the present analyses that include long-term outcome, patients who received palliative treatment or who had a previous or coexisting malignancy were excluded.

2.4. MR imaging

All patients underwent a pelvic MRI with standard T2W TSE sequences in three orthogonal directions (sagittal, axial and coronal) and an axial 3D T1W gradient echo (GRE) sequence. For nodal staging an axial T2*W GRE was performed with ultrasmall super paramagnetic iron oxide (USPIO), a lymph node specific contrast agent. The USPIO MR contrast agent (Sinerem, Guerbet Laboratories, Roissy, France) consists of low molecular weight iron oxide coated with dextran. Sinerem was administered at a dose of 2.6 mg Fe/kg by slow intravenous infusion during a period of 45 min, 24–36 h before the MRI scan. No side-effects were recorded during or after infusion. Imaging was performed on a 1.0/1.5 T MR scanner. Patients did not receive bowel or other preparation. Total scan time was approximately 40 min.

2.5. Image evaluation

All MRI scans were read by both a local radiologist and an expert reader, and evaluated for T-stage, N-stage, involvement of the mesorectal fascia and height of the tumour. USPIO images were read for the prediction of nodal status by predefined criteria based on contrast uptake, size and shape.[16,17]

2.6. Treatment stratification and strategy

In a multidisciplinary meeting the treatment plan for each individual patient was determined based on the clinical information, MR imaging of local disease and imaging for distant disease. Patients with widespread metastatic disease and/or a very poor general condition that precluded major surgery were considered for palliative treatment only, and are excluded from the present analysis. For the other patients the tumour was classified on the basis of the MR images patients as 'low', 'intermediate' and 'high' risk for local recurrence. Low risk was defined as T1-2N0 or T3N0 with a wide circumferential resection margin (CRM) (>2 mm) when localised in the proximal rectum. The definition of a wide CRM was chosen on the basis of the widely recognised 1 mm at histology with an additional 1 mm safety margin to compensate for small MR measurement errors. High risk was defined as tumours with circumferential resection margin <2 mm, distal tumours (i.e. <5 cm from the anal verge) or N2 status. All other tumours were considered as intermediate risk (see Fig. 1). Generally, low risk tumours were treated with surgery only, intermediate risk tumours were treated with 5×5 Gy (Gray) preoperative radiotherapy followed by surgery within 1 week after the last radiation fraction, and high risk tumours were treated with a long course of CRT and surgery after a 6–8 week interval.

This CRT consisted of radiation in 28 fractions of 1.8 Gy, on weekdays combined with oral capecitabine (825 mg/m^2, twice a day for 7 days a week), or capecitabine with oxaliplatin (oxaliplatin 130 mg/m^2 on day one) in patients with synchronous distant metastases. Patients underwent surgery 6–8 weeks after the last fraction of radiation therapy. One to two weeks before surgery patients underwent a new pelvic MRI, to evaluate local status as a roadmap for surgery.

Surgery consisted of a low anterior resection or abdominoperineal resection (APR) according to the TME-principle as described by Heald.[18] All surgeons were trained in high quality TME surgery as a result of the widespread implementation of TME after the results of the Dutch TME trial in The Netherlands. In selected cases of early tumours a local excision (snare polypectomy or transanal endoscopic microsurgery) was performed. For locally advanced tumours, the extent of the resection was based on the MR images. For large tumours the TME sometimes had to be

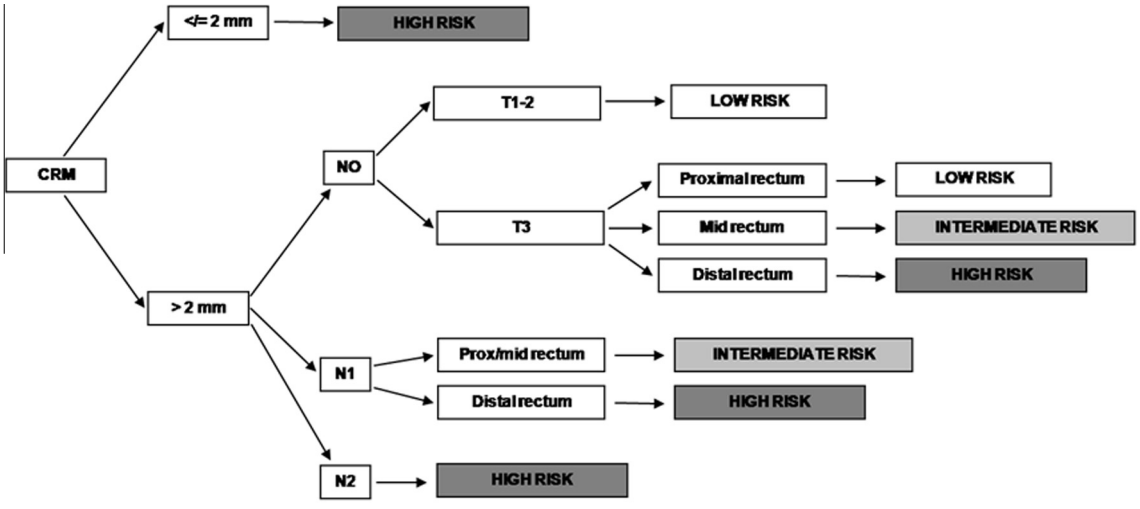

Fig. 1. MRI treatment stratification scheme.

extended beyond the mesorectal fascia, with an en-bloc resection of surrounding organs when required. Adjuvant chemotherapy was generally considered for all locally advanced tumours treated with CRT and for tumours with involved nodes at histology. Chemotherapy consisted of 6 courses of oral capecitabine (1000 mg/m^2 twice daily during 2 weeks) with intravenous oxaliplatin 130 mg/m^2 at day 1, or capecitabine (1000 mg/m^2) as monotherapy.

2.7. Histological evaluation

The resection specimen was evaluated in a standardised way, as described by Quirke.[19] A complete resection (R0) was defined as a circumferential resection margin of $\geqslant$1 mm. For the patients who underwent local excision, a complete resection of the tumour at histology as well as a confirmed N0 status at follow-up MRI was considered a complete resection.

2.8. Follow-up

Follow-up after treatment for rectal cancer followed the national guidelines: clinical examination every 6 months for the first 3 years, and yearly until 5 years of follow-up, carcinoembryonic antigen (CEA) measurements every 3 months for the first 3 years, and every 6 months until 5 years of follow-up and liver ultrasonography or CT-scan twice yearly in the first year and yearly thereafter until 5 years of follow-up. For those patients who underwent a local excision, follow-up MRI was performed at least after 6 months and 1 year, in addition to endoscopic follow-up. Local recurrence, distant recurrence, death or event-free interval from the day of surgery were scored for all patients.

2.9. Comparison with Dutch TME trial

Three-year survival data and the number of complete resections were compared to the individual data of the Dutch TME trial that were provided by the Dutch TME trial group. This was considered as the best available comparison as it is a large prospective database in the setting of a randomised controlled trial and reflects the outcome of patients with rectal cancer before the widespread use of MRI. The setting for the Dutch TME trial was comparable to the set-up of the current cohort study and the inclusion and exclusion criteria are very similar. Patients who were in a palliative setting were excluded from the Dutch TME trial. A difference in selection criteria between both studies is that the present study includes all comers, including the very early tumours and the very locally advanced tumours, whereas the Dutch TME trial did not include these two groups. The main difference between the two studies was that local staging with MRI was not mandatory in the Dutch TME trial, and was performed only in a minority of patients.[6] Because of the small but real difference in patient population the outcome results were compared without formal statistical comparison.

2.10. Statistical analysis

Baseline characteristics were prospectively collected. Postoperative course and complications were scored using the Dindo classification.[20] For the estimation of long term outcome Kaplan Meier survival functions were used. Local control was defined as the absence of pelvic recurrence; distant-metastasis free survival as the absence of distant metastasis outside the pelvis; disease-free survival as the absence of a local and distant recurrence and death from cancer-related cause; and overall survival as the absence of death from any cause. The chi-square test was used for comparison of proportions. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (version 16.0; SPSS, Chicago, IL) and STATA 11.0.

3. Results

Overall 296 patients were included. Of these patients, 13 were not evaluable because of MRI-related problems (artefacts, refusal) ($n = 5$) and refusal of treatment ($n = 8$). Of the remaining 283 patients five had a previous malignancy, one had a coexisting malignancy and 47 were not treated with a curative intent because of widespread unresectable metastatic disease ($n = 46$) and because of very poor general condition ($n = 1$).

Therefore, 230 patients could be included for this study. Sixteen of these patients presented with synchronous metastatic disease that was considered potentially curable. For these patients the three-year survival estimates are reported separately. Of the 230 included patients 134 (58%) were male. Mean age ($\pm$standard deviation (SD)) was 67 ($\pm$10.6) years.

In 31 patients the actual treatment differed from the MRI based proposal. This was most often due to advanced age or poor condition of the patient, illustrated by 20 patients with a locally advanced tumour on MRI who were treated with 5 $\times$ 5 Gy ($n = 18$) or surgery only ($n = 2$). In seven patients surgery without radiotherapy was chosen whereas MRI advised short course radiotherapy and four patients received a short course of radiotherapy whereas MRI advised surgery only. Fig. 2 shows the stratification of the actual received treatment.

3.1. Surgery and perioperative period

Twenty-one patients underwent a local excision, 134 a low anterior resection (11 of which with an extended TME), 71 an APR (25 'extended'), one patient a total

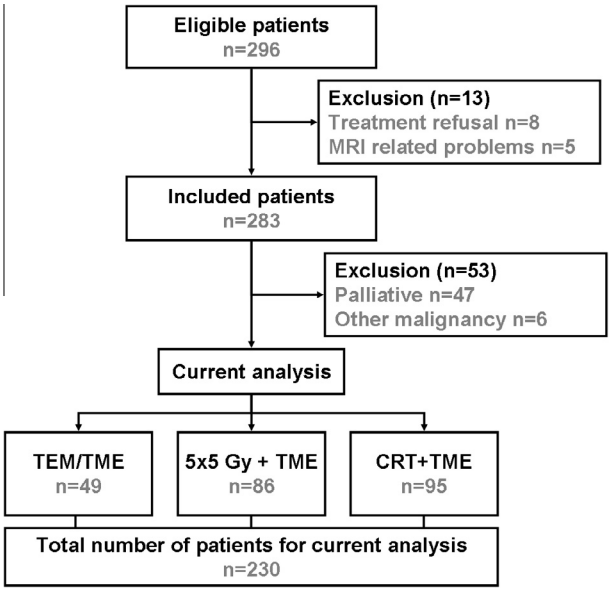

Fig. 2. Flow diagram of actual received treatment.

Table 1
Dindo classification of surgical complications.

	All patients, $n = 228$
No complications	46% (105/228)
Grade I	18% (40/228)
Grade II	10% (22/228)
Grade III A/B	20% (46/228)
Grade IV A/B	2% (5/228)
Grade V	4% (10/228)

Surgical complications according to Dindo et al.: grade I: any deviation from normal postoperative course that does not require treatment other than antiemetics/analgetics; grade II: complications requiring pharmacological treatment, e.g. urinary tract infection; grade III: complications requiring surgical/endoscopic/radiological intervention, (A) without general anaesthesia or (B) with general anaesthesia; grade IV: Life threatening complications requiring ICU admission, (A) with single organ dysfunction or (B) with multiorgan dysfunction; grade V: complications leading to death of the patient.

pelvic exenteration and one patient a posterior pelvic exenteration. Furthermore, two patients had a clinical complete response to CRT, confirmed by repeated biopsies and imaging. These patients preferred not to undergo surgery and are currently in a follow-up protocol. They were not included in the analysis for complete resections but were included in the analysis of long-term outcome.

All local excisions ($n = 21$) were performed during a short hospital stay of 2–3 days (TEM) or in the outpatient clinic (snare polypectomy) and were uncomplicated. For the other patients ($n = 207$), median hospital stay was 11 days (range: 4–199). There were 123 patients having one or more post-operative complications. The severity of the complications is graded using the Dindo-classification[20] in Table 1.

As shown in Table 1, 10 patients died postoperatively during their initial hospital stay (Dindo grade V), six of whom within 30 days. The postoperative mortality of all patients (including local excision) is 4.3% with a 30-days mortality of 2.6%. In four patients death was directly related to surgical complications, the other six patients died of (often multiple) systemic postoperative complications (e.g. myocardial infarction).

3.2. Histological examination

The number of complete resections and the distribution in the different stages at histopathological examination after surgery are shown in Table 2. The number of complete resections of 95.6% is much higher than the 84.1 in the Dutch TME trial (unpublished data). The number of complete resections did not differ significantly between the treatment groups in the present trial ($p = 0.201$). An involved margin after surgery was seen in 4.4% of patients ($n = 10$), and was due to (a combination of) (1) failure in surgical technique: tumour perforation during surgery ($n = 5$) or incomplete removal of the entire mesorectum, and/or (2) surgical planning ($n = 8$): insufficient attention to MR images after CRT by the surgeon, showing a margin that was still at risk. In none of these patients the cause of the incomplete resection could be traced to an underestimation of the circumferential resection margin on MRI as described by the radiologist. The incomplete resections are summarised in Table 3.

3.3. Adjuvant chemotherapy

Adjuvant chemotherapy was administered to all patients who had primary synchronous metastasis (7%, 16/230). In the other patients who were treated with curative intent adjuvant chemotherapy was administered in 19% of patients treated with surgery only, in 20% of patients treated with 5×5 Gy and surgery and in 60% of the patients treated with CRT and surgery.

3.4. Follow-up

The median follow-up was 41 (0–83) months. The three-year local recurrence rate was 2.2% (95% C.I.; 0.8–5.7%) for all patients (Fig. 3), as compared to 6.2% (95% C.I. 5.1–7.6%) from the individual data of the Dutch TME trial. The seven patients who developed a local recurrence are summarised in Table 4. None of the local recurrences occurred in the group of patients with an incomplete resection.

Three-year distant-metastasis-free survival, disease-free survival and overall survival were 85.5% (95% C.I.; 80–90%), 80.2% (74–85%) and 84.5% (79–89%), respectively (see Fig. 3). Three-year survival estimates

Table 2
Number of complete resections and distribution of American Joint Committee on Cancer (AJCC) stage at histology.

	N R0 (%)	0	I	II	III	IV
Local excision/total mesorectal excision (TME)	49/49 (100)	0	34	6	9	0
5 × 5 Gy (Gray) + TME	82/86 (95.3)	0	29	28	23	6
Chemoradiation (CRT) + surgery[a,b]	87/93 (93.5)	14	22	23	24	10
Total	218/228 (95.6)	14	85	57	56	16

[a] AJCC stage for these patients is stage after neoadjuvant therapy: ypTNM.
[b] 2/95 Patients of the CRT + surgery refused surgery after CRT and were therefore left out of the analysis of complete resections.

Table 3
Characteristics of patients with incomplete resections.

Patient	Treatment	Distance anal verge (cm)	(y)pTNcM	CRM involvement	LR	DR	DR time	Status	OS time
1	5 × 5 Gy + LAR	7	T3N0M0	+	–	–	n.a.	NED	43
2	5 × 5 Gy + APR	0	T3N0M0	+	–	–	n.a.	NED	38
3	CRT + APR	0	T3N1M0	+	–	+	13	DOD	18
4	CRT + APR	0	T2N0M0	+	–	+	29	AWD	54
5	CRT + LAR	2	T3N1M0	+	–	–	n.a.	NED	36
6	CRT + APR	7	T3N0M0	+	–	–	n.a.	NED	55
7	CRT + APR	3	T3N0M0	+	–	+	10	DOD	38
8	CRT + LAR	3	T3N0M1	–	–	–	n.a.	NED	48
9	5 × 5 Gy + APR	0	T3N1M0	+	–	–	n.a.	DOC	32
10	5 × 5 Gy + LAR	3	T3N0M0	–	–	–	n.a.	DOD	0

Gy = Gray; LAR = low anterior resection; APR = abdominoperineal resection; CRT = chemoradiation; CRM = circumferential resection margin; LR = local recurrence; DR = distant recurrence; NED = no evidence of disease; DOD = death of disease; AWD = alive with disease; DOC = death of other causes; OS = overall survival.

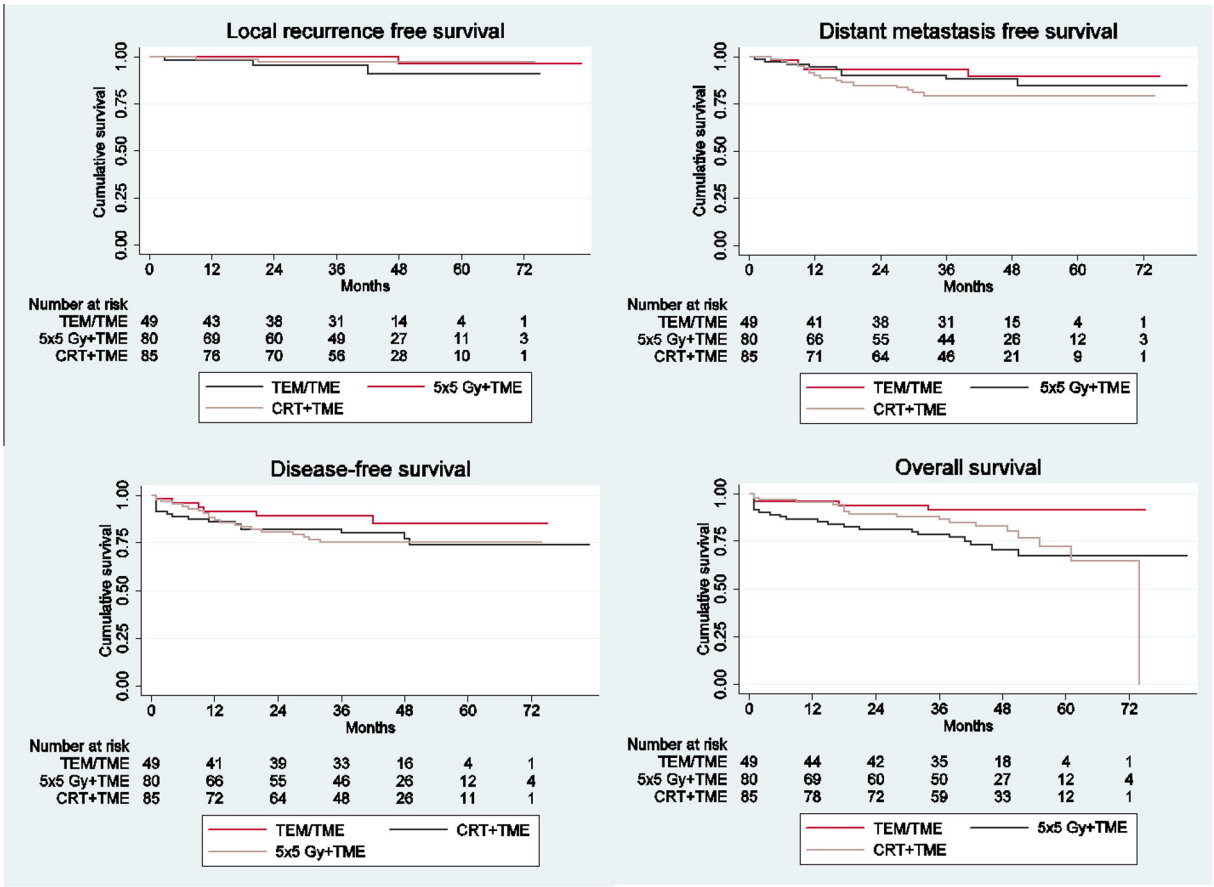

Fig. 3. Local recurrence-free, distant-metastasis-free, disease-free and overall survival curves of all patients treated with curative intent that did not have primary metastases at presentation.

for the primary metastasised patients that were treated with curative intent were 16% (3–40%), 13% (2–35%) and 44% (20–66%), respectively.

The Dutch TME trial shows a three-year distant-metastasis-free, disease-free and overall survival of 79.1% (95% C.I.; 77–81%), 76.8% (75–79%) and 81% (79–83%) respectively. Given the fact that in the Dutch TME trial locally very advanced tumours were excluded whereas they were included in the present study, there is a suggestion that the overall results have improved with the current MRI based strategy.

4. Discussion

This study shows that tailored treatment of primary rectal cancer based on preoperative MR imaging leads to a high rate (95.6%) of complete resections and an excellent three-year local control with a local recurrence rate of only 2.2%. Overall survival was 84.5%.

The number of complete resections is much better than older series on rectal cancer treatment, and much better than the 84.1% in the Dutch TME trial. The 2.2% local recurrence rate also compares favourably with 3.4% of the 5 × 5 Gy radiation group in the Dutch TME trial[21] and 4.4% at 3 years in the MRC CR07 trial.[22] In the trials on neoadjuvant CRT for locally advanced tumours the 5 year local recurrence rates were 7.6% (Bosset et al.) and 6% (Sauer et al.).[2,3] A strict comparison is however difficult as many series and randomised trials focus on a well-defined group of patients with rectal cancer whereas the present study includes 'all comers' without any selection. It is important to realise that the good results of the current study may be related to a number of recent improvements in the treatment of rectal cancer. In the Dutch TME trial, which ran from 1996 to 1999, a special emphasis was placed on quality assurance of surgical TME technique. With workshops, videos, visits of renowned rectal surgeons and a system of continued proctoring the TME technique became standard in most surgical practices. Additionally, up-to-date high resolution MR techniques were standard in the current study. MRI shows the proximity of the tumour to the important surgical planes in distal rectal cancer, and helps the surgeon to perform a complete resection.[23] MRI also identifies tumours that invade or come close to the mesorectal fascia, tumours that are best treated with a long course of neoadjuvant CRT rather than a short course of radiotherapy. The Mercury Study, a multicentre prospective study that used an MRI based selection similar to the present study, reported a 5 year local recurrence rate of 3.3% for the subgroup of patients (33% of the entire cohort) with a good prognosis who were treated without neoadjuvant therapy, with an overall and disease free survival of 68% and 85% respectively.[24] Although the MR based selection in the Mercury study was similar to our study, their treatment policy that followed this selection was much more restricted regarding the use of neoadjuvant therapy. In the Mercury study only 32% of patients received neoadjuvant therapy compared to 78% in our study.[25] The overall long term outcome results of the Mercury study have not yet been published, and it would be interesting to compare the local recurrence rates of these two policies. Another factor that may have contributed to the good outcome in the current study is the important role in the decision making process of the multidisciplinary team, a factor that is considered to be essential in modern rectal cancer treatment.[26–28]

4.1. Positive margins

An interesting and puzzling finding in this study is the fact that none of the patients with a positive margin at histology developed a local recurrence. A recent review confirmed the earlier observations that a positive margin is a risk factor for local recurrence, even more so when patients are treated with neoadjuvant CRT.[29,30] The fact that this is not observed in the present study could be just a chance observation, or be caused by a too short follow-up time. The strategy in the present study was specifically aimed at avoiding a positive margin, making optimal use of MRI, sound surgical technique and with liberal use of CRT for tumours close to the mesorectal fascia and for very distal tumours. Maybe the few tumours with positive margins that result from such a strategy are different from the tumours with positive margins in older series with a much higher rate of incomplete resections. It is therefore unclear whether a positive margin can still be used as a surrogate end-point for local recurrence.

APRs in rectal cancer surgery are often associated with a higher percentage of incomplete resections and an adverse outcome.[31] Presently, a wide cylindrical APR for distal rectal cancer is therefore advocated in literature,[32,33] as it would increase the chance for a complete resection. However, in this study a cylindrical resection for distal rectal tumours was not performed routinely, without apparently compromising outcome, although there were more incomplete resections in the APR group as shown in Table 3. Neoadjuvant CRT as well as dedicated MR imaging as a roadmap to the surgeon might again be responsible for this result. It is also in line with the retrospective analysis of Messenger et al.[34] in which similar incomplete resection and local recurrence rate were found as compared to studies advocating a wide cylindrical excision, in a group of patients in which >50% received neoadjuvant CRT.

This multicentre cohort study of unselected consecutive rectal cancer patients illustrates the morbidity and mortality that is associated with rectal cancer surgery. One out of five patients required an intervention after initial surgery, ranging from drainage of an abscess to

Table 4
Characteristics of patients who developed a local recurrence.

Patient	Treatment	Distance anal verge (cm)	R0/R1	(y)pTNcM	LR time	Treatment of recurrence	DR	DR time	Status	OS time
1	5 × 5 Gy + LAR	12	R0	T3N0M1	36	–	+	10	DOD	45
2	Local excision	15	R0	T1N0M0	42	LAR	–	n.a.	NED	52
3	CRT + APR	0	R0	T3N0M0	21	Surgery	–	n.a.	NED	33
4	Local excision	4	R0	T1N0M0	3	LAR	+	4	AWD	32
5	LAR	9	R0	T3N1M0	20	Surgery	+	40	AWD	57
6	CRT + APR	0	R0	T3N2M0	9	–	+	9	DOD	18
7	5 × 5 Gy + LAR	9	R0	T1N0M0	48	Surgery	–	n.a.	NED	50

Gy = Gray; LAR = low anterior resection; APR = abdominoperineal resection; CRT = chemoradiation; R0 = complete resection; R1 = incomplete resection; LR = local recurrence; DR = distant recurrence; NED = no evidence of disease; DOD = death of disease; AWD = alive with disease; OS = overall survival.

relaparotomy because of anastomotic leakage and the overall postoperative mortality is 4%. Old patients and patients with severe comorbidity were often treated with the short course radiotherapy ($n = 20$) or even no radiotherapy at all ($n = 7$) despite the presence of risk factors for local recurrence, because CRT was considered too toxic. This bias or 'confounding by indication' can explain the higher mortality in the short-course radiotherapy group as compared to the CRT group.

In addition to short-term morbidity, multimodal rectal cancer treatment is also associated with long term functional morbidity. This study did not assess the defecation and urogenital long term function. Undoubtedly the very low local recurrence rate had been achieved at the cost of functional long term morbidity. We have the feeling that many patients have been 'overtreated' with neoadjuvant therapy, and the question is still open how to find the optimal balance between local control and good functional outcome.

4.2. Improving survival

Multidisciplinary efforts to obtain a good local control of rectal cancer have paid off well. However, many patients still die of metastatic disease. In the present cohort 21% of patients at primary diagnosis presented with metastases, and 15% of the remaining patients developed metastatic disease at a later stage. Unfortunately only a minority of these patients are ultimately cured, despite aggressive multimodal treatment. Earlier detection of metastatic disease, more active systemic therapy and a more individualised approach using predictive factors could improve not only disease control, but also long term survival, especially when combined with metastasectomies. There is a new tendency to address the metastatic disease simultaneously with the primary tumour or even before the primary tumour, reflected in neoadjuvant systemic therapy protocols and in the surgical 'liver first approach' in which metastatic disease is resected before the primary tumour.[35] A major step forward in improving colorectal cancer survival is expected from large screening programs, that not only lower the overall incidence of colorectal cancer but also the proportion of advanced tumours.[36,37]

4.3. Limitations of the study

The main limitation of this study is that, in contrast to a randomised study, a cohort study cannot provide solid proof that a differentiated approach leads to a better outcome than a more uniform treatment schedule. Besides accurate and high quality MR imaging other factors contributed to our good outcome: improved TME surgery and multidisciplinary treatment. The primary aim of this study was, however, to evaluate the outcome of an MRI based treatment approach in this setting of high quality TME and multidisciplinary treatment. The study shows that with this approach in our setting an excellent local control can be achieved, although we cannot exclude that other factors could play a role too. Another limitation is a relatively short median follow-up of 3 years. Although 3 years is a well-accepted end-point in oncological research, late recurrences can occur after neoadjuvant CRT. A further limitation of the study is the practical difficulty of MR staging with the lymph node specific contrast agent USPIO, an agent that is no longer available on the market despite promising initial results.[14,15] Although with standard MR imaging without USPIO the accuracy of the predicted nodal status will be slightly lower, the key features in the MR stratification scheme – mesorectal fascia invasion, T-stage and tumour height will be equally accurate. Recent literature shows that there is a continued search for good lymph node contrast agents.[38]

5. Conclusion

With a differentiated multimodality treatment based on dedicated preoperative MR imaging, local recurrence is no longer the main problem in rectal cancer treatment. The new challenges are early diagnosis and treatment, reducing morbidity of treatment and prevention and treatment of metastatic disease.

Conflict of interest statement

None declared.

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