Original Research

Preoperative MRI accuracy after neoadjuvant chemoradiation for locally advanced rectal cancer

Anca-Raluca Popiţa[1,2], Adriana Rusu[3], Valentin Muntean[4], Patriciu Achimas Cadariu[1,5], Alexandru Irimie[1,5], Cosmin Lisencu[1,5], Bogdan Pop[1,6], Liliana Resiga[1], Zsolt Fekete[1,5], Radu Badea[2]

1) "Ion Chiricuţă" Oncology Institute, Cluj-Napoca, Romania

2) Medical Imaging Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Department of Diabetes and Nutrition Diseases, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

4) Department of Surgery, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

5) Oncology Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

6) Anatomical Pathology Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

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Address for correspondence:
ralucapopita@gmail.com

Abstract

Background and aims. To evaluate the performance of magnetic resonance imaging (MRI) in restaging locally advanced rectal cancers (LARC) after neoadjuvant chemoradiotherapy (nCRT), with pathologic correlation.

Methods. 80 patients with LARC treated with neoadjuvant therapy, with restaging MRI and surgery, were enrolled and prospectively reviewed. The diagnostic accuracy of the restaging MRI was assessed for tumor (ymrT), nodal status (ymrN), circumferential resection margin (ymrCRM), extramural vascular invasion (ymrEMVI) and tumoral deposits (ymrN1c) by calculating the sensitivity (Se), specificity (Sp), negative predictive values (NPV) and positive predictive values (PPV). Response to treatment was classified as good response (complete/near complete) vs. poor response (poor/partial response). The agreement between the tumor regression grade at MRI (mrTRG) and pathology (pTRG) was reported, as well the performance of mrTRG to identify good responders. The correlation between restaging MRI and histopathology was assessed by Spearman correlation coefficient.

Results. The MRI accuracy ranged between 63.8% and 92.5% for T stage and was 81.3% for N stage. All MRI parameters evaluated at restaging were statistically significant correlated with histopathology evaluation, but EMVI. There was moderate correlation for N and N1c and a positive strong correlation for T, CRM and TRG (Spearman correlation coefficient of 0.390 for mrN1c-pN1c, 0.428 for mrN-pN, 0.522 for mrCRM-pCRM, 0.550 for mrT-pT and 0.731 for mrTRG-pTRG). Diagnostic accuracy of anal sphincter invasion was 91.3%, with a negative predictive value (NPV) of 100%. Accuracy rate varied between 70% for partial response to 93.75% for complete response after nCRT.

Conclusions. MR imaging had good accuracy in restaging LARCs after nCRT. Our results showed high MRI accuracy in detecting anal sphincter involvement for low rectal tumors, with high NPV to exclude tumoral invasion. Restaging MRI predicted well the tumor regression grade, with good diagnostic performance in differentiating good responders from poor/partial responders. The accuracy was high for detecting complete response.

Keywords: rectal neoplasms, neoadjuvant chemoradiotherapy, magnetic resonance imaging, tumor response

Background and aims

Neoadjuvant chemoradiation therapy (nCRT) is the gold standard for locally advanced rectal cancers (LARCs), aiming to downsize and downstage the primary tumor. It increases the probability of an R0 resection, avoiding amputation or even surgery at all in case of clinical complete remission [1]. Chemoradiotherapy facilitates sphincter-preserving surgery for low rectal tumors, as well as standard total mesorectal excision (TME) for initially T4 tumors and decreases local recurrence rates [2,3]. For patients with good response to neoadjuvant treatment (good responders) it has the advantage of a "watch and wait" approach, avoiding radical surgery [4]. Therefore, assessment of tumor response is crucial before optimal surgical decision, being nowadays increasingly used to guide further treatment for each patient after neoadjuvant chemoradiation therapy.

Restaging magnetic resonance imaging (MRI), performed at least at 6-8 weeks after chemo-radiotherapy, is considered the best imaging technique for non-invasively evaluation of the tumor site and mesorectum [5]. High-resolution morphologic and functional MRI sequences are used to differentiate between residual tumor and radio-induced changes (fibrosis, edema, desmoplastic reaction, or mucin production) [6]. The tumor regression grade (TRG) reflects the proportion of residual tumor and fibrosis. Accurate restaging of treated rectal cancer must mention the presence or absence of residual tumor, specifying the depth of tumor extension through the layers of the rectal wall (T), detect positive lymph nodes (N) and establish the radial tumor spread (CRM). Persistence of extramural vascular invasion (EMVI) and tumor residual deposits harbored in the mesorectum (N1c) emphasize that radical local surgery must be accomplished. MRI TRG (mrTRG) is reported with the goal to predict pathology TRG (pTRG), having prognostic implications, correlated with disease free and overall survival [7,8].

In 2018 the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) working group updated the guidelines to provide standardization on the acquisition, interpretation and reporting of MRI for clinical staging and restaging of rectal cancer [5].

In the present study we evaluated the performance of MRI in restaging patients with LARC after neoadjuvant chemoradiation therapy, compared with pathological findings from surgical resection.

Methods

Study design and patients

This was a prospective, observational study performed between March 2017 and December 2021 in the Oncological Institute Cluj-Napoca. Patients with biopsy-proven locally advanced rectal adenocarcinoma, treated with preoperative neoadjuvant chemoradiation therapy, followed by surgery, were included in the study. The local staging criteria of inclusion were T3-T4 N0 or any T with N+ disease. Rectal MRI was performed before and after neoadjuvant chemoradiation therapy in all cases. We excluded patients with hip prosthesis or motion artifacts at MRI, non-oncologic death, and lack of histopathological data. pTRG was the reference standard.

This prospective study was approved by the local ethics committee, and written informed consent was obtained from all patients. The study was performed in agreement with The Code of Ethics of the World Medical Association (Helsinki Declaration) for experiments involving human subjects.

MRI protocol

MRI examinations were performed using a 1.5T equipment (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). The same protocol was used for all staging and restaging assessments, derived from the recommendations for MRI rectal cancer evaluation and reporting provided by the ESGAR guidelines [5]. T2WI, DWI with apparent diffusion coefficient (ADC) map, T2 high-resolution (T2HR) angulated perpendicular and parallel to the rectal tumor axis, and T1C sequences were performed (acquisition parameters are shown in table I). Gadolinium-based contrast agent was administered intravenously as bolus at a dose of 0.1 mmol/kg body weight followed by a 20-ml saline flush.

MRI was performed before the preoperative nCRT (baseline MRI) and just before surgery (restaging MRI).

MRI interpretation

Tumors with the lower edge located less than 6 cm above the anal verge were considered low rectal tumors. These cases were reported as mrLR at baseline, after the MRI staging system developed by Shihab et al [9].

Both baseline and restaging MRI examinations were read by the same radiologist, with 9 years of experience in rectal MRI. The images were analyzed using Syngo VB17 software, with the commercially available applications and OsiriX MD viewer.

Tumor reassessment (*ymrT* stage) was reported as T0-T4 according to the depth of invasion. The shortest distance between tumor and mesorectal fascia ≤ 1mm was defined a positive circumferential resection margin (*CRM+*) and was correlated with positive resection margins (R1) of the resected specimens. Anal sphincter involvement was considered positive when internal sphincter, intersphincteric plane, external sphincter or levator anal muscle invasion was seen.

The restaging MR imaging criteria for lymph nodes metastases (*ymrN+*) were the short axis >5 mm and residual intermediate or heterogeneous signal intensity on T2WI sequence [5].

Positive EMVI (ymrEMVI+) was reported at MRI when tumoral signal was seen into extramural vessels, as a continuity of the primary tumor, in tumors ≥T3.

Tumor deposits in the mesorectum (*ymrN1c present*) were described as nodules with tumoral signal and irregular contour, frequently with perivascular location, with different features than lymph nodes.

Table I. Restaging pelvic MRI acquisition parameters.

Magnetom Aera 1.5-T	Sagital T2WI	Axial T2WI	Oblique axial T2WI	Oblique coronal T2WI	Axial DWI	Axial T1+C (DCE)
Sequence	TSE	TSE	TSE	TSE	EPI DWI	VIBE
TR (ms)	5920	6380	5630	2670	6700	4.46
TE (ms)	108	114	108	108	75	1.72
ETL	17	17	17	17	-	5
FOV (mm²)	220	360	200	200	220	260
Flip angle (°)	160	160	160	160	-	12
Matrix	241x320	166x384	275x320	275x320	126x126	154x192
B-values	-	-	-	-	50, 500, 1000, 1500	-
Slice thickness (mm)	3	3	3	3	3	3,5
Gap (mm)	0	0,9	0	0	0	0,7

TR = repetition time; TE = echo time; ETL = echo train length; FOV = field of view; TSE = turbo spin echo; EPI = echo planar imaging; VIBE = ultra fast gradient echo; Oblique axial and coronal T2WI scans are oriented perpendicular and parallel to the rectal tumor axis, respectively.

Table II. Modified MRI tumor regression grade and pathologic tumor regression grade with modified Ryan scheme.

MRI	mrTRG	Response	pTRG	Pathology
Absence of tumor signal; linear/crescentic fibrotic scar in mucosa or submucosa	1	Complete response	0	No viable cancer cells
Dense hypointense fibrosis; no obvious residual tumor	2	Near complete response	1	Single cells or rare small groups of cancer cells
>50% fibrosis/mucin and visible residual tumor	3	Partial response	2	Residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells
Little areas of fibrosis/mucin but mostly tumor	4	Poor response	3	Extensive residual cancer with no evident tumor regression
Same appearances as baseline tumor or tumor regrowth	5	No response		

mrTRG = modified MRI tumor regression grade; pTRG = pathologic tumor regression grade.

mrTRG, adjusted after the system developed by the Mercury study group [10-12] was also reported, thus predicting good vs poor/partial response to treatment.

Image interpretation was done before surgery, so the radiologist was blinded to the pathological findings.

Definition of response and reference standards

Tumor response to neoadjuvant chemo-radiotherapy was evaluated with restaging MRI and correlated with the pathological reports from surgery (total mesorectal excision - TME) - the reference standard for all patients.

Histopathology analysis

Surgically resected specimens from TME were interpreted according to the guidelines of the American Joint Committee on Cancer, using the TNM staging system. The pathologist used a modified Ryan scheme (Table 2) for scoring pTRG after neoadjuvant therapy [13].

MRI was considered "true positive" for good responders (ymrTRG1/pTRG0 and ymrTRG2/pTRG1) as well as for partial/poor responders (ymrTRG3/pTRG2, ymrTRG4 or ymrTRG5/pTRG3) – if the histopathology analysis confirmed the MRI report (Table II). Also, lymph node metastases were considered "true positive" if pN1a, N1b, N2a or N2b were described at pathology.

Statistical analyses

Data were analyzed using MedCalc 20.026 (Ostend, Belgium: MedCalc Software Ltd) and IBM SPSS Statistics version 26 (Armonk, NY: IBM Corp). Numerical variables were summarized using descriptive statistics: number and proportion for qualitative variables, mean and standard deviation or median (quartile 1; quartile 3) for continuous variables. Chi square test was used to compare numerical variables.

The diagnostic performance of restaging MRI for T, CRM, N, EMVI, N1c, TRG was assessed by calculating the sensitivity (Se), specificity (Sp), negative predictive values (NPV) and positive predictive values (PPV). Accuracy rate was calculated as (*correctly predicted responses/ total number of patients assessed*) × 100%, separately for the four types of response (poor, partial, near complete and complete response) and for the two main types: good responders and partial/poor responders. The correlation between restaging MRI and histopathology was assessed by Spearman correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

During the above-mentioned period, 120 consecutive patients with locally advanced rectal cancer were assessed by pelvic MRI, before and after neoadjuvant chemoradiation therapy. After completion of neoadjuvant therapy, 85 patients underwent surgery. Five patients were excluded from the study due to artifacts from hip prosthesis and motion at MRI (3 patients), non-oncologic death (1 patient) and lack of histopathological data (1 patient). Finally, 80 patients (46 men and 34 women; median age 63.5 years; age range 25-80 years) met the inclusion criteria and were enrolled.

The median time between end nCRT and MRI was 6.5 weeks, and between restaging MRI and surgery 4 weeks. Initial MRI staging characteristics of the study cohort (T, N, CRM, EMVI, N1c) are depicted in table III.

Table III. Baseline participants characteristics.

Variable	N=80
Men, n (%)	45 (56.3%)
Age, years*	63.5 (52.5; 70.5)
Age groups, n (%)	
≤50 years	14 (17.5%)
51-60 years	18 (22.5%)
61-70 years	28 (35.0%)
≥71 years	20 (25.0%)
Tumor location, cm	
< 6 cm	23 (28.7%)
≥ 6 cm	57 (71.3%)
Time nCRT to restaging MRI, weeks	6.5 (6.0; 8.5)
Time from MRI to surgery, weeks	4.0 (2.0; 6.5)
Time from MRI to surgery intervals, n (%)	
0-4 weeks	50 (62.5%)
5-8 weeks	15 (18.8%)
9-12 weeks	13 (16.3%)
>12 weeks	2 (2.5%)
mrT baseline, n (%)	
≤ T3b	22 (27.5%)
≥ T3c	58 (72.5%)
mrN baseline, n (%)	
N0	10 (12.5%)
N+	70 (87.5%)
mrCRM baseline, n (%)	
CRM+	44 (55.0%)
CRM-	36 (45.0%)
mrEMVI baseline, n (%)	
EMVI+	38 (47.5%)
EMVI-	42 (52.5%)
mrN1c baseline, n (%)	
absent	53 (66.3%)
present	27 (33.8%)

n (%) = number (percentage) of patient; nCRT= neoadjuvant chemoradiotherapy; mrEMVI = extramural vascular invasion at MRI; mrCRM = circumferential resection margin at MRI; mrT = T stage at MRI; mrN = N stage at MRI ; mrN1c = tumoral deposits at MRI
*data are presented as median (quartile 1; quartile 3)

Low rectal tumors were present in 28.7% of cases (Table 3). They were reported as mrLR2 (3 cases), mrLR3 (12 cases) and mrLR4 (8 cases); 91.3% of all distal rectal tumors had positive circumferential resection margin (CRM+) at initial staging. Of the 23 patients with distal rectal tumors who underwent an abdomino-perineal resection, 4 patients were assessed to have sphincteric involvement by restaging MRI, giving a diagnostic accuracy of sphincteric evaluation of 91.3 %, with a negative predictive value (NPV) of 100% (Table IV).

Table IV. Sphincter involvement at restaging MRI and histopathology.

ymr sphincter invasion	yp sphincter invasion	
	Present	Absent
Present	2	2
Absent	0	19
Total	2	21

ymr sphincter invasion = sphincter invasion at restaging MRI; yp sphincter invasion = sphincter invasion at pathology.

The main two types of histopathologic treatment response (good response vs. poor/partial response) according to baseline MRI tumor characteristics is presented in table V. No statistically significant differences between baseline MRI characteristics that could predict tumor response could be identified.

The distribution of ypT and ymrT staging is shown in table VI. In this study cohort, 12 patients (15.0%) had ypT0, 7 (8.75%) ypT1, 16 (20.0%) ypT2, 42 (52.5%) ypT3 and 3 cases (3.75%) ypT4, based on the pathological staging. The MRI accuracy for T restaging was 92.5% for T0 and T4, 80.0% for T2 and 63.8% for T3 (Table VI). There were no ymrT1 cases reported prior to surgery. For T restaging the statistical analysis showed overstaging in 23 patients (28.8%), accurate staging in 48 patients (60.0%) and understaging in 9 (11.3%) cases. A patient with ypT0 at restaging MRI, confirmed by histopathological report from surgery, is presented in figure 1.

The pathological reports found ypN0 in 63 cases and ypN+ (including pN1a, N1b, N2a or N2b) in 17 cases. MRI accuracy was 81.3% for detecting N0 and N+ cases (Table VII). Overstaging was observed in 7 patients (8.7%), accurate staging in 65 (81.3%) and understaging in 8 (10.0%) cases.

A patient with partial response at restaging MRI (ymrT3 CRM- N+ N1c absent EMVI-, mrTRG3) and poor response at histopathology (yp T3N1cL0V1R0, pTRG 3) is presented in figure 2.

Table V. Histopathologic treatment response - baseline MRI tumor characteristics.

	Baseline tumor characteristics		p-value
	mrT ≤T3b N=22	**mrT ≥3c N=58**	0.543
Poor/partial response, n (%)	14 (63.6%)	41 (70.7%)	
Good response, n (%)	8 (36.4%)	17 (29.3%)	
	mrN 0 N=10	**mrN + N=70**	0.121
Poor/partial response, n (%)	9 (90.0%)	46 (65.7%)	
Good response, n (%)	1 (10.0%)	24 (34.3%)	
	mrCRM + N=44	**mrCRM – N=36**	0.904
Poor/partial response, n (%)	30 (68.2%)	25 (69.4%)	
Good response, n (%)	14 (31.8%)	11 (30.6%)	
	mrEMVI + N=38	**mrEMVI – N=42**	0.673
Poor/partial response, n (%)	27 (71.1%)	28 (66.7%)	
Good response, n (%)	11 (28.9%)	14 (33.3%)	
	mrN1c absent N=53	**mrN1c present N=27**	0.080
Poor/partial response, n (%)	33 (62.3%)	22 (81.5%)	
Good response, n (%)	20 (37.7%)	5 (18.5%)	

mrT ≤ T3b includes tumors that invade through the muscularis propria into the perirectal fat: T3a (< 1 mm), T3b (1-5 mm) and mrLR2 (low rectal tumor invades the full thickness of the internal anal sphincter without extending into the intersphincteric plane); mrT≥ T3c includes: T3c (5-15 mm), T3d (>15 mm), T4a (tumor invades peritoneum or peritoneal reflection), T4b (tumor invades adjacent organs or structures), mrLR3 (tumor extending into the low mesorectum to within 1 mm of the levator muscle), mrLR4 (tumor reaching levator muscle);

N/n (%) = number (percentage) of patients; mrT = T stage at MRI; mrCRM = circumferential resection margin at MRI; mrN = N stage at MRI; mrEMVI = extramural vascular invasion at MRI; mrN1c = tumoral deposits at MRI.

Table VI. Results of pathological examination and MRI for **T** restaging after neoadjuvant chemoradiotherapy

Histopathology	Cases	Restaging MRI (ymr)					Accuracy rate (%)
		T0	T1	T2	T3	T4	
ypT0	12	9	0	0	3	0	92.5%
ypT1	7	1	0	2	4	0	-
ypT2	16	0	0	7	9	0	80%
ypT3	42	2	0	5	30	5	63.8%
ypT4	3	0	0	0	1	2	92.5%
Total	80	12	0	14	47	7	

yp = stage at pathology; ymr = restaging MRI.

Table VII. Results of pathological examination and MRI for **N** restaging after nCRT.

Histopathology	Cases	Restaging MRI (ymr)		Accuracy rate (%)
		N0	N+	
ypN0	63	56	7	81.3%
ypN+	17	8	9	81.3%
Total	80			

yp = stage at pathology; ymr = restaging MRI.

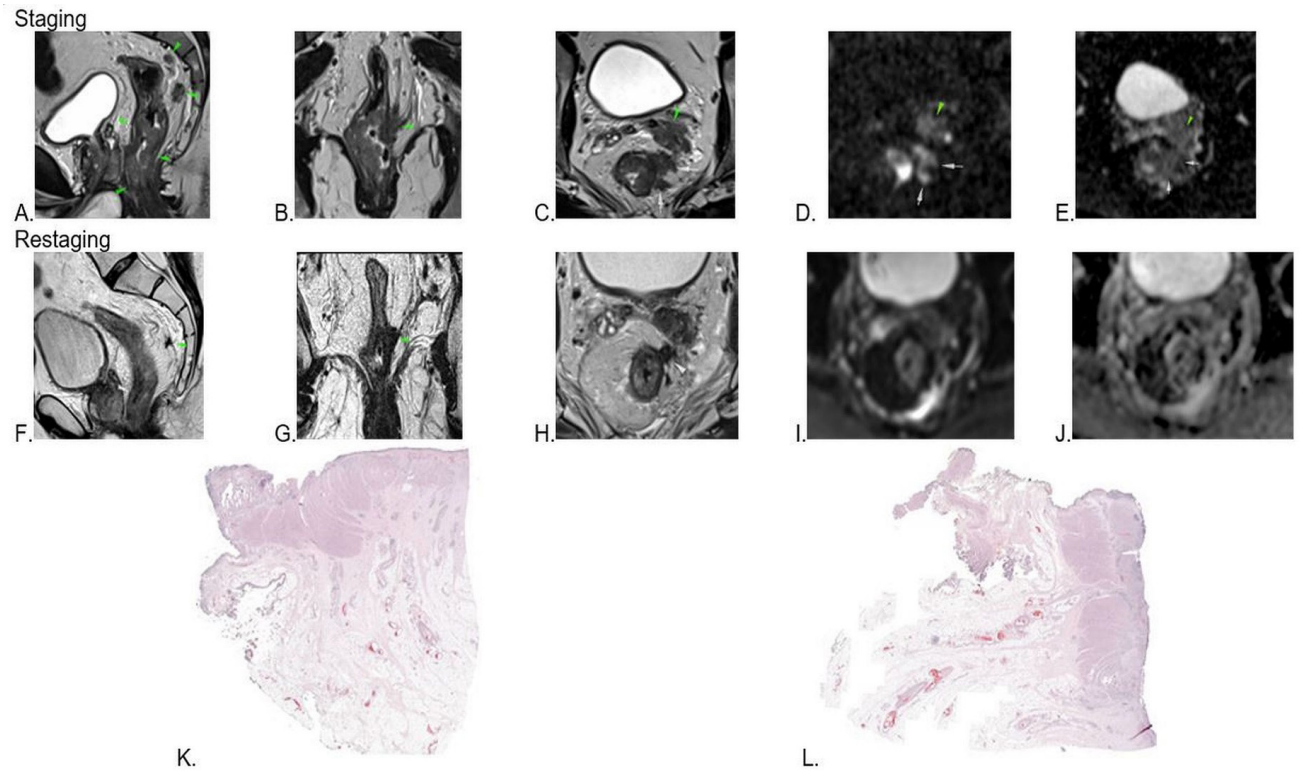

Figure 1. A 33-year-old male patient, initially staged mrLR4 CRM+ N+ N1c+ EMVI+ with good response at restaging MRI and histopathology (ymrT0N0, mrTRG1; ypT0N0, pTRG 0).
A - E Staging MRI: sagittal (A), coronal (B) and axial (C) T2WI HR showing a locally advanced tumor in the distal rectum, with extensive mesorectal fascia and left seminal vesicle invasion (green arrowheads); (D)-(E) restriction of diffusion (including the left seminal vesicle – green arrowhead). F - J Restaging MRI after nCRT: sagittal (F), coronal (G) and axial (H) T2WI HR showing marked reduction in tumor size, with fibrotic transformation of the tumor bed, pronounced hypointense on T2WI (arrow); no residual hyperintense signal on DWI, b=1000 (I), without low ADC (J); K, L: hematoxylin & eosin-stained 4-µm cut slices through the tumor scar illustrating dense fibrosis in the submucosa, thickened muscularis propria and fibrosis in the perirectal fat; no viable cancer cells.

Table VIII. Correlations between restaging MRI and histopathology.

Variables for which the correlation was tested	Spearman correlation coefficient	p-value
ymrT_– ypT	0.550	<0.001
ymrCRM - ypCRM (R)	0.522	<0.001
ymrN - ypN	0.428	<0.001
ymrEMVI - ypEMVI	0.124	0.272
ymrN1c - ypN1c	0.390	<0.001
ymrTRG_– ypTRG	0.731	<0.001

yp = stage at pathology; ymr = restaging MRI; T = T stage; CRM = circumferential resection margin; N = N stage; EMVI = extramural vascular invasion; N1c= tumoral deposits; mrTRG = MRI tumor regression grade; pTRG = pathologic tumor regression grade.

All MRI parameters evaluated at restaging were statistically significant correlated with histopathology evaluation, but EMVI. The Spearman coefficients showed a positive moderate correlation for N1c and N and a positive strong correlation for T, CRM and TRG (Table VIII).

Among the operated patients, 15.0% (n=12) had pathologic complete response (pTRG0), 16.25% (n=13) had near complete response (pTRG1), 53.75% (n=43) had partial response (pTRG2) and 15.0% (n=12) had poor response (pTRG3). Reporting with restaging MRI 13.8% (n=11) of patients were complete responders (mrTRG1), 26.3% (n=21) near complete responders (mrTRG2), 51.2% (n=41) partial responders (mrTRG3) and 8.8% (n=7) poor responders (Table IX).

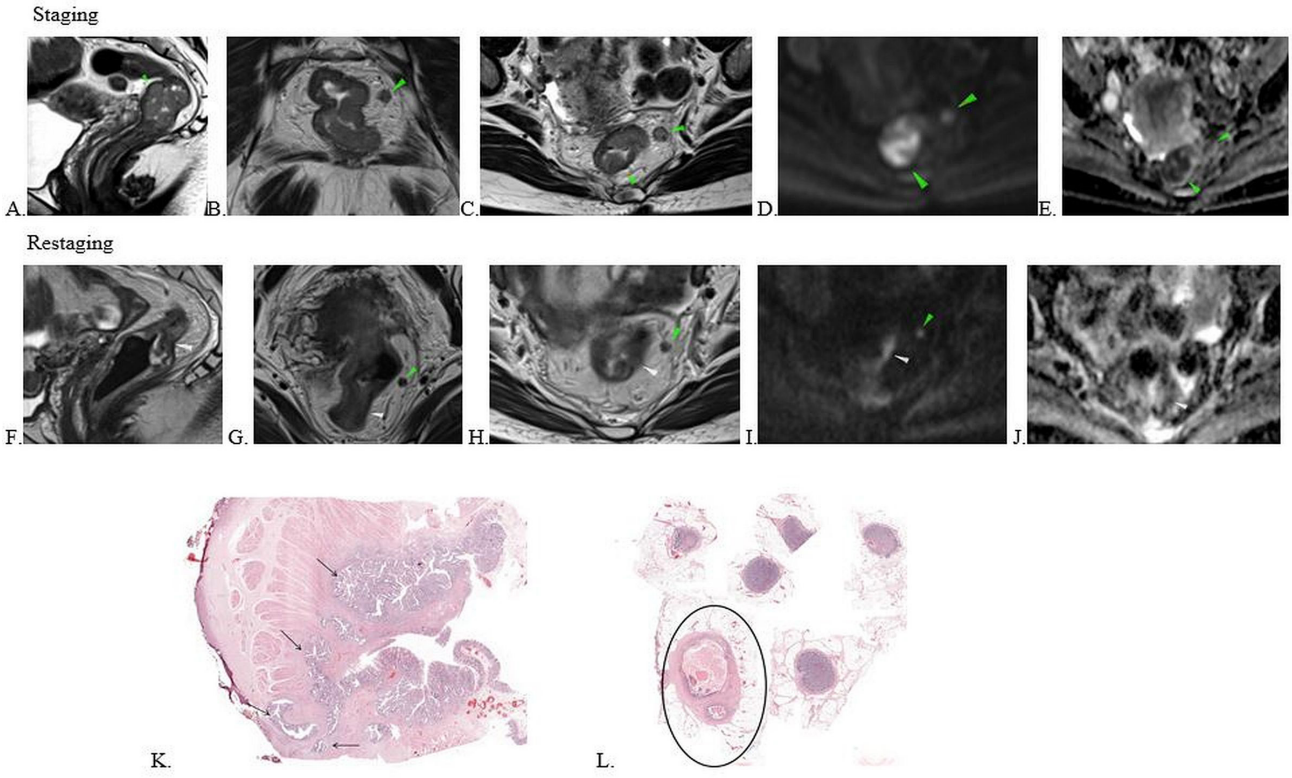

Figure 2. A 41-year-old female with partial response at restaging MRI (ymrT3 CRM- N+ N1c absent EMVI-, mrTRG3) and poor response at histopathology (yp T3N+L0V1R0, pTRG 3).

Table IX. Treatment response based on modified MRI tumor regression grade and pathologic tumor regression grade.

mrTRG	pTRG				
	Poor response N=12	Partial response N=43	Near complete response N=13	Complete response N=12	Total N=80
Poor response, n (%)	4 (33.3%)	3 (7.0%)	0	0	7 (8.8%)
Partial response, n (%)	8 (66.7%)	30 (69.8%)	3 (23.1%)	0	41 (51.2%)
Near complete response, n (%)	0	9 (20.9%)	9 (69.2%)	3 (25.0%)	21 (26.3%)
Complete response, n (%)	0	1 (2.3%)	1 (7.7%)	9 (75.0%)	11 (13.8%)

N/ n (%) = number (percentage) of patients; mrTRG = MRI tumor regression grade; pTRG = pathologic tumor regression grade.

Table X. Diagnostic performance of MRI for identifying poor, partial, near complete, and complete response.

	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	AUC (95%CI)	Accuracy rate, %
Poor response	33.3 (9.9;65.1)	95.6 (87.6; 99.1)	57.1 (25.4; 83.9)	89.0 (84.4; 92.4)	0.645 (0.530; 0.748)	86.3
Partial response	69.8 (53.9; 82.8)	70.3 (53.0; 84.1)	73.2 (61.5; 82.3)	66.7 (54.8; 76.7)	0.700 (0.587; 0.798)	70.0
Near complete response	69.2 (38.6; 90.0)	82.1 (70.8; 90.4)	42.9 (28.6; 58.4)	93.2 (85.8; 96.9)	0.757 (0.648; 0.846)	80.0
Complete response	75.0 (42.8; 94.5)	97.1 (89.8; 99.6)	81.8 (52.5; 94.8)	95.7 (89.2; 98.3)	0.860 (0.765; 0.928)	93.75

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value, AUC = area under the curve.

Table XI. Diagnostic performance of MRI in detecting good responders vs poor/partial. responders.

mrTRG	pTRG		
	Poor/partial response N=55	Good response N=25	Total N=80
Poor/partial response, n (%)	45 (81.8%)	3 (12.0%)	7 (8.8%)
Good response, n (%)	10 (18.2%)	22 (88.0%)	41 (51.2%)

N/ n (%) = number (percentage) of patients; mrTRG = MRI tumor regression grade; pTRG = pathologic tumor regression grade.

MRI accuracy was highest for complete response (Table X). Combining patients with complete response and near complete response, restaging MRI detected good responders with a Se of 88.0% (95%CI: 68.8 - 97.5), a Sp of 81.8% (95%CI: 69.1 - 90.9), a NPV of 93.7% (95%CI: 83.7 - 97.8), a PPV= 68.7% (95%CI: 55.2 - 79.7) and an accuracy rate of 83.75% (Table XI).

Discussion

This study prospectively assessed the diagnostic accuracy of restaging MRI, after neoadjuvant radiochemotherapy, with the pTRG from surgery as gold standard. From the characteristics chosen at the initial MRI staging, we found no statistically significant differences to predict the type of tumor response. There were high-risk rectal tumors (T ≥3c, CRM+ EMVI+, N+, N1c+) with complete response, as well as low-risk tumors at baseline (T ≤3b, CRM-, EMVI-, N0, N1c-) with poor/partial response to neoadjuvant chemoradiation therapy (Table III).

Among the patients with low rectal tumors included in this study, 91.3% had positive circumferential resection margin (CRM+) at baseline MRI. Our study found that restaging MRI had a high accuracy (91.3%) and a high NPV in ruling out sphincter invasion preoperatively. Based on our results, 82.6% patients could have been spared from an abdominoperineal resection (APR). For tumors that threaten or involve the intersphincteric plane, the external sphincter muscle or the levator ani muscle, sphincter-sparing surgery is not feasible. However, if the tumor shows a good response to neoadjuvant chemoradiation therapy, organ-preserving surgery may be an option, preserving the anus and making a coloanal anastomosis [14]. Similar to our results, a recent study from Laohawiriyakamol et al. [15] reported a high MRI diagnostic accuracy (90%; k 0.53) to determine sphincter invasion, with very high NPV for excluding sphincter involvement. Another study from 2020 showed that MRI can predict feasibility of successful sphincter preservation with an overall diagnostic performance of 0.84-0.87 [16].

Concerning the local tumor status, ymrT3 as well as ypT3 were the most frequent encountered T-categories in the MRI reports (58.7%), and pathology (52.5%). The diagnostic accuracy of ymrT restaging in our study was high for T0 and T4 (92.5%), 80.0% for T2 and moderate for T3 (63.8%). Our data are in accordance with other studies from the literature, in which a diagnostic accuracy of 93% was obtained for yT4b and of 84% for yT0 [15]. There were no yT1 tumors reported, as MR imaging cannot differentiate between yT1/yT2 tumor, ecoendoscopy being necessary in these cases. In other studies MRI predicted confinement of the tumor to the rectal wall (yT2) with an area under the curve of 0.86 [17]. In our study, accurate T staging occurred in 60.0% of cases, consistent with data from other studies [3,18,19]. Overstaging was more common (28.8%) than understaging (11.3%), reflecting the tendency to overestimate the amount of tumor within fibrosis after neoadjuvant chemoradiation therapy.

MRI correlated well with histopathology concerning the circumferential resection margin (CRM). Results on persistence of mesorectal fascial invasion after neoadjuvant chemoradiation therapy vary in the literature. Van der Paardt and colleagues calculated a moderate performance of MRI to predict tumor-free mesorectal fascial after neoadjuvant chemoradiation therapy [20]. Vliegen et al. showed that if there is a dense fibrotic infiltration of the mesorectal fascia, CRM is positive in around 50% of cases at histopathology [21].

Regarding the lymph node reassessment, we noted in each MRI report the total number of suspicious mesorectal and extramesorectal (lateral) nodes, specifying the location of the suspicious lateral nodes when present. ymrNo (80%) and ypN0 (78.7%) were most common encountered. MRI had good accuracy (81.3%) for nodal restaging. Understaging was more common (10%) than overstaging (8.7%) and this was also described in other studies [15]. In the literature nodal restaging was more accurate than primary nodal staging, with a NPV to predict ypN0 of up to 95% [22,23]. The study of Heeswijk et al. [24] demonstrated that the absence of nodes on DWI sequence, on restaging MRI is a reliable predictor of ypN0. But in most of our cases few small nodes were still visible on restaging DWI, which could not be characterized on ADC. DWI sequence has great conspicuity to detect lymph nodes but cannot differentiate benign from malignant ones [18]. The lateral nodes are

an important site to be evaluated at staging and restaging MR imaging, as the malignant nodes have high risk of local recurrence, and the decision of lateral pelvic nodes dissection must rely on post-neoadjuvant chemoradiation therapy MRI [25].

Extramural vascular invasion (EMVI) represents an important prognostic factor and is recognized as a predictor of local recurrence, distal metastases and poorer overall survival [26]. In our study, EMVI was detected at initial staging in 38 (47.5%) of cases and at restaging in 10 (12.5%) of cases, but 9 of 10 were "false positive". 36.8% of cases with initial EMVI+ turned into good responders after neoadjuvant treatment, when fibrotic signal intensity was described on T2WI sequences with no diffusion restriction. Other studies reported a low sensitivity (62%) and high specificity (88%) in detecting EMVI using pathology as gold standard [27].

N1c is described at pathology when no regional lymph nodes are positive, but tumor deposits are present in the subserosa and nonperitonealized perirectal tissue. If a vessel wall is identified, the lesion is classified as lymphovascular invasion (either lymphatic or venous) and if there are neural structures, perineural invasion is noted [13]. For the patient outcome it is important to note extranodal tumor in MRI reports, even if this might be a positive lymph node with extracapsular extension, a tumoral deposit or discontinuous EMVI [28]. In this study 18.5% of cases with initial N1c+ at MRI turned into good responders after neoadjuvant treatment. MRI correlated well with histopathology concerning the tumor deposits (N1c).

We obtained a good correlation comparing the tumor regression grade at restaging MRI and pathology (mrTRG-pTRG). Accuracies varied among different types of treatment response, being highest for complete response (93.7%). These results emphasize the important role of restaging MRI in identifying patients with complete response, as they may benefit from a "watch and wait" approach. This strategy is increasingly used for patients with low rectal tumors with complete response after neoadjuvant therapy. The goal of watchful waiting approach is to identify complete responders and then strictly follow-up them with digital rectal exam (DRE), endoscopy and MRI, with surgery in case of tumor recurrence [29-31]. Restaging MRI had a good accuracy in evaluating treatment response compared to histopathology with an AUC of 0.849 and an overall accuracy of 83.75%. We obtained better Sp (81.8.0%), Se (88.0%), NPV (93.7%), PPV (68.7%) for identifying good responders vs poor/partial responders compared to prior studies [19].

The staging and restaging MRI protocol we used is reliable for optimizing the type and need of radical surgery after neoadjuvant therapy.

There are several strengths and limitations of the study. We believe that the use of a rigorous methodology and the use of pathology results as comparators for MRI represent the main strength of this research, increasing the reliability of our results. A single MRI reader might be a flaw of this study as did not allow us to assess the inter-reader agreement, however it may also represent a strength as it provides homogenous interpretation of acquired images. We did not routinely use other complementary methods for locoregional restaging. Endoscopy was not done routinely before surgery for patients with good response at MRI. A subset of patients was evaluated with PET-CT but we did not compare these findings in the current study. The complementary techniques we mentioned could improve the locoregional restaging, further studies being needed to confirm these data. The time from the end of neoadjuvant chemoradiation therapy-restaging MRI and MRI-surgery varied among included patients and this might have been influenced the results. We don't have the evidence that the same lymph nodes and tumor deposits were compared at MRI and pathology, so the resected specimens might not have been a perfect reference standard. In the restaging MRI report we did not subdivide the ymrN+ cases in subcategories according to the number of lymph nodes involved, so that we do not have a precise correlation with pathology. The correlation is also affected by the lack of precise location of the involved nodes in the mesorectum as well as by the lack of resection of the extramesorectal nodes. Nevertheless, restaging MRI helps for an improvement in terms of treatment options, as imaging interpretation of ymr T, N, CRM, EMVI, N1c and of involvement of anal sphincter complex play an important role in rectal cancer management. Furthermore, this is a single center study; its results need to be confirmed by further studies with larger samples.

Conclusions

MR imaging had a good accuracy in restaging LARC after neoadjuvant chemoradiation therapy; for T and N stage, circumferential resection margin and tumoral deposits detection, a good correlation with pathology was obtained. Our results showed high MRI accuracy in detecting anal sphincter involvement for low rectal tumors, with high negative predictive value in ruling out tumoral invasion. Restaging MRI of LARC after neoadjuvant chemoradiation therapy predicted well the tumor regression grade, with good diagnostic performance in differentiating good responders from poor/partial responders. The accuracy was high for detecting complete response. This is important for further personalized treatment after neoadjuvant chemoradiotherapy.

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