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ORIGINAL ARTICLE

Endoscopy and MRI for restaging early rectal cancer after neoadjuvant treatment

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Abstract

Aim: Chemoradiotherapy (CRT) has great potential to downstage rectal cancer. Response assessment has been investigated in locally advanced rectal cancer but not in early stage rectal cancer. The aim is to characterize the diagnostic accuracy of endoscopy performed by surgical endoscopists compared to (diffusion-weighted, DWI) MRI only and a multimodal approach combining (DWI-)MRI and endoscopic information both analysed by an abdominal radiologist for response assessment in early rectal cancer after neoadjuvant CRT.

Materials and methods: Patients treated with neoadjuvant CRT for early distal rectal cancer (cT1–3 N0) followed by transanal endoscopic microsurgery were included. Three separate reassessment groups were analysed for response assessment using endoscopic evaluation alone versus (DWI-)MRI alone versus the combination of endoscopy with (DWI-)MRI with a focus on sensitivity and specificity and analysis using receiver operating characteristic curves.

Results: Three cohorts ($N = 36$, $N = 25$ and $N = 25$, respectively) were analysed for response assessment. Of the endoscopy cohort, 16 of the 36 patients had a complete response. Area under the curve was 0.69 (0.66–0.74; pooled sensitivity 55.3%, pooled specificity 80.0%). Agreement for scoring separate endoscopic features was poor to moderate. Of the (DWI-)MRI cohort, 11 of the 25 patients had a complete response. Area under the curve for (DWI-)MRI alone was 0.55 (sensitivity 72.7%, specificity 42.9%). The areas under the receiver operating characteristic curve improved to 0.68 (sensitivity 90.9%, specificity 75.0%) when (DWI-)MRI was combined with endoscopic information, with 11 out of 25 patients with a complete response. The most accurate response assessment was made by combining endoscopy and (DWI-)MRI with a high negative predictive value (90.9%).

Conclusion: Good and complete responders after chemoradiation of early stage rectal cancer can be best assessed using a multimodality approach combining endoscopy and (DWI-)MRI.

KEYWORDS
chemoradiotherapy, diffusion-weighted imaging, early rectal cancer, endoscopy, magnetic resonance imaging, response assessment

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) in rectal cancer treatment has been proved to significantly downstage locally advanced rectal cancer (LARC) [1, 2]. The downstaging effect varies between patients, with the potential to lead to a pathological complete response (pCR; ypT0N0) in 15%–25% of LARC as observed in total mesorectal excision (TME) specimens [3]. Although oncological outcomes are good, TME surgery causes substantial morbidity and occasionally mortality [4–6]. These findings have led to the exploration of organ-preserving approaches in good or complete response patients aiming to reduce the morbidity of conventional rectal cancer treatment whilst maintaining oncological outcome and quality of life.

A watch-and-wait strategy instead of TME surgery in this specific group has been the subject of many studies [7, 8]. Also, resection of the residual tumour mass after chemoradiation can be performed safely with local excision techniques, such as transanal excision, transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery [9–11]. Long-term follow-up with close clinical follow-up reveals that this strategy is also a safe alternative for TME [8, 12–16].

The key to selecting patients for an organ-preserving approach is a dedicated diagnostic work-up with high accuracy. For restaging rectal cancer after CRT, digital rectal examination (DRE) and endoscopy are essential [17, 18]. However, these examinations only provide information on the (intra)-luminal presence of the tumour. T2-weighted (T2W) MRI is the superior modality for (re)staging rectal cancer, providing the best anatomical relationship of the tumour to key surgical landmarks [19, 20]. Together with diffusion-weighted imaging (DWI) a strong indication can be made whether there is remaining residual tumour and/or lymph node involvement. The combination of DRE, endoscopy and (DWI-)MRI has provided the most accurate assessment of the response in LARC [21].

Most publications on the accuracy of restaging rectal cancer after neoadjuvant CRT have focused predominantly on LARC treated with neoadjuvant chemoradiation. Nowadays, organ-preserving treatment is studied for less advanced stages such as early stage (cT1–3 N0) rectal cancer. So far, the performance of (DWI-)MRI and its additional value to endoscopy for the assessment of good and completely responding early rectal cancer patients is unknown and therefore the subject of the present study.

What does this paper add to the literature?

This study reveals that a multimodality approach using endoscopy and (DWI) -MRI is most accurate in the assessment of response after neoadjuvant chemoradiotherapy in early rectal tumours. The optimal identification of good and complete responders, will aid in the patient selection for organ-preserving treatment.

MATERIALS AND METHODS

This study was approved by the institutional review board of the participating hospitals. For inclusion in the current study, endoscopic images and/or (DWI-)MRI images before and after neoadjuvant CRT had to be available for reassessment. Patients who participated in the CARTS study ($N = 55$; registered at clinicaltrials.gov; NCT01273051) [15, 22] and patients treated with a similar organ-sparing regime at the Laurentius Hospital ($N = 22$; a tertiary referral centre for local excision) in the period after the CARTS study were screened for eligibility. Based on the availability of the clinical data of these 77 patients, three reassessment cohorts could be formed: (1) reassessment of endoscopy alone, (2) reassessment of (DWI-)MRI data alone and (3) a multimodal reassessment combining (DWI-)MRI with endoscopic information. Informed consent for re-evaluation of the clinical examinations was obtained at initial inclusion in the CARTS study. Patients included at the Laurentius Hospital provided their written informed consent separately.

Patients

The selected patients for reassessment in this study were treated in nine Dutch referral centres for rectal cancer treatment with an expertise in TEM surgery. Patients with a histologically proven rectal cancer, staged cT1–3 N0 and located within the distal 10 cm of the rectum were evaluated for inclusion. All patients were treated between December 2010 and June 2017 and were scheduled for an organ-preserving treatment consisting of neoadjuvant CRT with a prolonged interval (≥5 weeks) to surgery. Patients were included if initial as well as restaging clinical endoscopy images and/or reports and MRI examinations were available. Exclusion criteria were (1) no availability of clinical investigations, (2) no TEM resection, (3) no DWI at restaging MRI, (4) use of endorectal gel as MRI intra-luminal contrast, (5) insufficient image quality or (6) presence of poor prognostic factors such as tumour budding, extramural venous invasion or lymphovascular invasion. Patients were analysed prospectively with standard investigations according to the guidelines for rectal cancer treatment [23].

Treatment regimen

Chemoradiotherapy consisted of a total dose of 50 or 50.4 Gy given in 25 fractions of 2 Gy or in 28 fractions of 1.8 Gy, respectively, with concomitant capecitabine 825 mg/m^2 twice daily on all days. Restaging examinations were performed with a preferred interval of 6–16 weeks after completion of (C)RT. Residual tumour or scar tissue was removed by performing a TEM procedure with a preferred maximum interval of 8 weeks after restaging.

Clinical reassessment

In this study, the main outcome was the predictive value of (1) endoscopy alone, (2) (DWI-)MRI alone and (3) a multimodal approach for

response assessment after neoadjuvant CRT. The predictive value of DRE was not part of the analysis. The endoscopic and MRI readers selected for reassessment were not the patients' treating clinicians and thus DRE was not incorporated in the reassessment. For endoscopic, (DWI-)MRI reassessment and/or multimodal reassessment, availability of pre- and post-CRT images was essential. For the endoscopic reassessment, the images of the restaging endoscopy had to be available from the treating hospitals. For the MRI only cohort as well as for the multimodal reassessment cohort, at least the MRI images had to be available from the treating hospitals. For the multimodal approach, endoscopic images or endoscopic reports had to be available, so non-availability of endoscopic images was not an exclusion criterion for this analysis. In the case of incomplete data, patients were excluded from (one of the) cohort analyses. As a result, some patients could be included in either one reassessment cohort or in the case of all available data in all reassessment cohorts (endoscopy alone, (DWI-)MRI alone and multimodal reassessment).

Clinical assessment: endoscopy cohort

Endoscopy was used in the clinical setting to determine the location of the tumour, reveal residual tumour, white scar, erythematous ulcer or any form of irregular wall thickening. Endoscopic ultrasound was not a standard part of the evaluation. Endoscopic images were presented to five colorectal surgeons with endoscopic experience (SB, GB, AB, EdG, HdW). The surgeons performed a re-evaluation blinded to histopathological data by using a score form including the following tumour characteristics: (1) elevated tumour tissue, (2) residual ulcer, (3) flat scar, (4) telangiectasia and (5) adenomatous residual tissue. Response assessment to neoadjuvant treatment was performed with the following five point confidence level scores: (1) complete response, (2) complete response is likely, (3) not sure of a complete response, (4) complete response is not likely and (5) not a complete response.

Clinical assessment: (DWI-)MRI cohort

MRI was clinically used for locoregional (re)staging of the tumour, nodal status and potential involvement of the mesorectal fascia. All MR examinations were performed according to local clinical protocols, using a 1.5 or 3 T MRI scanner. MRI consisted of axial, coronal and sagittal T2W images with additional axial DWI. The para echo planar imaging sequence was acquired in an axial plane, perpendicular to the tumour bed, identical to the angle of the T2W axial scans at *b* values of 0, 800, 1000 s/mm and 5 mm thickness. Patients received antispasmodic medication prior to the MRI examination unless a contraindication was present. No enema was given prior to MRI examination.

All MRI images, primary as well as the restaging datasets, were separately reviewed and revised by an expert radiologist (R.B.T.) with 20 years of experience in abdominal MRI. The reader was blinded to clinical, histopathological data and to endoscopic findings of both the local surgeon and the surgeons in the study. A standardized scoring form, based on European Society of Gastrointestinal and Abdominal Radiology guidelines, was used for revision of available primary and restaging MR datasets [24]. The re-evaluation focused on clinical T and N staging, tumour size diameter, location and morphological characteristics as well as extramural depth. On restaging (DWI-)MRI, the percentage of tumour size regression, absence or presence of residual tumour and/or fibrosis were evaluated, using five point confidence level scores.

Clinical assessment: multimodal reassessment using endoscopy and (DWI-)MRI

Directly after the MRI response reporting session the restaging endoscopy reports of the local hospitals including endoscopic images were shown to the expert abdominal radiologist while the (DWI-)MRI restaging images were still available to evaluate the additional value of (DWI-)MRI to endoscopy. By doing so, the radiologist was able to provide a multimodal response assessment by combining (DWI-)MRI with endoscopic information focusing on absence or presence of residual tumour using five point confidence level scores.

Histopathology

Histopathology of the TEM resection specimens was used as reference standard for the clinical reassessments. TEM specimens were evaluated by colorectal pathologists from participating centres according to the method described by Quirke et al. [25]. A tumour regression grading scale was not consistently used. Since only TEM resections were available for histological evaluation, only T stage was used as a reference for response evaluation. A ypT0 tumour was considered a complete response, any other ypT stages as residual tumour.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 22. The main outcome was the predictive value of endoscopy alone, (DWI-)MRI alone and (DWI-)MRI combined with endoscopy. Sensitivity and specificity rates were provided for all three approaches. Sensitivity and specificity were presented with the areas under the receiver operating characteristic (ROC) curve (AUC) based on the five point confidence level scores used. A dichotomous parameter of the assessment was then used to calculate sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values, dividing the response assessment into clinical CR and no CR (score 1–2 vs. score 3–4–5 of the five point confidence level scores, respectively). Baseline data were retrieved for all patients. Nominal data are presented as absolute frequencies and percentages. Nominal and ordinal values are presented in two-way contingency tables, with *P* values ≤0.05 considered to be statistically significant. Discrepancies regarding T and N staging of the tumours

between the data of the treating hospitals and the findings of the expert radiologist could occur but had no influence on the inclusion or exclusion of patients. Agreement in evaluating endoscopic images was calculated using the Fleiss kappa value (agreement was poor if $\kappa \leq 0.20$, fair if $0.21 \leq \kappa \leq 0.40$, moderate if $0.41 \leq \kappa \leq 0.60$, substantial if $0.61 \leq \kappa \leq 0.80$, good if $\kappa > 0.80$). Pathological complete response rates were given to provide an insight into the potential for downstaging of (C)RT in early rectal cancer.

RESULTS

Seventy-seven patients were identified as potentially eligible for endoscopic evaluation, (DWI-)MRI evaluation or multimodal assessment. The patient flowchart is displayed in Figure 1. A total of 44 patients were included for one or more of the reassessment cohorts. This led to two patient cohorts for three reassessment cohorts: 36 patients for the endoscopic re-evaluation and 25 patients for either the (DWI-)MRI re-evaluation or for the multimodal reassessment. Patients were excluded for the following reasons: unavailable endoscopic images ($N = 26$), incomplete MRI datasets ($N = 35$), LARC ($N = 10$), initial watch-and-wait strategy ($N = 3$), recurrent disease ($N = 2$) or use of endorectal gel ($N = 2$). Clinical data of the local hospitals and baseline patient characteristics are shown in Table 1, in which the assessment groups are separately described. All patients received neoadjuvant CRT prior to TEM surgery. Histopathological findings of the TEM specimens are presented in Table 2.

Endoscopy images available for 36 patients were taken after a median interval of 6 (range 4–10) weeks after the final dose of (C)RT. TEM resection in this cohort was performed after a median 3 (range 1–9) weeks after endoscopy. Table 3 shows the parameters scored during endoscopic re-evaluation of the five surgeons. Agreement for scoring the endoscopic features between all readers was moderate for elevated residual tumour ($\kappa = 0.551$), fair for residual ulcer

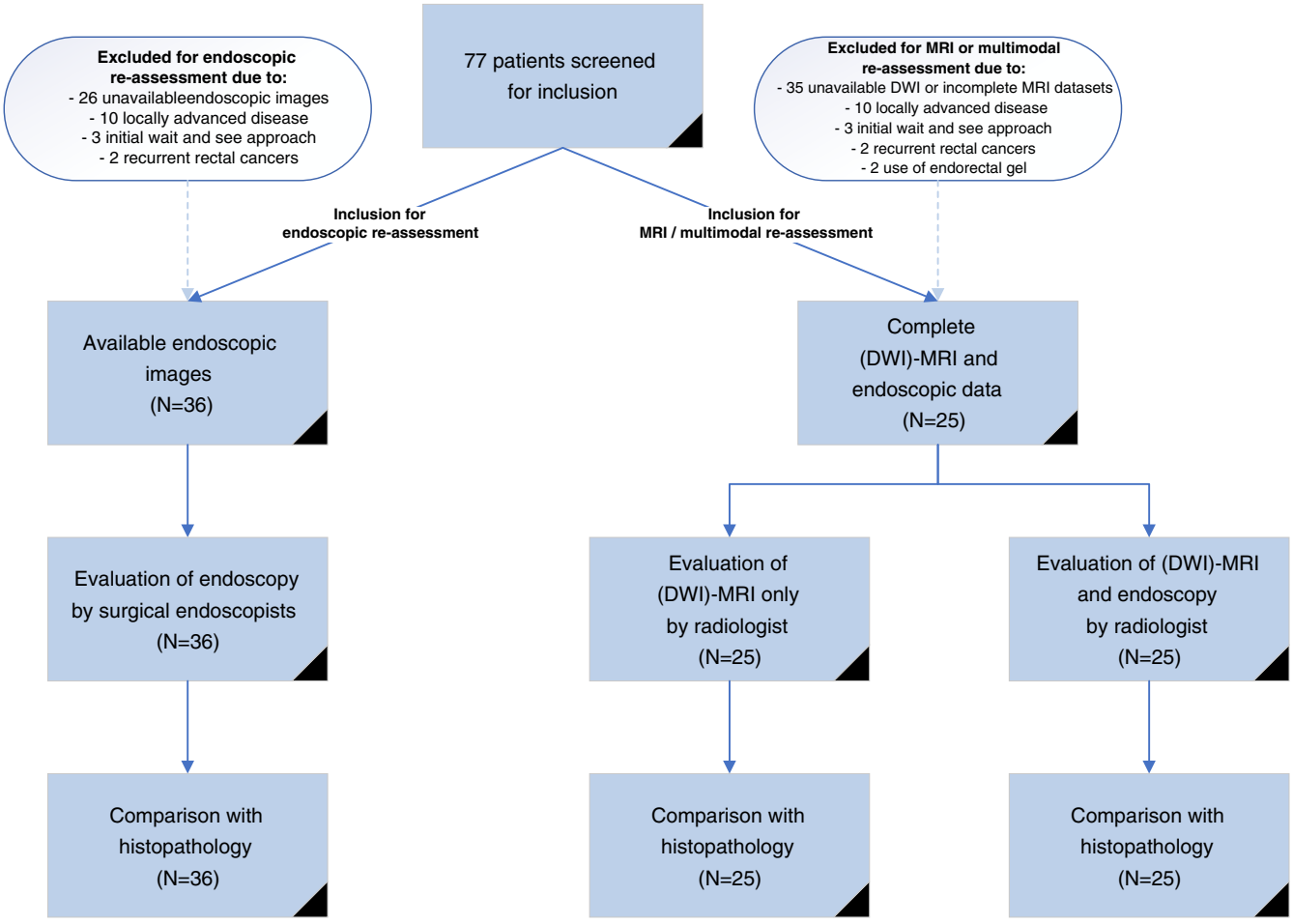


FIGURE 1 Flowchart of the included patients. The 77 potentially eligible patients consisted of 55 patients of the CARTS study and 22 patients from the Laurentius Hospital who were treated with a similar treatment scheme. Of the 77 potentially eligible patients, 36 patients had available endoscopic images pre- and post-CRT which could be used for endoscopic re-evaluation (left column). Twenty five patients had available (DWI-)MRI images for MRI response assessment (middle column). For the multimodal response assessment, 25 patients had available (DWI-)MRI images as well as available endoscopic data (right column). This led to two patient cohorts for three separate reassessment cohorts. Reasons for exclusion for the endoscopic cohort are mentioned in the above left box; reasons for exclusion for the MRI only cohort and the multimodal cohort are mentioned in the above right box.

TABLE 1 Baseline characteristics (before re-evaluation by experienced abdominal radiologist) of the patients based on the two subgroups endoscopic and (DWI-)MRI re-evaluation

	Patients with available endoscopy images	Patients with available MRI datasets and endoscopy reports
Baseline characteristics	**Patients (*N* = 36)**	**Patients (*N* = 25)**
Sex		
Male	19	12
Female	17	13
Mean age (SD)	66 (46–83)	64 (45–82)
cT stage		
cT1–2	26	18
cT3a,b	10	7
cT3c,d	0	0
cT4	0	0
cN stage		
cN0	36	25
cN1	0	0
Neoadjuvant therapy		
Short course radiotherapy (25 Gy)	0	0
Chemoradiotherapy (50.0–50.4 Gy)	36	25
Type of chemotherapy (%)		
Capecitabin	36 (100%)	25 (100%)
Surgical procedure		
Transanal endoscopic microsurgery	36 (100%)	25 (100%)
Interval neoadjuvant treatment—restaging (weeks)	6 (4–10)	6 (4–12)
Interval restaging—surgery (weeks)	3 (1–9)	3 (1–11)

TABLE 2 Histopathology characteristics of the two subgroups

Pathological characteristics		
	Endoscopic cohort	**(DWI-)MRI cohort**
Pathology findings	**Specimens (*N* = 36)**	**Specimens (*N* = 25)**
Histology		
No tumour found	13	7
Villous adenoma	3	4
Adenocarcinoma	20	14
Differentiation grade		
Well differentiated	23	14
No malignant cells	13	11
Mean size of specimen (SD)	3.8 (1.2)	3.7 (1.2)
Mean size of lesion (SD)	1.0 (0.8)	1.4 (1.3)
ypT stage		
ypT0	16	11
ypT1	7	8
ypT2	13	6
ypN stage		
ypN0	35	25
ypN1	1	0
Lymph nodes harvested	2	2
Radical TEM resection		
R0	36	25
R1	0	0

Abbreviation: TEM, transanal endoscopic microsurgery.

(κ = 0.281), fair for flat scar (κ = 0.225), poor for telangiectasia (κ = 0.170), fair for adenomatous residual tissue (κ = 0.305), poor for overall response assessment (κ = 0.198) and moderate for complete response assessment (κ = 0.581). Endoscopic evaluation performed by each of the five surgeons was accurate for assessing the response in 24 (67%), 22 (61%), 25 (69%), 26 (72%) and 26 (72%) of the total of 36 patients, respectively. The ROC curves together with AUC for assessing a cCR are displayed in Figure 2A together with all diagnostic accuracy parameters.

Restaging MRI examinations of the 25 patients were performed with a median interval of 6 (range 4–12) weeks after neoadjuvant treatment. TEM resection was performed a median of 3 (range 1–11) weeks after MRI examination. At initial pre-treatment staging, the mean tumour diameter was 2.6 ×2.4 mm measured in two dimensions (sagittal–axial). All MRI datasets were re-evaluated by the radiologist, primary as well as response assessment. Tumours were initially staged by the radiologist as follows: 23 cT1–2 N0 and two cT1–2 N1. No patient had an involved/threatened mesorectal fascia. The restaging MRI datasets showed a tumour volume reduction of >75% in 23/25 of the tumours with a mean tumour diameter after CRT of 0.3 ×0.4 cm (sagittal–axial; P <0.001). Residual tumour on T2W-MRI was detected in 5/25 of the patients, with visible fibrosis in all but one patient. Fifteen tumours were restaged as ycT0 N0 and 10 tumours as ycT1–2 N0 (Table 4). Sensitivity and specificity rates of assessing a cCR using (DWI-)MRI only was 72.7% and 42.9% (PPV 50.0%, NPV 66.7%) and improved to 90.9% and 75.0% (PPV 71.4% and NPV 90.9%) using (DWI-)MRI together with clinical endoscopy findings, respectively. ROC curves together with AUC for (DWI-)MRI with and without endoscopy findings are displayed in Figure 2B. Examples of a clinical complete response on MRI and at endoscopy (Part I) and a clinical response on MRI but not at endoscopy (Part II) are displayed in Figure 3.

As a result of the intentional organ-preserving approach all included patients in the three reassessment cohorts (N = 44) underwent TEM after CRT. In the case of a pT2, an irradical resection or the

TABLE 3 Endoscopic features scored by the colorectal surgeons

Patients with available endoscopy images						
Evaluated by five experienced surgical endoscopists						
	Surgeon 1	**Surgeon 2**	**Surgeon 3**	**Surgeon 4**	**Surgeon 5**	**κ value[a]**
Elevated residual tumour						
None	22	20	17	23	16	0.551
Small amount of residue	10	8	12	9	12	
Big amount of residue	4	8	7	4	8	
Residual ulcer						
None	27	32	29	26	12	0.281
Small ulcer	7	1	3	4	12	
Big ulcer	2	2	3	2	9	
Ulcer with elevated edges	0	1	1	4	3	
Flat scar						
None	20	22	17	12	26	0.225
White scar	8	5	6	5	7	
White scar with fair amount of redness	7	0	8	9	1	
Red scar	1	9	5	10	2	
Telangiectasia						
No	14	16	31	27	29	0.170
Yes	22	20	5	9	7	
Adenomatous residual tissue						
None	20	22	13	24	14	0.305
Possible	10	6	20	7	19	
Evident	6	8	3	5	3	
Overall response assessment						
A complete response	6	4	4	9	6	0.198
A complete response is likely	11	7	6	8	5	
Maybe a compete response	7	4	10	11	2	
A complete response is not likely	8	4	9	4	13	
No complete response	4	17	7	4	10	

[a]Calculated using the Fleiss kappa.

presence of risk factors a completion TME was recommended. Four patients with a ypT2 tumour underwent completion TME without evidence of residual tumour. Eleven patients refused completion TME. Based on pathological staging, 67% of the patients (30 of the 44 included patients with a ypT0–1 after TEM) were successfully treated with the organ-preserving approach.

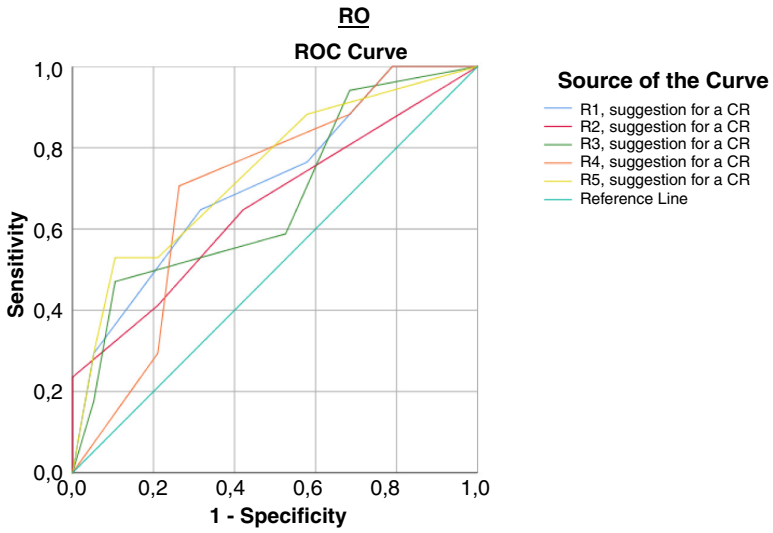
DISCUSSION AND CONCLUSIONS

In the present study, both a single and multimodality approach were evaluated for the assessment of response after a median interval of 6 weeks after completing neoadjuvant CRT in early rectal tumours (cT1–3 N0). Great interobserver variations were shown in assessing endoscopic specific features alone. Endoscopy on its own performed by five expert colorectal surgeons was with an AUC of 0.66–0.74 superior to (DWI-)MRI by an expert radiologist for the assessment of complete response, but the highest accuracy can be achieved with the combination of (DWI-)MRI with endoscopy. In almost all cases, the two modalities complemented each other. The main pitfall was false-negative assessments due to microscopic residual disease within the irradiated tumour bed without any visible residual disease at endoscopy or MRI.

Literature on response assessment in rectal cancer patients after CRT using endoscopy alone or endoscopy combined with other modalities is scarce and focuses predominantly on LARC after chemoradiation. For restaging LARC patients, the most reliable information on response evaluation is obtained by combining (DWI-)MRI, endoscopy and DRE with a diagnostic AUC of 0.89 [21]. Recent studies showed similar diagnostic performances for the assessment of pCR

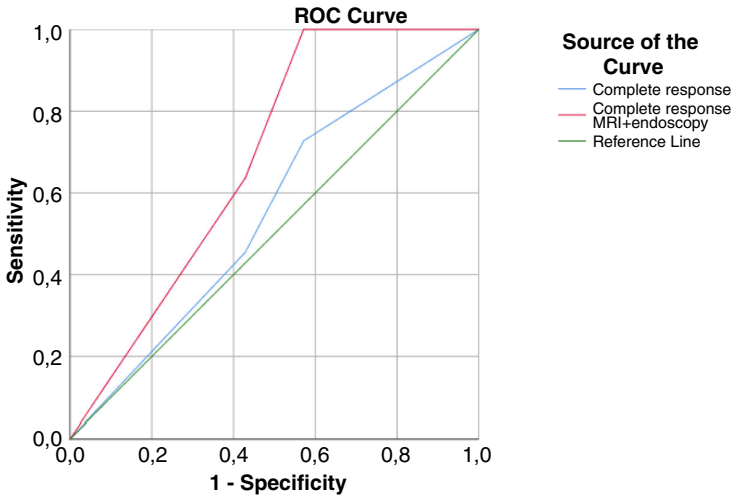
FIGURE 2 (A) Area under the curve for the prediction of complete response ($N = 36$) performed by five experienced surgical endoscopists. (B) Area under the curve for predicting a complete response using (DWI-)MRI only and (DWI-)MRI plus endoscopic reports.

(A)



Surgeon	AUC (95% CI)	PPV	NPV	Sensitivity	Specificity
1	0.714 (0.545-0.882)	64.7%	68.4%	64.7%	68.4%
2	0.656 (0.475-0.838)	63.6%	60.0%	41.2%	78.9%
3	0.672 (0.493-0.851)	80.0%	65.4%	47.1%	89.5%
4	0.701 (0.526-0.877)	70.6%	73.7%	70.6%	73.7%
5	0.741 (0.578-0.905)	81.8%	68.0%	52.9%	89.5%

(B)



	AUC (95% CI)
(DWI-)MRI only	0.552 (0.322-0.782)
(DWI-)MRI plus endoscopy	0.682 (0.471-0.893)

in LARC patients with a diagnostic accuracy of 90% when combining both modalities [26, 27]. When comparing these accuracies with the current study outcomes, these good diagnostic outcomes can be translated to tumours of an earlier stage which are treated with similar neoadjuvant treatment regimens.

Endoscopic assessment by five surgical endoscopists after CRT resulted in mean sensitivity and specificity rates of 54.5% and 79.1%, respectively. Comparing with (DWI-)MRI assessed by an expert radiologist, endoscopic evaluation by experienced surgeons performs equally well [28]. Endoscopic information is essential for detection of mucosal abnormalities, which can vary widely after CRT. White scar tissue (with or without telangiectasia) or normalized mucosa after irradiation has been suggested to represent a complete response. Other residual superficial ulceration or mucosal irregularity must alarm the observer for potentially viable tumour, but can still be a good responder with a tumour in remission [29, 30]. Moreover, according to the current study there is variation in interpretation of endoscopic findings. Despite certain variations in interpretation, endoscopic evaluation by expert surgical endoscopists in the current study was able to select good responding tumours after CRT sufficiently when accepting an underestimation of complete responders.

The complementary effect of the two modalities was well demonstrated in the present study. (DWI-)MRI misdiagnosed tumours after CRT in eight out of 25 cases, but accuracy was considerably enhanced by the addition of endoscopic information of the local surgeon mainly by upstaging the tumour remnant. In only one case, the (DWI-)MRI was negatively influenced by the addition

TABLE 4 MRI parameters for the re-evaluation of primary and restaging (DWI-)MRI performed by the abdominal radiologist

Patients with available MRI datasets and endoscopy reports				
Evaluated by one experienced abdominal radiologist				
MRI 1—Pre-CRT	**Patients (*N* = 25)**	**MRI 2—Post-CRT**	**Patients (*N* = 25)**	***P* value**
Mean sagittal tumour diameter (SD)	2.6 (1.1)	Mean sagittal tumour diameter (SD)	0.3 (0.6)	<0.001 (*t* test)
Mean axial tumour diameter (SD)	2.4 (1.0)	Mean axial tumour diameter (SD)	0.4 (0.7)	<0.001 (*t* test)
		Mean distance to anorectal junction		
Mean distance to anorectal junction	2.5 (1.8)	Not consequently scored	0.5 (0.8)	NA
MRF free	25	MRF free	25	1.000
Location of the tumour				
Anterior	8	Anterior	8	
Posterior	7	Posterior	7	
Right lateral	2	Right lateral	3	
Left lateral	1	Left lateral	1	
Anterolateral right	1	Anterolateral right	1	
Anterolateral left	2	Anterolateral left	2	
Posterolateral right	1	Posterolateral right	1	
Posterolateral left	2	Posterolateral left	2	–
Histology		Residual tumour T2		
Adenocarcinoma	24	Yes	5	
Mucinous carcinoma	1	No	20	–
Morphology		Fibrosis		
Annular	12	Yes	24	
Polypoid	12	No	1	–
Sessile	1	Volume reduction		
Ulcerative	0	>75%	23	-
Perforated	0	<75%	2	
cT stage		ycT stage		
cT0	0	ycT0	15	
cT1–2	25	ycT1–2	10	
cT3a,b	0	ycT3a,b	0	
cT3c,d	0	ycT3c,d	0	0.444 (χ^2)
cN stage		ycN stage		
cN0	23	cN0	25	
cN1	2	cN1	0	
cN2	0	cN2	0	-
Number of nodes				
Suspicious	4	Suspicious	0	0.078 (*t* test)
Total	85	Total	41	0.05 (*t* test)

Abbreviations: CRT, chemoradiotherapy; MRF, mesorectal fascia.

of endoscopy. (DWI-)MRI evaluation by an expert radiologist is supplemented by local endoscopic findings, resulting in the most accurate post-CRT assessment of pCR with good PPV and high NPV. (DWI-)MRI is known to be most reliable in confirming residual tumour [31]. In some cases, both endoscopy and (DWI-)MRI missed residual disease but these were cases with only microscopic disease scattered in the fibrosis within the irradiated rectal wall. Whether these residual lesions are tumours in remission or residual disease that will progress to recurrent disease remains to be seen on long-term follow-up.

An adequate interval between neoadjuvant treatment and restaging the disease plays an important role in determining adequate treatment. It has been shown that pCR rates increase when exceeding the classical interval of 6–8 weeks after neoadjuvant treatment, without compromising surgical or oncological outcomes [32, 33]. Translating this to multimodality reassessment, residual mucosal abnormalities 6–8 weeks after CRT may still evolve and eventually turn into a complete response [34]. Therefore, when restaging early tumours after neoadjuvant treatment, one should not focus on a single observation but consider clinical findings in relation to initial staging and its time interval.

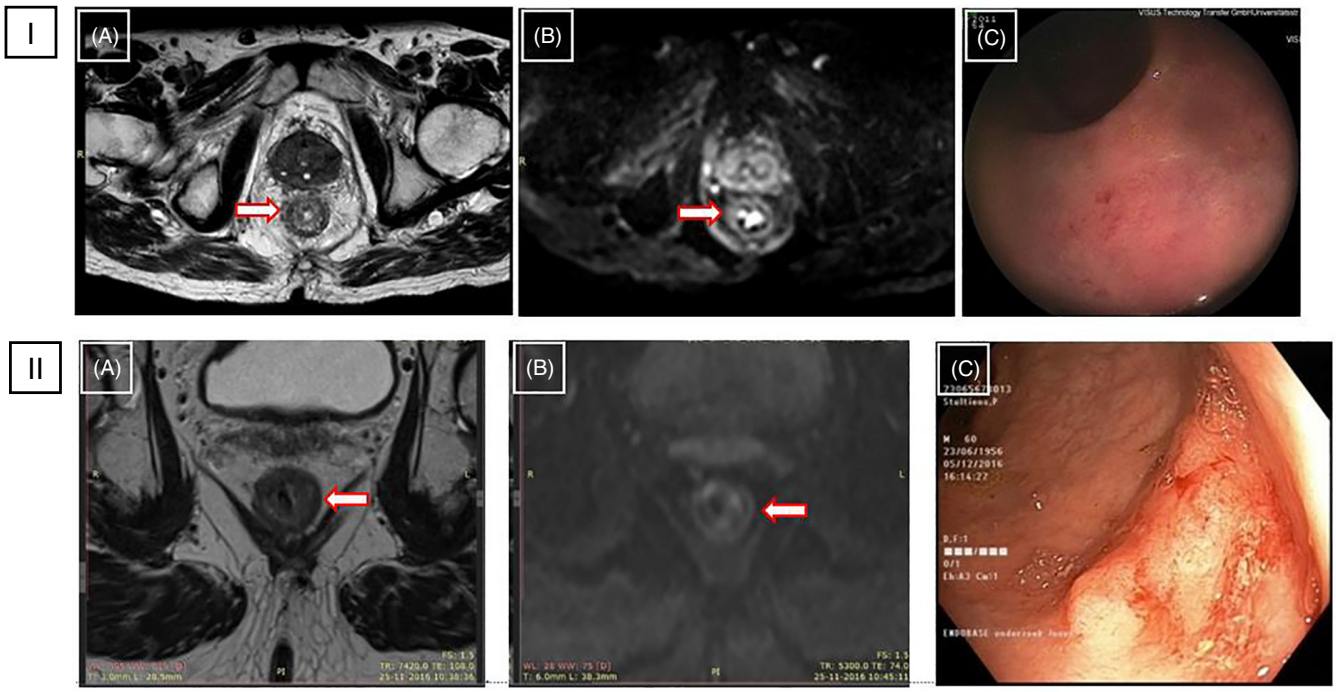


FIGURE 3 (I) Example of a tumour staged as a definite clinical complete response on T2-weighted MRI (A), DWI-MRI (B) and on endoscopy (C) which was confirmed by histopathology. (II) Example of a tumour staged as a clinical complete response on T2-weighted (A) and DWI-MRI (B), but on endoscopy (C) with a residual lesion which was confirmed as a ypT2 tumour on histopathology.

In general, early rectal tumours in the present study responded well to neoadjuvant CRT with a pCR rate of 42%. This is in line with available literature showing pCR rates after neoadjuvant treatment in early rectal cancer patients varying between 18% and 48% [14, 22, 35, 36]. These patients would have been eligible for a watch-and-wait strategy, which was not chosen in the present series. The majority of the tumours showed a reduction of tumour volume on MRI of more than 75%, which suggests that good response to treatment is occurring. Based on the results of this study, the combination of endoscopy and (DWI-)MRI enables assessment of tumour regression and complete response and can be used to select a group in which it appears safe to wait. Although it was not the goal of the current study, the results of our study suggest that a multidisciplinary team approach of a team consisting of experts would lead to the most reliable performance in selecting patients with a complete response.

This leads the discussion further on what to do after reassessment of the irradiated early rectal cancer with a clinical good or complete response. One may choose immediate local excision thereby saving the rectum and harvesting more (histological) information about the tumour, but probably also causing discomfort and some loss of function [15, 16]. Previous rectal preserving studies demonstrated good oncological outcomes after local excision, but functional outcomes might be better when local surgery can be avoided [8, 37]. Therefore, time can also be a good diagnostic tool, and good responders can be followed up and reassessed at a later stage. The non-responding tumours can usually be identified in time for TME surgery. This suggests that, when aiming for a rectal preserving strategy in early rectal cancer patients, a restaging protocol with standard evaluation interval after 6–8 weeks post-neoadjuvant treatment can also be performed merely to distinguish good from bad responders. When a good responder or a potential complete responder is identified, no direct (local) intervention is needed and further response can be awaited [38]. A second restaging moment at least 6 weeks later may then be used to definitely opt for either watch-and-wait, local excision or completion TME which should be endorsed by an expert multidisciplinary team [39].

The current study has some limitations. It was a challenge to collect available clinical examinations from patients treated with this organ-preserving treatment due to the long inclusion period. Fortunately, two overlapping cohorts were available for the evaluation of response assessment. The external validity of the study needs confirmation: the (DWI-)MRI images were evaluated by an expert in the field of restaging rectal cancer. It is unclear whether the performance of these evaluations can be extrapolated to any other radiologist who works in the field of abdominal or colorectal imaging. For endoscopic evaluation, not all primary endoscopy images were available, which made it more difficult to evaluate the response after neoadjuvant treatment. The endoscopic data were assessed by surgeons looking at images of lesions instead of in real time which would be more accurate. As with the radiological evaluation, the external validity is to be confirmed.

To conclude, the current study shows that a multimodality approach in expert hands combining endoscopy for intra-luminal and (DWI-)MRI for extra-luminal evaluation of any residual disease provides the best

available information to identify good and complete responders after irradiation of early stage rectal cancer. The addition of (DWI-)MRI to endoscopy was especially helpful to improve the selection of patients who are potentially eligible for organ-preserving treatment.

AUTHOR CONTRIBUTIONS

All authors contributed to this paper with either conception and design of the study, literature review and analysis, drafting and critical revision and editing, or final approval of the final version.

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CONFLICT OF INTEREST

No conflicts of interest.

ETHICS APPROVAL

The study was approved by the medical ethical committee of the Radboud Medical Centre Nijmegen, The Netherlands. Permission to reproduce material from other sources.

INFORMED CONSENT

All patients provided written informed consent.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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