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Ann Surg Oncol (2020) 27:2732–2739
https://doi.org/10.1245/s10434-020-08334-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Selection of Patients for Organ Preservation After Chemoradiotherapy: MRI Identifies Poor Responders Who Can Go Straight to Surgery

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ABSTRACT

Objective. The aim of this study was to evaluate whether magnetic resonance imaging (MRI) can accurately identify poor responders after chemoradiotherapy (CRT) who will need to go straight to surgery, and to evaluate whether results are reproducible among radiologists with different levels of expertise.

Methods. Seven independent readers with different levels of expertise retrospectively evaluated the restaging MRIs (T2-weighted + diffusion-weighted imaging [T2W + DWI]) of 62 patients and categorized them as (1) poor responders – highly suspicious of tumor; (2) intermediate responders – tumor most likely; and (3) good – potential (near) complete responders. The reference standard was histopathology after surgery (or long-term follow-up in the case of a watch-and-wait program).

Results. Fourteen patients were complete responders and 48 had residual tumor. The median percentage of patients categorized by the seven readers as 'poor', 'intermediate', and 'good' responders was 21% (range 11–37%), 50% (range 23–58%), and 29% (range 23–42%), respectively. The vast majority of poor responders had histopathologically confirmed residual tumor (73% ypT3-4), with a low rate (0–5%) of 'missed complete responders'. Of the 14 confirmed complete responders, a median percentage of 71% were categorized in the MR-good response group and 29% were categorized in the MR-intermediate response group.

Conclusions. Radiologists of varying experience levels should be able to use MRI to identify the ± 20% subgroup of poor responders who will definitely require surgical resection after CRT. This may facilitate more selective use of endoscopy, particularly in general settings or in centers with limited access to endoscopy.

In 2004 Habr-Gama et al. introduced the concept of 'watch and wait' (W&W) in rectal cancer, where patients with a clinical complete response (cCR) after neoadjuvant chemoradiotherapy (CRT) are deferred from surgery and are instead closely monitored.[1] Since then, the W&W strategy has been successfully adopted by other clinical research groups[2–5] and W&W patients from 47 centers worldwide are now being registered in the International Watch and Wait Database (IWWD), the results of which, after the first 1000 inclusions, were recently published.[6]

First Received: 14 November 2019;
Published Online: 14 March 2020

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One of the key issues in the W&W approach is how to best select the right candidates. Methods to assess response differ between published reports and centers,[6–8] but data from the IWWD showed that endoscopy and magnetic resonance imaging (MRI) are the two tools most frequently used. Endoscopy is the most powerful tool to allow detailed assessment of the luminal response. MRI, particularly when combined with diffusion-weighted imaging (DWI), is a valuable adjunct to assess the lumen, and is of added benefit to diagnose any extraluminal findings, such as remaining positive lymph nodes, that may render W&W less feasible. In 64% of registered patients in the IWWD, a combination of both MRI and endoscopy was employed; it is generally acknowledged that this combination, together with clinical evaluation of the tumor, offers the best overall diagnostic performance to assess a complete (or near complete) response after CRT.[6,9] Although both endoscopy and MRI are included in the selection process in most highly specialized centers that offer W&W as an alternative to resection, this cannot always be easily implemented in less specialized centers with limited access to both modalities. The question is whether we can be more selective in the use of endoscopy. For example, it could be argued whether an endoscopy is necessary if MRI can accurately show that the patient has gross residual disease and needs to go straight to surgery. If this is the case, it is critical that the multidisciplinary management team can rely on the findings of the radiologist and that the performance of the expert can be generalized.

Therefore, the primary goal of our study was to evaluate whether MRI can be used to accurately identify gross residual disease (poor response) after CRT, with a secondary goal of testing the reproducibility of MRI among radiologists with different levels of expertise.

METHODS

The retrospective use of imaging data for the purpose of this study was approved by the local Ethical Review Board. Informed consent was waived.

Patient Selection

The hospital's database (2011–2016) was searched for all non-metastatic, locally advanced, and/or distal rectal cancer patients who were diagnosed, staged with a standardized MRI protocol, and treated with long-course neoadjuvant treatment at Maastricht University Medical Center. Inclusion criteria for this retrospective study consisted of (1) biopsy-proven rectal adenocarcinoma; (2) neoadjuvant treatment consisting of long-course CRT or short-course radiotherapy with a prolonged waiting interval of at least 6 weeks; (3) availability of a good-quality restaging MRI, including a DWI sequence; and (4) availability of a valid standard of reference to establish the final response outcome, consisting of either histopathology after surgery (performed within 50 days following MRI) or a sustained cCR during long-term (> 2 year) follow-up in case of inclusion in a W&W program. Based on these inclusion criteria, a total of 62 eligible patients were identified.

Magnetic Resonance Imaging

All MRI examinations were performed on a 1.5T MR system (Philips Healthcare, Best, The Netherlands), according to protocols previously reported.[10,11] In short, the protocol consisted of standard T2-weighted (T2W) turbo spin echo sequences in three directions (axial, sagittal, coronal; 3–5 mm slice thickness), an axial echo planar imaging (EPI) DWI sequence, with the highest *b*-value being b1000 (slice thickness 5 mm), and corresponding apparent diffusion coefficient (ADC) map calculated from the DWI sequence. The transverse T2W and DW axial images were angled in identical planes, perpendicular to the tumor axis, as identified on the sagittal T2W MRI. Since March 2014, patients routinely received a micro-enema prior to scanning (Microlax®; McNeil Healthcare, Dublin, Ireland) to avoid susceptibility artefacts on DWI.[11] The micro-enema consisted of a 5 mL solution and was self-administered by patients approximately 15 min prior to MRI. No other bowel preparation or spasmolytic agents were used.

Image Evaluation

MR images were read by seven independent readers with different levels of expertise (one resident reader, one abdominal radiologist working at a general non-academic center, two abdominal radiologists working at a general academic center, one abdominal radiologist working at an oncologic referral center, and two rectal MR experts working at an oncologic referral center). The readers were blinded to each other's results, the treatment following CRT (surgery or W&W), and the final response outcomes. Readers were asked to assess response on the restaging MR images, using a simplified three-category response system for which the readers were provided with a case report form (CRF) that was constructed for the purpose of this study. The CRF (illustrated in Fig. 1) included imaging examples of all three response categories and was composed taking into account findings from previous publications on T2W MRI (including the MRI tumor regression grade [mrTRG]) and diffusion-weighted MRI response patterns.[12–14] Patients were categorized as:

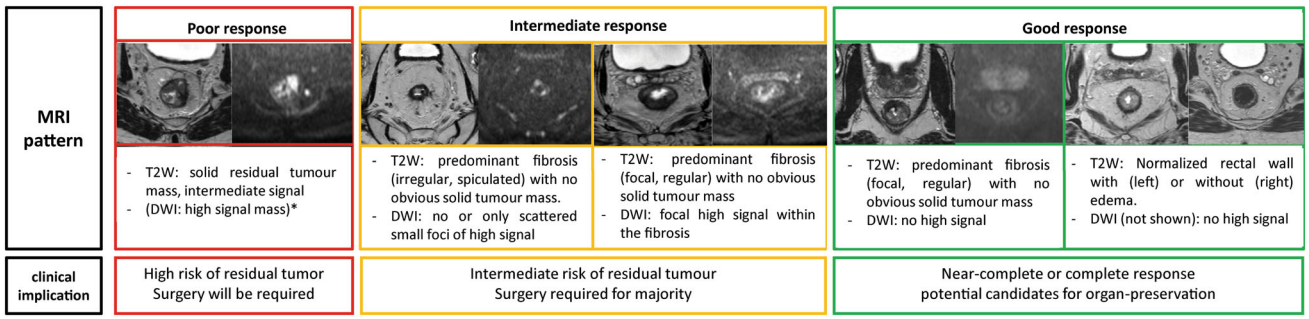


FIG. 1 Three-category case report form to differentiate between poor, intermediate, and good responders based on MRI. The response categories take into account the morphology on T2W MRI (in concordance with the mrTRG score, with poor response corresponding to mrTRG 4–5, intermediate response corresponding to to mrTRG 3, and good response corresponding to mrTRG 1–2)[13,14] as well as previously reported DWI signal patterns.[12] * For the assessment of a poor response, with an obvious solid residual mass, availability of DWI is not mandatory to make the diagnosis. *T2W* T2-weighted imaging, *DWI* diffusion-weighted imaging, *MRI* magnetic resonance imaging, *mrTRG* MRI tumor regression grade

(a) poor responders, i.e. patients with a high risk of residual tumor (in whom surgery will typically be required);
(b) intermediate responders, i.e. patients with an intermediate risk for residual tumor (in whom surgery will likely be required for the majority);
(c) good responders, i.e. patients who may have a near-complete or complete response.

In addition, the readers were asked to document any suspicious extraluminal findings, including pathologic lymph nodes (defined as any nodes $\geq$ 5 mm, according to recent guidelines published by the European Society of Gastrointestinal and Abdominal Radiology[15]), mesorectal tumor deposits, or the presence of gross extraluminal tumor extension (including extramural venous invasion).

Correlation with Final Response Outcome

The final response outcome (complete response [CR] vs. non-CR/residual tumor) was defined based on histopathology (ypT0 vs. ypT1-4) in surgically managed patients and on clinical follow-up in patients with a cCR who were included in a W&W program. In the latter group, a local regrowth-free follow-up period of at least 2 years was considered a surrogate endpoint for a CR (yT0N0).[6] In the operated patients, the TRG[16] was also documented when available.

Data Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics and contingency tables were constructed to compare the findings of the seven different readers and the patients' final response outcomes. Extraluminal findings on MRI were classified as true positive when positive nodes or deposits were confirmed at histopathology, or when the pathological resection specimen indicated a yT3-4 tumor to confirm extraluminal tumor extension on MRI. Interobserver agreement between individual readers was calculated using a weighted Kappa method with quadratic kappa weighting. Overall agreement between the seven readers was calculated using Kendall's coefficient of concordance.

RESULTS

Demographics

Demographics of the 62 study patients are shown in Table 1. Forty-one patients were male (66%) and median age was 67 years (range 45–83). In total, 14 (23%) patients were complete responders—3 with ypT0 after surgery and 11 with a sustained ycT0 undergoing W&W, the latter with a median follow-up period of 49 months (range 35–66) at the time of writing. Forty-eight (77%) patients had a residual tumor after surgery (of whom 45 underwent immediate surgery and 3 had a regrowth within 3, 4, and 6 months, respectively, after initial inclusion in a W&W program). In the residual tumor group, 3 patients had ypT1 (6%), 15 patients had ypT2 (31%), 27 patients had ypT3 (57%), and 3 patients had ypT4 disease (6%). The TRG was 2 in 13 (27%) patients, 3 in 15 (31%) patients, 4 in 14 (30%) patients, and 5 in two (4%) patients; in 4 (8%) patients, the TRG was missing. Of the operated patients, 16 patients had N-positive disease.

Correlation between MR Response Categories and Final Response Outcome

Figure 2 shows the correlation of the MR scores of the seven different readers, with the final response outcome.

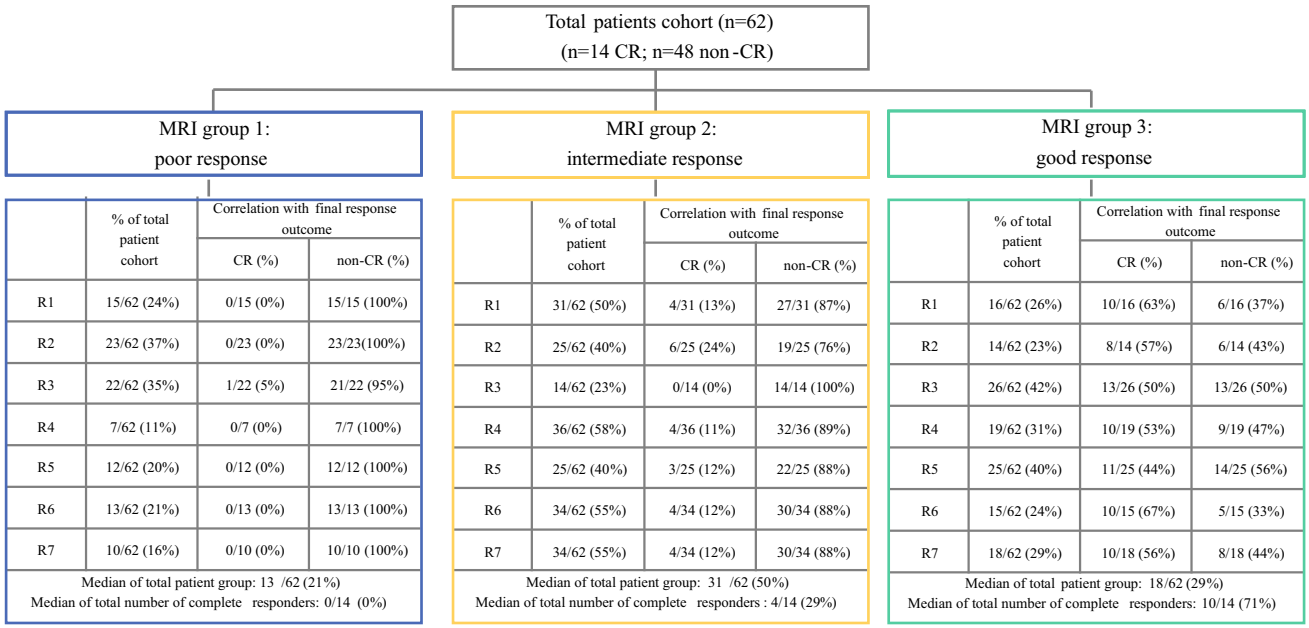
TABLE 1 Patient demographics

Variables		Total [n = 62]	
Age, years			
Median (range)		67 (45–83)	
Sex			
Male		41 (66)	
Female		21 (34)	
cT stage at primary staging			
1–2		8 (13)	
3		48 (77)	
4		6 (10)	
cN stage at primary staging			
0		13 (21)	
1		8 (13)	
2		41 (66)	
Neoadjuvant treatment			
5 × 5 Gy		7 (11)	
CRT		55 (89)	
Time between last Rtx and restaging MRI (days)			
Median (range)		56 (48–137)	
Time between restaging MRI and surgery (days)			
		16 (6–50)	
Final treatment			
W&W		14 (23)	
Immediate surgery		48 (77)	
Final response outcome			
CR		14 (23)	
	W&W	11	
	pCR	3	
Non-CR		48 (77)	
	Primary surgery	45	
			3ypT1
			13ypT2
			26ypT3
			3ypT4
	Delayed surgery (W&W with regrowth < 1 year)	3	
			2ypT2
			1ypT3

Data are expressed as n (%) unless otherwise specified

CRT chemoradiation, *W&W* watch and wait, *CR* complete responders, *pCR* pathological complete response, *MRI* magnetic resonance imaging

The median percentage of patients categorized into the poor, intermediate, and good response groups by the seven readers was 21% (range 11–37), 50% (range 23–58), and 29% (range 23–42), respectively. When considering the total of 14 patients with a proven CR, the median percentage of these patients when categorized into the poor, intermediate, and good response groups was 0%, 29%, and 71%, respectively, indicating that the majority were correctly classified as good responders. Apart from one patient with a CR who was misclassified in the poor response group by one of the seven readers, all patients categorized as MR-poor responders had confirmed residual tumor at histopathology, of whom the majority had advanced disease at histopathology (73% ypT3-4 tumors). The majority



	% of total patient cohort	Correlation with final response outcome	
		CR (%)	non-CR (%)
R1	15/62 (24%)	0/15 (0%)	15/15 (100%)
R2	23/62 (37%)	0/23 (0%)	23/23(100%)
R3	22/62 (35%)	1/22 (5%)	21/22 (95%)
R4	7/62 (11%)	0/7 (0%)	7/7 (100%)
R5	12/62 (20%)	0/12 (0%)	12/12 (100%)
R6	13/62 (21%)	0/13 (0%)	13/13 (100%)
R7	10/62 (16%)	0/10 (0%)	10/10 (100%)
Median of total patient group: 13 /62 (21%) Median of total number of complete responders: 0/14 (0%)			

	% of total patient cohort	Correlation with final response outcome	
		CR (%)	non-CR (%)
R1	31/62 (50%)	4/31 (13%)	27/31 (87%)
R2	25/62 (40%)	6/25 (24%)	19/25 (76%)
R3	14/62 (23%)	0/14 (0%)	14/14 (100%)
R4	36/62 (58%)	4/36 (11%)	32/36 (89%)
R5	25/62 (40%)	3/25 (12%)	22/25 (88%)
R6	34/62 (55%)	4/34 (12%)	30/34 (88%)
R7	34/62 (55%)	4/34 (12%)	30/34 (88%)
Median of total patient group: 31 /62 (50%) Median of total number of complete responders : 4/14 (29%)			

	% of total patient cohort	Correlation with final response outcome	
		CR (%)	non-CR (%)
R1	16/62 (26%)	10/16 (63%)	6/16 (37%)
R2	14/62 (23%)	8/14 (57%)	6/14 (43%)
R3	26/62 (42%)	13/26 (50%)	13/26 (50%)
R4	19/62 (31%)	10/19 (53%)	9/19 (47%)
R5	25/62 (40%)	11/25 (44%)	14/25 (56%)
R6	15/62 (24%)	10/15 (67%)	5/15 (33%)
R7	18/62 (29%)	10/18 (56%)	8/18 (44%)
Median of total patient group: 18/62 (29%) Median of total number of complete responders: 10/14 (71%)			

FIG. 2 Response categorization results for the seven respective readers versus the final response outcome. *Rx* reader *x*, *CR* complete responders

(76–100% for the seven different readers) of the MR-intermediate responders also had confirmed residual tumor, of whom 58% still had ypT3-4 disease.

Extraluminal Findings

Table 2 describes the extraluminal findings as reported by the seven different readers. All patients (100% for all readers) who were scored as having extraluminal tumor extension had confirmed ypT3-4 residual disease at histopathology. Extraluminal tumor extension was only observed in the MR-poor responders (40–69%) and MR-intermediate responders (3–9%). None of the patients in the MR-good response group had any extraluminal tumor extension on MRI. In the good, intermediate, and poor response groups, the seven readers identified positive nodes (or tumor deposits) in 0–19%, 13–36%, and 8–50% of patients, respectively, which resulted in false positive rates ranging between 0 and 29% for the different readers, as illustrated in Table 2.

Interobserver Agreement

Kendall's coefficient showed substantial overall agreement between the seven readers (W 0.65). Quadratic weighted kappa values between the different individual readers are listed in Table 3. Agreement between the most experienced readers (readers 1–3) was good (κ 0.64–0.68), while agreement between the remaining readers was moderate (κ 0.48–0.60), except for fair agreement between readers 2 and 5 (κ0.38) and good agreement between readers 1 and 7 and readers 3 and 4 (κ 0.64 and κ 0.67, respectively).

DISCUSSION

This study has shown that although agreement between individual readers was not always perfect, radiologists with varying levels of expertise in interpreting rectal cancer MRIs were able to correctly identify the ± 20% of poor responders who will definitely require surgery and typically present with substantial (ypT3-4) residual disease at histopathology.

Interpretation of MRIs after CRT is well-known to be hampered by difficulties in discerning fibrosis from residual disease. Different MR interpretation and classification systems have been suggested focusing on specific morphological T2W-MRI patterns (including mrTRG) and/or DWI signal patterns to assess response after CRT.[12–14,17] However, these systems require a certain level of expertise, and, in particular, for DWI there are some known pitfalls that may lead to misinterpretations.[10] The results as reported for expert readers in published reports may therefore be less reproducible in less experienced hands, and may be difficult to translate to general everyday practice.

Our study shows that when using a simplified three-category response evaluation system to make a more approximate estimate of the risk of residual disease (Fig. 1), all readers, regardless of the level of expertise, were able to identify, on MRI, the group of poor responders with gross residual disease. Moreover, of the 14 confirmed

TABLE 2 Extraluminal findings

Extraluminal findings	Patients classified in the MR-poor response group		Patients classified in the MR-intermediate response group		Patients classified in the MR-good response group	
	Total (%)	FP (%)[a]	Total (%)	FP (%)[a]	Total (%)	FP (%)[a]
Nodes or deposits						
R1	2/15 (13)	0 (0)	4/31 (13)	1 (3)	3/16 (19)	2 (13)
R2	4/23 (17)	1 (4)	6/25 (24)	1 (4)	2/14 (14)	1 (7)
R3	9/22 (41)	2 (9)	4/14 (29)	0 (0)	1/26 (4)	0 (0)
R4	2/7 (29)	2 (29)	13/36 (36)	4 (11)	2/19 (11)	1 (5)
R5	6/12 (50)	1 (8)	8/25 (32)	5 (20)	2/25 (8)	0 (0)
R6	1/13 (8)	1 (8)	10/34 (29)	3 (9)	0/15 (0)	NA
R7	4/10 (40)	0 (0)	7/34 (21)	1 (3)	3/18 (17)	2 (1)
	Total (%)	FP (%)[b]	Total (%)	FP (%)[b]	Total (%)	FP (%)[b]
Extraluminal tumor extension						
R1	6/15 (40)	0 (0)	1/31 (3)	0 (0)	0/16 (0)	NA
R2	11/23 (48)	0 (0)	2/25 (8)	0 (0)	0/14 (0)	NA
R3	11/22 (50)	0 (0)	1/14 (7)	0 (0)	0/26 (0)	NA
R4	4/7 (57)	0 (0)	1/36 (3)	0 (0)	0/19 (0)	NA
R5	5/12 (42)	0 (0)	2/25 (8)	0 (0)	0/25 (0)	NA
R6	9/13 (69)	0 (0)	1/34 (3)	0 (0)	0/15 (0)	NA
R7	4/10 (40)	0 (0)	3/34 (9)	0 (0)	0/18 (0)	NA

[a] yN1-N2 detected in pathological specimens

[b] yT3-T4 detected in pathological specimens

FP false positives, *Rx* reader *x*, *NA* not applicable

TABLE 3 Interobserver agreement between readers

	R1	R2	R3	R4	R5	R6	R7
R1	NA	0.65	0.68	0.56	0.47	0.61	0.64
R2			0.64	0.56	0.38	0.53	0.57
R3				0.67	0.53	0.60	0.55
R4					0.54	0.59	0.53
R5						0.49	0.53
R6							0.57
R7							NA

R1 reader 1, rectal MRI expert working in an oncologic referral center, *R2* reader 2, rectal MRI expert working in an oncologic referral center, *R3* reader 3, abdominal radiologist working in an oncologic referral center, *R4* reader 4, abdominal radiologist working in an academic center, *R5* reader 5, abdominal radiologist working in an academic center, *R6* reader 6, abdominal radiologist working in a non-academic center, *R7* reader 7, radiologist trainee with no specific MRI expertise, *NA* not applicable, *MRI* magnetic resonance imaging

complete responders, the majority (71%) were correctly categorized into the MR-good response group and the remaining 29% were categorized into the MR-intermediate response group. Together, these patients thus represent the largest subgroup of ± 80% of patients who benefit most from detailed response evaluation with endoscopy combined with MRI, to make a fully informed decision between TME, local excision in case of a small residual tumor lesion, or W&W in case of a confirmed cCR. Although some researchers have reported that patients with a CR may still show some mucosal abnormalities on endoscopy, and that false negative and positive biopsies may occur,[18,19] endoscopy is generally acknowledged as an invaluable tool to assess luminal response after CRT in rectal cancer.[9,20] In the setting of organ preservation, the combined use of clinical evaluation, MRI, and endoscopy thus remains the preferred and most accurate selection method. In a setting where there is less access to both selection modalities, one could be more selective with the use of endoscopy and refer patients straight for surgery based on MRI only if the MRI shows gross residual disease after CRT.

In addition to luminal response assessment, MRI is particularly valuable for identifying extraluminal tumors and remaining mesorectal nodes/deposits, which could be a contraindication for W&W. In the current study, all patients with MR-detected extraluminal tumor extension had confirmed ypT3-T4 tumor according to histopathology.

Our results regarding detection of the remaining vital lymph node metastases and tumor deposits were unfortunately not so good and a variable number of false positive findings occurred, which is in line with the known inaccuracies of MRI for nodal staging.[21,22] Nevertheless, the number of false positive findings in the MR-good response group was low, ranging between only 0 and 13% for the seven different readers.

This study has several limitations, in addition to its relatively small-sized cohort and retrospective nature. First, not all patients had histopathological confirmation. However, patients with a sustained cCR all had a follow up of > 2 years (range 35–66 months), which will generally be considered a good surrogate endpoint of a complete remission as most regrowths are known to occur in the first 2 years.[6] Second, our study design was based on a clinical scenario assuming routine use of MRI as a first-line response tool. One could argue that, depending on local policy and availability of the respective modalities, an alternative strategy applying endoscopy as a first-line tool with more selective use of MRI could be just as effective; however, exploring this alternative strategy was outside the scope of this retrospective study. Finally, although the readers in our study had varying levels of expertise, the majority were relatively experienced abdominal readers with at least an affinity for reading rectal MRIs. Prospective and large-scale validation will therefore be required to further validate our findings in more general clinical settings.

CONCLUSIONS

Our study suggests that regardless of their level of expertise, radiologists should be able to accurately identify, on MRI, the ± 20% subgroup of patients with gross residual disease who can go straight to surgery and who would benefit less from further endoscopic assessment. We support previous evidence that for the remaining majority of patients, a combined use of clinical evaluation, MRI, and endoscopy remains the preferred response evaluation method when aiming to select patients for organ preservation (W&W). Once validated prospectively, such an approach could allow more selective use of diagnostic tools, thereby facilitating the implementation of W&W in busy everyday practice.

ACKNOWLEDGEMENTS The authors have no acknowledgments to disclose.

DISCLOSURES Hester E. Haak, Monique Maas, Max J. Lahaye, Thierry N. Boellaard, Andrea Delli Pizzi, Casper Mihl, Dennis van der Zee, Cristina Fabris, Marit E. van der Sande, Jarno Melenhorst Regina G.H. Beets-Tan, Geerard L. Beets, and Doenja M.J. Lambregts have no conflicts of interest to declare.

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