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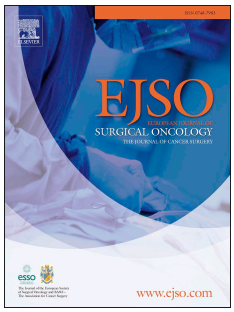

Response assessment after (chemo)radiotherapy for rectal cancer: Why are we missing complete responses with MRI and endoscopy?

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Title

Response assessment after (chemo)radiotherapy for rectal cancer: why are we missing complete responses with MRI and endoscopy?

ABSTRACT

Purpose: To evaluate what features on restaging MRI and endoscopy led to a false clinical diagnosis of residual tumour in patients with a pathological complete response after rectal cancer surgery.

Methods: Patients with an 'unrecognized' complete response after (chemo)radiotherapy were selected in a tertiary referral centre for rectal cancer treatment. An 'unrecognized' complete response was defined as a clinical incomplete response at MRI and/or endoscopy with a pathological complete response of the primary tumour after surgery. The morphology of tumour bed and lymph nodes were evaluated on post-CRT T2-weighted MRI (T2-MRI) and diffusion weighted imaging (DWI). Post-CRT endoscopy images were evaluated for residual mucosal abnormalities. MRI and endoscopy features were correlated with histopathology.

Results: Thirty-six patients with an unrecognized complete response were included. Mucosal abnormalities were present at restaging endoscopy in 84%, mixed signal intensity on T2-MRI in 53%, an irregular aspect of the former tumour location on T2-MRI in 69%, diffusion restriction on DWI in 51% and suspicious lymph nodes in 25%.

Conclusions: Overstaging of residual tumour after (chemo)radiotherapyin rectal cancer is mainly due to residual mucosal abnormalities at endoscopy, mixed signal intensity or irregular fibrosis at T2-MRI, diffusion restriction at DWI and residual suspicious lymph nodes. Presence of these features is not definitely associated with residual tumour and in selected cases an extended waiting interval can be considered.

KEYWORDS

Rectal cancer; Organ preservation; Complete response; Magnetic Resonance Imaging; Endoscopy

INTRODUCTION

Fifteen to twenty percent of patients with rectal cancer present with a pathological complete response (pCR) after chemoradiotherapy (CRT) and total mesorectal excision (TME) [1]. TME is associated with substantial morbidity and mortality and therefore the need for major surgery is questioned in good and complete responders. Moreover, it has raised interest in organ-preserving alternatives to major surgery, such as a local excision in near complete responders or a watch-and-wait policy in complete responders [2-6].

Selection of patients who may benefit from organ preservation requires an accurate identification of complete responders. Main tools for response assessment have included clinical assessment with digital rectal examination, endoscopy and biopsy, and imaging such as MRI and endorectal ultrasound [4, 5, 7]. However, when used individually, none of these techniques are able to accurately predict pCR after CRT, due to overestimation of residual tumour [8-10]. The combined use of these techniques increases the diagnostic accuracy [11]. It is currently recommended to combine digital rectal examination, endoscopy and MRI (including diffusion weighted imaging (DWI)) [11]. This strategy is aimed at minimizing the risk of missing residual tumour and therefore minimizing the risk of undertreating patients. Mainly patients with a typical clinical complete response, fulfilling strict selection criteria that include whitening of the mucosa with teleangiectasia and mucosal integrity on endoscopy combined with absence of luminal and nodal disease on (DWI-)MRI, are considered for organ preservation [11, 12]. However, due to these strict criteria up to 30% of the complete responders are not recognized at clinical response assessment, with the consequence that these patients undergo major surgery while organ preservation could be a possibility [11, 13]. In order to reduce the number of unrecognized complete responders it is important to see what we can learn from these unrecognized complete responders. Specifically, we should evaluate whether there are distinct features on MRI and endoscopy that lead to the false diagnosis of residual tumour at response assessment, so that these pitfalls may be used as a teaching reference and to optimise the identification of complete responders in the future. Therefore, the aim of this study was to evaluate what features on restaging MRI and endoscopy led to a false diagnosis of residual tumour in patients with a pathological complete response after rectal cancer surgery.

PATIENTS AND METHODS

The need for informed patient consent was waived by the institutional ethics review board due to the retrospective nature of this study. This study was performed in a referral centre for organ preservation in rectal cancer (Maastricht University Medical Centre, Maastricht, the Netherlands), where restaging after neoadjuvant treatment was routinely performed. In our centre, all patients with a complete clinical response are offered organ preservation, and patients with an incomplete clinical response are offered standard treatment with resection. Criteria for a clinical complete response have been described previously [14]. However, some patients with an incomplete clinical response showed pathological complete response after resection, and could be considered 'unrecognized' clinical complete responses. These patients were included in the present retrospective study, providing they met the following inclusion criteria: (1) biopsy proven primary rectal cancer, (2) treatment with surgery after either a long course of CRT or a short course of radiotherapy (5x5Gy) followed by a prolonged waiting interval, between July 2006 and December 2015, (3) availability of restaging MRI (and endoscopic) examinations for response assessment after neoadjuvant treatment, and (4) complete response of the primary tumour at histopathology after surgery (ypT0). Referred patients had surgery in their primary hospital. Patients were excluded if they had surgery for persisting symptoms (e.g. obstructive stenosis).

Restaging MRI was routinely performed and available for all study patients. Until 2012, endoscopy was only performed upon indication (i.e. in case of a good response on imaging). From 2012 on, endoscopy was routinely performed as part of the response assessment in all patients.

Re-evaluation of MRI

All MR imaging was performed with a 1.5T system (Intera (Achieva) or Ingenia, Philips Medical Systems, Best, The Netherlands) using a phased array body coil. Sequences included T2-weighted MRI and diffusion-weighted MRI. Detailed sequence parameters of the sequences used during the study period are provided in the **Supplementary File 1**. The primary staging MRIs performed before treatment were also at the reader's disposal. Images were analysed by a single expert radiologist (M.M.) with 8 years of experience in reading rectal cancer MRI. As this study aimed at identifying features leading to unrecognized complete response and not at assessing diagnostic performance to assess response, the reader was aware that all patients had a pathological complete response in the resected specimen.

The following features were evaluated on the restaging T2-weighted images: signal intensity of the tumour bed, pattern of fibrosis, presence of rectal wall oedema, EMVI and lymph node morphology. The signal intensity of

the tumour bed was scored to be either hypo-intense or consisting of mixed signal intensity. Pattern of fibrosis was scored as normalised rectal wall, minimal fibrosis, or regular/irregular full-thickness fibrosis [15]. **Figure 1** shows examples of the MRI features that were evaluated. Lymph node morphology was assessed by evaluating the border, contour, the signal intensity heterogeneity of the nodes and the presence of fibrosis within the nodes. Examples of irregular nodes are shown in **Figure 2**.

On restaging DWI-MRI, the presence and distribution (focal or diffuse) of diffusion restriction (high signal intensity on b1000 DW-images and corresponding low signal on the apparent diffusion coefficient maps) within the tumour bed were recorded.

Re-evaluation of endoscopic images

Endoscopy with a flexible endoscope was performed after a phosphate enema, by one of six surgeons who were specialized in endoscopic response assessment. The digitally stored endoscopy images (white light images only) were re-evaluated for this study by a single experienced surgeon (G.B.) with 12 years of experience in restaging endoscopy. The presence of a white scar, a flat ulcer, a deep ulcer with irregular borders, polypoid tissue or gross tumour mass was scored. Examples of these endoscopic findings are shown in **Figure 3**. If biopsies were taken at the time of endoscopy, results were also provided to the reader and taken into account during scoring. Similarly to MRI, the reader was aware that all patients had a pathological complete response in the resected specimen.

Correlation with histopathology

Surgical specimens were assessed according to international guidelines [16]. The histopathology reports of the surgical specimens were reviewed to correlate histopathology features with MRI and endoscopic features. The presence of the following histopathologic features were scored: dysplasia, inflammation, fibrous tissue, acellular mucin, ulceration or calcifications. Examples of these histopathological findings can be found in the **Supplementary file 2**.

Statistical analysis

Statistical analyses were performed with SPSS Statistics 22 (IBM, Armonk, NY). Baseline data were collected for all patients and included age, sex, baseline clinical staging, neoadjuvant therapy, type of surgical procedure and histopathological staging. Descriptive statistics were calculated for the baseline characteristics and MRI, endoscopic and histopathologic features.

RESULTS

Study population

Thirty-nine rectal cancer patients with pathological complete response of the primary tumour (ypT0) after surgery were considered for inclusion. Three patients were excluded because they had an indication for surgery irrespective of the clinical response of the tumour for the following reasons: stenosis, incontinence and rectal stent. In total, 36 patients were included (24 men, 12 women; mean age at diagnosis 64 ± 13 years, for details see **Table 1**). Of the 36 patients, 8 patients had nodal metastases at histopathology (7 ypN1, 1 ypN2). These patients are separately described on their lymph node assessment below. The median interval from completion of (chemo)radiotherapy to response assessment was 8 weeks (IQR 8-17 weeks). Median interval from response assessment to resection was 28 days (IQR 15-36 days). Twenty (56%) patients underwent low anterior resection, 13 (36%) patients had an abdominoperineal resection and 3 (8%) patients had a full-thickness local excision. The 3 patients with local excision all had a disease-free follow-up of > 3 years, and are therefore considered to be ypT0N0.

T2-weighted MRI

Overall, in 26 (78%) patients features of residual luminal tumour were present on the restaging T2-weighted MRI. Mixed signal intensity was present in 19 (53%) patients. Full-thickness or irregularly shaped fibrosis was seen in 25 (69%) patients. EMVI was recorded in 3 (8%) of the patients and oedema in 17 (47%) patients.

Diffusion-weighted MRI

In 33 out of 36 patients a DWI sequence was available. Sixteen (49%) patients showed no residual diffusion restriction. In the remaining 17 patients, either focal diffusion restriction (n=14, 42%) or diffuse diffusion restriction (n=3, 9%) was found at re-evaluation.

Endoscopy

Restaging endoscopy was performed in 19 (53%) of the 36 patients. Only 3 patients (16%) presented with a flat scar without mucosal abnormalities. Polypoid tissue was present in 4 (21%) patients, a flat ulcer in 5 (26%) patients, an ulcer with irregular borders in 6 (32%) patients and gross residual tumour was present in 1 (5%) patient. Biopsies were taken in 10 patients. In 4 patients, this led to a suspected residual tumour: 3 patients showed high grade dysplasia and one biopsy adenocarcinoma, while in the resection specimen no adenocarcinoma was found in any of these patients.

Lymph nodes

In the 28 patients with ypT0N0, suspected residual mesorectal nodal metastasis was present in 7 (25%) patients, these nodes showed fibrosis and/or a spiculated border. In the 8 patients with ypT0N+, 5 (71%) patients also showed a fibrotic appearance or spiculated border of their nodes.

One of the patients with ypT0N0 showed a suspicious extramesorectal node in the right obturator area at MRI and underwent a TME resection with removal of the lateral node. The lateral node was negative on histology.

Correlation of imaging and endoscopy features with histopathology

Correlations between histopathology findings and MRI and endoscopic features are presented in **Tables 2 and 3**. All patients had a pathological complete response of the primary tumour (ypT0) and in six (19%) specimens foci of low- or high grade dysplasia at the former tumour location were found. Histopathology reports describe fibrosis in 30 (83%) patients, ulceration in 19 (53%) patients and inflammation in 18 (50%) patients. Acellular mucin was present in 5 (14%) surgical specimens and dystrophic calcifications were seen in 5 (14%) specimens. Fibrous tissue was more frequently found in patient with mixed signal intensity on T2-weighted MRI than in patients with homogeneous signal (100% vs. 65%). Microscopic ulceration was also found more frequently in patients with mixed T2-weighted signal (74% vs. 29%) and in patients with a high signal on the DWI-MRI (77% vs. 38%), see **Table 2**. Presence of acellular mucin or calcifications did not differ between patients with and without signs of residual disease on MRI. Dysplasia was found more frequently in patients with clinically suspected residual tumour at endoscopy than in patients without suspected residual tumour (100% vs. 17%).

DISCUSSION

The selection of patients with a complete response for organ preservation remains a challenge, with overstaging of residual tumour being the main source of error. This can lead to not recognizing patients with a complete response, who subsequently have a major resection of the rectum while they could have been treated with organ preservation. The goal of this study was to evaluate what features on restaging MRI and endoscopy led to a false diagnosis of residual tumour in these unrecognized complete responses. Overall, the commonest pitfalls were mucosal abnormalities on endoscopy, mixed signal or irregular aspect on T2-weighted MRI and a residual high signal on DWI-MRI. Overstaging of nodes was another important pitfall. For some of the pitfalls on MRI and endoscopy a potential substrate was found when reviewing histopathology.

Mucosal abnormalities such as an ulcer or polypoid tissue were present in the majority (88%) of the unrecognized complete responders at restaging endoscopy. These findings are in line with the study by Nahas et al [13], who showed that 89% of the patients with an unexpected pCR after TME resection showed gross mucosal abnormalities at restaging endoscopy. Two other studies showed that in 61-74% of the patients downstaged to ypT0, macroscopic residual mucosal abnormalities were found in the surgical specimen [17, 18]. Routine biopsies have been advocated to distinguish residual tumour from healing mucosa or residual adenoma. However, because of sampling errors there is a substantial risk for false negative biopsies [19]. In the present study there is even a false positive finding: one patient had adenocarcinoma in the biopsy taken at restaging endoscopy while having a pCR at resection only two weeks later.

Similar to endoscopy, T2-weighted MRI tends to overestimate the presence of residual tumour, mainly because of the presence of residual wall thickening at the former tumour location [9]. If this residual wall thickening shows a dark homogeneous fibrotic aspect, experienced radiologists will generally be able to identify this as a complete response. However, when the residual lesion shows a mixed signal, radiologists will interpret this as a sign of residual tumour. Although mixed signal is most often associated with residual tumour, this is not always the case. In patients with a pathological complete response this heterogeneous wall thickening is probably a mixture of fibrosis and oedema in the healing phase of the bowel wall, that in due time will proceed to full thickness homogeneous dark fibrosis. The addition of diffusion-weighted imaging to standard T2-weighted imaging can help to differentiate between scar tissue and residual tumour, as areas with residual diffusion restriction are suspicious for residual tumour [20]. A meta-analysis on the assessment of response to CRT in rectal cancer patients showed that the addition of DWI results in a significantly improved sensitivity from 50% with standard T2-weighted sequences to 84% with DWI [9]. In the present study approximately half of the

unrecognized complete responders showed residual (focal) diffusion signal abnormalities. Probably, this can be explained by interpretation errors caused by persisting T2 signal from the rectal wall which is not entirely suppressed at DWI. Due to the small size of these foci, evaluation on the quantitative ADC map is difficult and leads to failure in recognizing these areas as T2 shine through [21]. Histological reactive changes, e.g. an ulcer, may cause a false high signal leading to interpretation errors. Similar interpretation pitfalls have been reported for DWI-MRI after transanal endoscopic microsurgery [22, 23].

Another reason for not recognizing a complete response was the erroneous interpretation of a residual node as malignant. A common feature in overstaged nodes was the presence of border irregularity, a feature that is also found in many malignant nodes. While in primary staging the accuracy for nodal staging improves by the addition of morphological criteria to size criteria [24, 25], for nodal response assessment after neoadjuvant treatment the use of morphological criteria can be confusing as both normal and metastatic nodes can show abnormal nodal morphology [26, 27]. With a complete response in the primary tumour, there is a low a-priori risk of about 3-5% for residual nodal disease [1]. Therefore, in order to avoid needless surgery, it is worth considering (in patients with a clinical complete response in the primary tumour) to observe small residual irregular nodes for an additional period, especially when the nodes have decreased in size.

In many centres, organ preservation is only considered if a patient presents with a typical clinical complete response: a white scar with absence of mucosal abnormalities on endoscopy and no signs of residual luminal and nodal disease on MRI. The results of this study show that patients with mixed T2 signal, residual diffusion restriction, mucosal abnormalities or irregular nodes do not necessarily have residual disease. In selected patients an extended waiting interval can be considered to provide a more convincing picture on whether or not there is a complete response. In our current clinical practice we have implemented an extended waiting interval in patients who show a ‘near-CR’ at first response assessment 8-10 weeks after neoadjuvant treatment, to allow for further regression to a complete response[28]. How many and what combinations of the abovementioned equivocal features allow for safe extension of the waiting interval remains unclear. The more of these features are present, the less likely it seems a patient is going to have a complete response. This should be further evaluated.

Our study has some limitations. First, during the long study period the response evaluation strategy after (chemo)radiotherapy gradually changed, which led to missing endoscopy images in the early patients. Second, the time between response assessment and resection was rather long in some patients, so it is possible that patients did not have a pathological complete response during response assessment, but developed a complete

response during the interval to surgery and thus were actually not overstaged. Third, histopathology reports were used to compare imaging findings with histological findings. By using standard clinical reports rather than doing a reassessment of histopathology it is possible that histological reactive changes were not always reported when present. Last, as we only included patients with a pathological complete response of the primary tumour and did not have a control group, we cannot draw conclusions about the incidence of the discussed features on patients with true residual tumour, which would provide insight into the prevalence of these features and their clinical impact.

CONCLUSION

Overstaging of residual tumour after CRT is mainly caused by the presence of residual mucosal abnormalities at endoscopy, mixed signal or irregular fibrosis at T2-weighted MRI, focal diffusion restriction at diffusion-weighted MRI and residual irregular nodes. Knowledge of these pitfalls can help clinicians to improve the selection of complete responders. In patients with a very good clinical response, the abovementioned features should not be regarded as unequivocal signs of residual tumour and an extended waiting interval followed by a reassessment can be considered to provide a more convincing picture of the presence of a complete response. Advances in imaging techniques, endoscopy and tumour markers will in the future hopefully overcome the challenges in response assessment.

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Competing interests

The authors declare that they have no competing interests.

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FIGURES AND TABLES

Figure 1. Examples of main pitfalls in restaging MRI in ypT0 patients leading to overstaging of residual tumour. Mixed signal intensity (white arrowhead) within an area of fibrosis (arrows) (a), thick fibrosis in (b) and irregular fibrosis (white arrowheads) in (c) at T2-weighted MRI; massive diffusion restriction (d) and focal diffusion restriction (e) at DWI-MRI.

Figure 2. Irregular nodes in yN0 patients (a+b) and in yN+ (c+d) patients.

Figure 3. Examples of mucosal abnormalities at restaging endoscopy in ypT0 patients. A red scar with an adenomatous nodule (white arrowheads) (a), a scar with residual flat mucosal ulceration (b), deep mucosal ulceration with fibrinous tissue (c) and gross residual mass (d). All patients had ypT0 at histopathology after rectal cancer surgery.

Table 1. Patient characteristics (n=36).

Table 2. Frequency of histological features per MRI feature (n=36).

Table 3. Frequency of histological features per endoscopic finding (n=19).

Table 1. Patient characteristics (n=36).

Characteristic	Number of patients
Sex	
Male	24 (67%)
Female	12 (33%)
Mean age, in years (SD)	64 (13)
cT stage	
T1-2	7 (19%)
T3ab	14 (39%)
T3cd	9 (25%)
T4	6 (17%)
cN stage	
N0	6 (17%)
N1	8 (22%)
N2	22 (61%)
Neoadjuvant therapy	
CRT (50.0-50.4Gy)	34 (94%)
Short course RT + waiting interval (25Gy)	2 (6%)
Surgical procedure	
LAR	20 (56%)
APR	13 (36%)
FTLE	3 (8%)
Median CRT-restaging interval, in weeks (IQR)	8 (8-17)
Median restaging-resection interval, in days (IQR)	27 (15-36)
Abbreviations: CRT=chemoradiotherapy, RT=radiotherapy, LAR= low anterior resection, APR=abdominoperineal resection, FTLE=full thickness local excision, IQR=interquartile range.	

Table 2. Frequency of histological features per MRI feature (n=36).

		Mixed T2-weighted signal		Full thickness/ irregular fibrosis		Diffusion restriction		Oedema		EMVI	
	Total	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**
Dysplasia	6	4 (23.5)	2 (10.5)	2 (18.2)	4 (16.0)	3 (18.8)	3 (17.6)	5 (27.8)	1 (5.9)	6 (18.2)	- (0.0)
Fibrous tissue	30	11 (64.7)	19 100.0)	7 (63.6)	23 (92.0)	11 (68.8)	16 (94.1)	14 (77.8)	15 (88.2)	27 (81.8)	3 (100.0)
Inflammation	18	5 (29.4)	13 (68.4)	3 (27.3)	15 (60.0)	6 (37.5)	11 (64.7)	7 (38.9)	11 (64.7)	16 (48.5)	2 (66.7)
Acellular mucin	5	1 (5.9)	4 (21.1)	2 (18.2)	3 (12.0)	1 (6.3)	4 (23.5)	1 (5.6)	4 (23.5)	3 (9.1)	2 (66.7)
Ulceration	19	5 (29.4)	14 (73.7)	3 (27.3)	16 (64.0)	6 (37.5)	13 (76.5)	6 (33.3)	12 (70.6)	17 (51.5)	2 (66.7)
Dystrophic calcifications	5	2 (11.8)	3 (15.8)	- (0.0)	5 (20.0)	1 (6.3)	3 (17.6)	1 (5.6)	4 (23.5)	5 (15.2)	- (0.0)

Abbreviations: DWI=diffusion weighted imaging; EVMI=extramural venous invasion
Numbers between parentheses are percentages

Table 3. Frequency of histological features per endoscopic finding (n=19).

		Scar		Flat ulcer		Ulcer with irregular border		Polypoid tissue		Residual tumour	
	Total	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**
Dysplasia	4	4 (25.0)	- (0.0)	3 (21.4)	1 (20.0)	3 (23.1)	1 (16.7)	3 (20.0)	1 (25.0)	3 (16.7)	1 (100.0)
Fibrous tissue	17	15 (93.8)	2 (66.7)	12 (85.7)	5 (100.0)	12 (92.3)	5 (83.3)	13 (86.7)	4 (100.0)	16 (88.9)	1 (100.0)
Inflammation	8	7 (43.8)	1 (33.3)	5 (35.7)	3 (60.0)	4 (30.8)	4 (66.7)	8 (53.3)	- (0.0)	8 (44.4)	- (0.0)
Acellular mucin	2	2 (12.5)	- (0.0)	1 (7.1)	1 (20.0)	1 (7.7)	1 (16.7)	2 (13.3)	- (0.0)	2 (11.1)	- (0.0)
Ulceration	10	9 (56.3)	1 (33.3)	6 (42.9)	4 (80.0)	5 (38.5)	5 (83.3)	10 (66.7)	- (0.0)	10 (55.6)	- (0.0)
Dystrophic calcifications	4	4 (25.0)	- (0.0)	3 (21.4)	1 (20.0)	2 (15.4)	2 (33.3)	3 (20.0)	1 (25.0)	4 (22.2)	- (0.0)

Numbers between parentheses are percentages.