



Diagnostic performance of magnetic resonance to assess treatment response after neoadjuvant therapy in patients with locally advanced rectal cancer

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Abstract

Purpose Our study aimed to evaluate the diagnostic performance of rectal magnetic resonance imaging (MRI) for local restaging in patients with non-metastatic locally advanced rectal cancer (LARC) after neoadjuvant chemoradiotherapy (CRT) using surgical histopathology of total mesorectal excision as the reference standard.

Methods Ninety-five patients with LARC who underwent rectal MRI after CRT between January 2014 and December 2016 were included. Accuracy, sensitivity, specificity, positive, and negative predictive value for local staging regarding T-stage, N-stage, circumferential resection margin, and MRI tumor regression grade (ymriTRG) were calculated, and inter-test agreements were assessed.

Results 22/95 (23.2%) patients had radiological complete response (rCR), whereas 20/95 (21.1%) had pathological complete response (pCR). Among the patients with pCR, 11/20 (55%) had rCR. Fair agreement was demonstrated between ymriTRG and pathological TRG (ypTRG) ($\kappa = 0.255$). The sensitivity and specificity for detection of pCR were 61.1% (95% CI 35.7–82.7) and 89.6% (95% CI 80.6–95.4). For the detection of ypTRG grades 1 and 2, the corresponding values were 67.2% (95% CI 54.3–78.4) and 51.6 (95% CI 33.1–69.8). The accuracy of ymriTRG was 24.2% (95% CI 15.6–32.8). Inter-test agreement in TRG between MRI and pathology was overall fair ($\kappa = 0.255$) and slight ($\kappa = 0.179$), if TRG 1 + 2.

Conclusion Qualitative assessment on MRI for diagnosing pCR showed moderate sensitivity and high specificity, whereas the diagnosis of TRG had moderate sensitivity and low specificity with slight to fair inter-test agreement when compared with pathological specimens.

Keywords Rectal neoplasms · Magnetic resonance · Neoadjuvant therapy

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Introduction

The treatment of patients with locally advanced rectal cancer (LARC) consists of neoadjuvant chemoradiotherapy (CRT) and total mesorectal excision (TME). This approach has obtained benefits in relation to overall survival, disease-free survival, and recurrence [1–3]. After neoadjuvant treatment, more than half of patients are downstaged and around 20% show pathological complete response (pCR) after surgery [4–8]. In this context, patients with radiological complete response (rCR) have been included in a conservative non-operative protocol (watch-and-wait). This protocol is not yet the standard of care in the guidelines, but it has been repeatedly evaluated in several studies with good results [9–11]. Considering that, the evaluation of rCR after CRT has become increasingly relevant, but it is still challenging to be accurately assessed.

Currently, patients with LARC receive neoadjuvant CRT and subsequently are restaged with rectal digital examination, colonoscopy, and rectal magnetic resonance imaging (MRI) [4, 9, 10, 12]. The restaging MRI is indicated to evaluate tumor regression grade (TRG), including the diagnosis of complete radiological response, yT- and yN-stage, and circumference resection margin (yCRM) status. In 2011, MERCURY study demonstrated that MRI assessments of TRG (ymriTRG) and CRM were predictors of survival outcomes [13].

However, the use of ymriTRG has shown some limitations in clinical practice, since it demonstrated low sensitivity and positive predictive value and suboptimal inter-reader agreement [14–16]. Accurate and reproducible evaluation of clinical response after neoadjuvant CRT is of key importance, mainly regarding differentiation between partial and complete clinical response, in order to assist

the multidisciplinary team in tailoring the best treatment options.

In this aforementioned scenario, this study aimed to evaluate the diagnostic performance of rectal MRI for local restaging in patients with non-metastatic LARC after neoadjuvant CRT using surgical histopathology of TME as the reference standard.

Materials and methods

Study population

The institutional review board from Instituto do Câncer do Estado de São Paulo (ICESP) of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) approved this observational retrospective study and waived the requirement for patient informed consent.

We searched our surgical database for consecutive patients who underwent LARC between January 2014 and December 2016. The inclusion criteria were as follows: (a) histopathological diagnosis of rectal adenocarcinoma; (b) absence of distant metastases; (c) T3–4 regardless of N-stage, N positive regardless of T-stage, or T2 with indication of abdominoperineal resection; (d) standard neoadjuvant CRT; and (e) restaging rectal MRI.

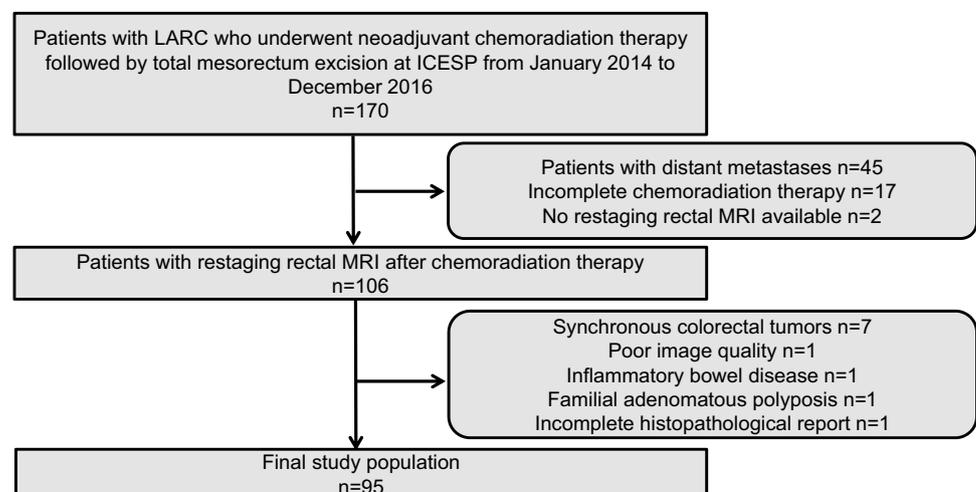
The exclusion criteria were synchronous colorectal tumors, association with inflammatory bowel disease or familial adenomatous polyposis, poor image quality, and incomplete histopathological report.

The patient accrual is summarized in Fig. 1.

Standard management

For local staging, all patients at our institution underwent digital rectal examination, colonoscopy or proctoscopy,

Fig. 1 Flowchart summarizing patient accrual



and rectal MRI. For distant staging, chest and abdominal computed tomography were performed. Patients with non-metastatic LARC (T3–4 regardless of N-stage or N positive regardless of T-stage) and with T2 with indication of abdominoperineal resection underwent neoadjuvant CRT. All of those patients received 5-FU-based chemotherapy with leucovorin by intravenous bolus injection on days 1 to 5, concomitant with radiation therapy in weeks 1 and 5. The total dose of pelvic radiation was 5040 Gy given in 28 sessions. The same imaging modalities used in primary staging were performed for restaging 8 weeks after the end of CRT.

Rectal MRI protocol

All rectal MRI were performed at our institution using a 1.5T unit (Signa HDx, GE Healthcare, Waukesha, WI, USA). The MRI scans were performed with a 16-channel phased-array pelvic receiver coil following a standard protocol. The sequence that was performed was 2D fast-recovery fast spin-echo (FRFSE) T2-weighted image (WI) without fat suppression with different field of view (FOV), slice thickness, and planes. The large FOV was acquired in axial and sagittal plane, while small FOV with thin slice thickness was acquired on oblique axial plane (perpendicular to tumor) and coronal plane (parallel to anal canal). MRI parameters are summarized in Appendix 1.

Image review

One abdominal radiologist with 10 years of experience after fellowship and with 8 year of experience in rectal MRI reviewed the studies. The radiologist was aware that the patients had LARC after neoadjuvant CRT and blinded to ypTNM. The baseline rectal MRI used for primary staging

before CRT was available for review in order to help the identification of the treated tumor.

The following imaging features were assessed: yT-stage, yN-stage, ymriTRG [13] (Table 1), presence of rCR (defined as ymrTRG1 and N0), and yCRM. yT-stage was defined as the depth of tumor penetration into the rectal wall into the mesorectum and adjacent structures, as follows: yT1 infiltration into the submucosa, yT2 infiltration into the muscularis propria, yT3 infiltration beyond muscularis propria, and yT4 tumors which infiltrates peritoneal reflection or other pelvic organs. yN-stage relied on the morphological characteristics of the lymph nodes; the nodes with irregular border or heterogeneous signal intensity were defined as positive. yCRM was defined as the smallest distance between the remaining tumor and the mesorectal fascia [17].

Histopathological examination

The reference standard in our study was the histopathological report of the surgical specimens of the TME. Pathology reports were retrospectively reviewed for ypT-stage, ypN-stage, ypTRG, presence of ypCR (defined as ypTRG1 and ypN0), and ypCRM. TRG was described according to the 5-degree system of Mandard (Table 1) [18]. All histopathological interpretations were done by specialized gastrointestinal pathologists with 5 to 10 years of experience after fellowship training.

Statistical analysis

The continuous variables were summarized using median and interquartile range (IQR), and the categorical variables were expressed as counts and proportions. The frequencies of TRG in MRI and pathology were described. Inter-test agreement between MRI and pathology was evaluated using

Table 1 Five-tier classification system for ymrTRG and ypTRG

ymriTRG [13]	ypTRG [18]
Grade 1 Absence of any tumor signal	Grade 1 No residual cancer cells
Grade 2 Small amounts of residual tumor visible but with a predominant fibrotic low signal intensity	Grade 2 Rare cancer cells
Grade 3 Mixed areas of low signal fibrosis and intermediate signal intensity present but without predominance of tumor	Grade 3 Fibrosis outgrowing residual cancer
Grade 4 Predominantly tumor signal intensity remains with minimal fibrotic low signal intensity	Grade 4 Residual cancer outgrowing fibrosis
Grade 5 No fibrosis evident, tumor signal visible only	Grade 5 Absence of regressive change

ymriTRG magnetic resonance imaging tumor regression grade, ypTRG pathological tumor regression grade

Table 2 Radiological and histopathological staging from 95 included patients with LARC after neoadjuvant CRT

	<i>n</i>	%
yT		
yT0	21	22.1
yT1	2	2.1
yT2	25	26.3
yT3	37	38.9
yT4	10	10.5
yN		
yN–	71	74.7
yN+	24	25.3
yCRM		
yCRM–	72	75.8
yCRM+	23	24.2
ypT		
pT0	20	21.1
pT1	9	9.5
pT2	27	28.4
pT3	33	34.7
pT4	6	6.3
ypN		
pN–	66	69.5
pN+	29	30.5
ypCRM		
pCRM–	76	80
pCRM+	19	20

CRM circumferential resection margin

kappa statistic and weighted *kappa*. κ values were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [19].

The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of rectal MRI were estimated along with 95% confidence intervals (95% CI).

All statistical analyses were performed using the statistical program software IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

The final study population consisted of 95 consecutive patients, 58/95 (61%) were men and 37/95 (39%) were women, and the median age was 62.9 years (range 27–75). The median interval between the end of CRT and restaging rectal MRI was 8.3 weeks (IQR 7.6–9.1) and the median interval between restaging MRI and TME was 2.1 weeks (IQR 1.6–3.2).

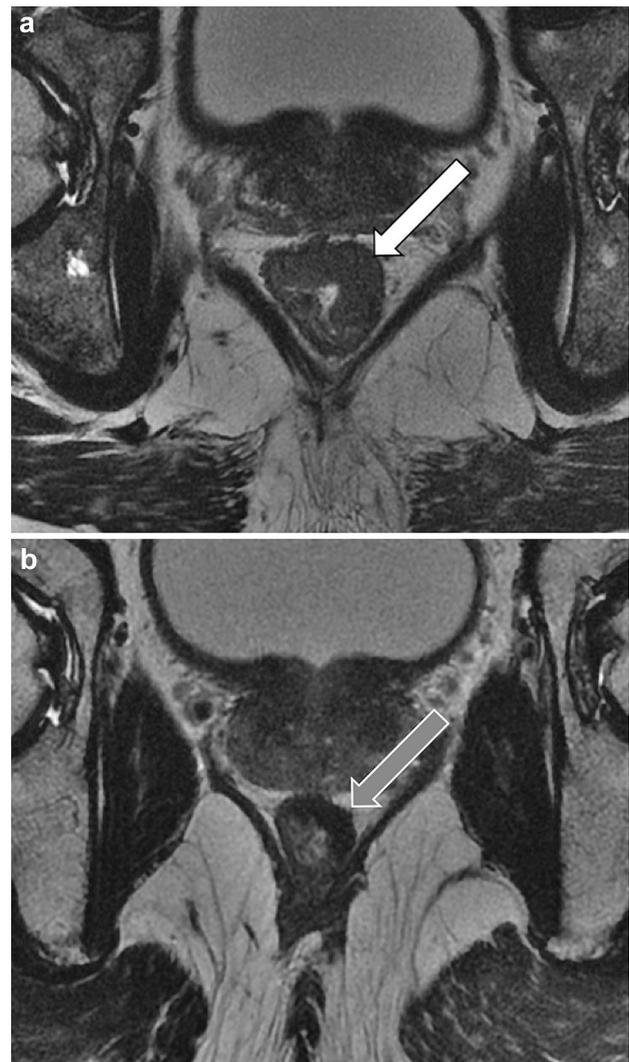


Fig. 2 A 62-year-old man with low rectal adenocarcinoma who underwent neoadjuvant chemoradiotherapy followed by total mesorectal excision, which showed residual tumor. **a** Baseline rectal MRI demonstrated the tumor (white arrow) and **b** restaging MRI classified the patient as complete response, due to absence of any tumor signal (gray arrow). The histopathological staging was ypT2N0

The results from restaging MRI and histopathological examination of the surgical specimens of TME are shown in Table 2. Of note, 21/95 (22.1%) patients were classified as having rCR and 20/95 (21.1%) patients obtained pCR. When comparing MRI and pathological results, 11/20 (55%) patients with pCR had rCR on restaging MRI. Thus, 10 patients were incorrectly deemed as rCR, 8/10 (80%) of them were misclassified due to tumor wall status, and 2/10 (20%) due to lymph node status. Figure 2 demonstrates one of these cases. Additionally, 9 patients were wrongly classified as no complete response on MRI when they were in fact pCR, 6/9 (66.7%) of them were misclassified due to tumor wall status, 2/9 (22.2%) due to both nodal and tumor

Table 3 Comparison between radiological and pathological TRG classification

	ymriTRG	ypTRG					Total
		1	2	3	4	5	
1		11	7	2	1	0	21
2		7	8	8	9	5	37
3		1	2	8	6	3	20
4		1	1	8	3	4	17
5		0	0	0	0	0	0
Total		20	18	26	19	12	95

ymriTRG magnetic resonance imaging tumor regression grade, *ypTRG* pathological tumor regression grade

wall status, and 1/9 (11.1%) due to lymph node status only. Table 3 demonstrates a comparison between radiological and pathological TRG classification.

The diagnostic performance of MRI and inter-test agreement between MRI and histopathological results are summarized in Table 4. Of note, there was a moderate agreement in the detection of yT0, yCRM status, yN-stage, and rCR (yTON0), with κ values of 0.534, 0.512, 0.452, and 0.497, respectively. Fair agreement was demonstrated for yT-stage ($\kappa = 0.353$) and ymriTRG evaluation ($\kappa = 0.255$), and slight agreement for the evaluation of ymriTRG 1 + 2 with κ value of 0.179.

With regard to yT-stage, overall accuracy of MRI was 51.7%, while using yT0 criteria the accuracy was 84.2%, sensitivity 65%, specificity 89.3%, PPV 61.9%, and NPV 90.5%. Using yTON0 criteria, the values were comparable. Regarding yN-stage, the accuracy of MRI was 77.9%, sensitivity 55.2%, specificity 87.9%, PPV 66.7%, and NPV 81.7%. The assessment of CRM status had high accuracy, specificity and negative predictive value (83.2, 86.8, and

91.7%, respectively), and moderate sensitivity and positive predictive value (68.4% and 56.5%).

Regarding TRG assessment, overall accuracy was 24.1%; however, separating TRG 1 + 2 from the other grades, the accuracy was higher (62.1%), with sensitivity, specificity, PPV, and NPV of 67.2, 51.6, 74.1, and 43.2%, respectively.

The evaluation of the distribution of pCR among different ymriTRG showed that 55% of the patients classified as ymriTRG 1 had pCR, 90% of the patients deemed as ymriTRG 1 + 2 had pCR, and 95% of the patients with ymriTRG 1 + 2 + 3 had pCR (Table 5).

Discussion

In this study population, 21.1% of the patients had pCR and 55% of them were classified as rCR on restaging MRI, with a moderate agreement between MRI and pathology. Overall, the diagnostic performance of MRI in the evaluation of T-stage, N-stage, and CRM status had high specificities and

Table 4 Diagnostic performance and inter-test agreement between MRI and histopathological results

MRI versus Pathology	κ (CI 95%)	Accuracy (CI 95%)	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
yT versus ypT	0.353 (0.233 to 0.474)	51.7 (46.7–56.7)	–	–	–	–
yT0 versus ypT0	0.534 (0.326 to 0.742)	84.2 (76.9–91.5)	65 (40.8–84.6)	89.3 (80.1–95.3)	61.9 (38.4–81.9)	90.5 (81.5–96.1)
yN (\pm) versus ypN (\pm)	0.452 (0.254 to 0.65)	77.9 (69.6–86.2)	55.2 (35.7–73.6)	87.9 (77.5–94.6)	66.7 (44.7–84.4)	81.7 (70.7–89.9)
yTON0 versus ypTON0	0.497 (0.277 to 0.717)	84.2 (76.9–91.5)	61.1 (35.7–82.7)	89.6 (80.6–95.4)	57.9 (33.5–79.7)	90.8 (81.9–96.2)
yCRM (\pm) versus ypCRM (\pm)	0.512 (0.304 to 0.72)	83.2 (75.7–90.7)	68.4 (43.4–87.4)	86.8 (77.1–93.5)	56.5 (34.5–76.8)	91.7 (82.7–96.9)
ymriTRG/ypTRG	0.255 (0.137 to 0.374)	24.2 (15.6–32.8)	–	–	–	–
ymriTRG 1 + 2 versus ypTRG 1 + 2	0.179 (– 0.021 to 0.379)	62.1 (52.3–71.9)	67.2 (54.3–78.4)	51.6 (33.1–69.8)	74.1 (61–84.7)	43.2 (27.1–60.5)

CI confidential interval, CRM circumferential resection margin, NPV negative predictive value, PPV positive predictive value, *ymriTRG* magnetic resonance imaging tumor regression grade, *ypTRG* pathological tumor regression grade

Table 5 Pathological complete response according to different ymriTRG

ymriTRG	% of patients with pCR	
	n	%
1	11	55
1 + 2	18	90
1 + 2 + 3	19	95

pCR pathological complete response, ymriTRG magnetic resonance imaging tumor regression grade

negative predictive values, and moderate sensitivities and positive predictive values. The assessment of TRG had low diagnostic performance, with slight and fair agreement when compared with pathology.

The number of patients included in our cohort is the second largest among unicentric studies (Table 6). We performed rectal MRI using comparable technical parameters and evaluated similar imaging findings. The criteria used for rCR vary in the literature as well as the system used for pathological TRG, as shown in Table 5. Using ymriTRG1 as the criteria for rCR, our frequency of rCR was higher than the other studies (23.2% vs. 7.3% and 18%) [15, 20]. When rCR was defined as ymriTRG 1 + 2 or 1 + 2 + 3, our results were also higher (61.1% vs. 45.5% and 82.1% vs. 60%, respectively) [14, 15, 21] (Table 7).

The frequency of pCR in our population was 21.1%, which is comparable with previous studies, which ranged from 15 to 38% [6–9, 13, 15, 22–25]. In the current era of non-operative approach of selected patients with rCR, a reliable assessment of clinical response after CRT has become crucial, but still challenging. Overall the diagnostic performance of MRI in detecting rCR in our study is in line with other results found in the literature; however, those results are quite variable with an accuracy ranging from 50 to 90% [26–29]. Our results demonstrated that MRI detected with good accuracy T0, T0N0, and CRM positivity with high specificities and negative predictive values. These results are similar to those found by Nahas et al. [9] and Van der Broek et al. [29].

On the other hand, the accuracy of MRI in predicting TRG was low. When we focused on the detection of TRG 1 + 2, the diagnostic performance of MRI increased and we obtained a higher PPV compared with a previous study [15]; however, our sensitivity and specificity were lower than those demonstrated by Sclafani et al. We also observed that 95% of the patients classified as ymriTRG 1 + 2 + 3 had pCR, whereas the ones deemed as ymriTRG 1 and ymriTRG 1 + 2, 55%, and 90% had pCR, respectively. Slight agreement was found between MRI and pathological TRG, which is comparable to the results demonstrated by Sclafani et al. [15]. Furthermore, interobserver agreement of ymriTRG

Table 6 Characteristics of studies about MRI and pathological assessment of clinical response and pathological response in rectal cancer post CRT

Author	Centers	n	MRI unit	rCR, n (%)	Criteria of rCR	Pathological TRG	pCR, n (%)	Restaging time (weeks)	Readers	Inter-reader agreement (κ)	ymriTRG vs ypTRG (κ)
Patel et al. [13]	> 2	111	1.5 T	32 (28.8)	mrTRG 1 + 2 + 3	NA	NA	4–6	3	0.65	NA
Patel et al. [14]	> 2	78	1.5 T	47 (60)	mrTRG 1 + 2 + 3	Dworak, five tier	27 (34.6)	6–8	2	0.55	NA
Bhoday et al. [21]	1	143	NA	111 (77.6)	mrTRG 1 + 2 + 3	yT0N0, EVMI (–) for pCR	18 (13)	6–8	1	–	NA
Sclafani et al. [15]	> 2	191	NA	14 (7.3)	mrTRG 1	Dworak, five tier	26 (13.6)	4.1	2	0.84	0.24
Van der Broek et al. [29]	1	48	NA	NA	NA	Mandard, five tier	6 (13)	4.5	3	0.25–0.36	NA
Our study	1	95	1.5 T	22 (22.1)	mrTRG 1	Mandard, five tier	20 (21)	8	1	–	0.25

ymriTRG magnetic resonance imaging tumor regression grade, ypTRG pathological tumor regression grade

Table 7 Frequency of clinical complete response depending on the following criteria: mriTRG 1, mriTRG 1 + 2, mriTRG 1 + 2 + 3

	mriTRG 1		mriTRG 1 + 2		mriTRG 1 + 2 + 3	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Fayaz et al. [20]	11	18				
Sclafani et al. [15]	14	7.3	87	45.5		
Patel et al. [14]					47	60
Bhoday et al. [21]					111	77.6
Our study	21	23.2	58	61.1	78	82.1

ymriTRG magnetic resonance imaging tumor regression grade

had a wide variability in the literature, varying from slight to almost perfect [13, 15, 16], as demonstrated in Table 6.

From this perspective, we believe that our results support previous studies suggesting that although TRG has demonstrated to be a relevant predictor of survival outcomes [13, 30], it is not a reproducible and precise MRI parameter to be assessed after CRT, resulting in difficulties in the identification of patients with rCR. Considering the current importance of a trustworthy diagnosis of rCR, novel techniques are being tested with this purpose, including dynamic contrast-enhanced imaging [31], magnetic transfer ratio [32, 33], and textural analysis (radiomics) [34–36]. Although promising, these techniques still await validation and generalization is still limited.

Our study had some limitations, such as its retrospective design and radiological assessment performed by one radiologist; thus, interobserver agreement was not possible to be evaluated and the reproducibility of the results may be impaired. We also did not evaluate the diagnostic performance of diffusion-weighted imaging in the assessment of radiological response after CRT. Therefore, further prospective and randomized studies are needed to define the most reliable parameters in predicting rCR after CRT.

Conclusion

Qualitative assessment of MRI for the diagnosis of pCR showed moderate sensitivity and high specificity, whereas the diagnosis of TRG had moderate sensitivity and low specificity with slight inter-test agreement when compared with pathological specimens. Our results suggest that the five-tier TRG may not be an effective tool to evaluate response of patients with rectal cancer after CRT.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

Ethical approval For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Appendix

See Table 8.

Table 8 MRI parameters at our institution

Parameter	Pulse sequence	TR/TE (ms)	Matrix	FOV (mm)	ST/SG (mm)
Axial T2WI	FRFSE	3600/160	320 × 224	300	7/2
Sagittal T2WI	FRFSE	3300/120	256 × 256	200	3/0
Oblique axial T2WI	FRFSE	3600/120	256 × 256	160	3/0
Coronal T2WI	FRFSE	4250/160	256 × 256	200	3/0.4

FOV field of view, *FRFSE* fast-recovery fast spin-echo, *SG* section gap, *ST* slice thickness, *TE* echo time, *TR* repetition time, *T2WI* T2-weighted image

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