Original Article

Predictive Parameters in Magnetic Resonance Imaging for Tumor Regression after Neoadjuvant Chemoradiotherapy Applied for Rectal Cancer

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ABSTRACT

Background:
To date, magnetic resonance imaging (MRI) plays a critical role in the management of rectal cancer. Although neoadjuvant chemoradiotherapy (nCRT) is a gold standard approach in advance to surgical management, it might alter the tissue texture, affecting MRI findings applied for decision-making in a procedural approach.
Aim: The current study aimed to assess the predictive parameters in MRI associated with response to nCRT in rectal cancer.

Materials and Methods:
The current cross-sectional study has been conducted on 50 patients with rectal cancer who were candidates for nCRT during 2020-21. Data including tumor markers and MRI parameters including tumor signal, tumor stage (TMN), lymph node involvement, mesorectal fascia (MRF), extramural venous invation (EMVI), peritoneal reflection invasion and tumor size were gathered at baseline and within 4-6 weeks after nCRT. The predictive factors for response to nCRT were evaluated using tumor regression grade (TRG) and TNM staging.

Results:
Tumor size (P<0.001), MRI signal intensity (P=0.038), tumor appearance in diffuse weighted imaging (DWI) (P<0.001), tumor stage (P<0.001), lymph node involvement (P<0.001), MRF (P<0.001), EMVI (P<0.001), and peritoneal reflection invasion (P<0.001) remarkably improved in post-nCRT assessments. Tumor size was associated with 3.75 (95%CI: 1.61-8.72) and 2.64 (95%CI: 1.40-4.97) folds, and lymph node involvement was associated with 77% (95%CI: 0.21-15.02) and 60% (95%CI: 0.21-11.96) increased probability of response to treatment based on TRG and TNM, respectively.

Conclusion:
Based on the findings of this study, nCRT could remarkably improve adenocarcinoma of rectal cancer-related laboratory and imaging parameters; however, tumor size and lymph node involvement were the only predicting factors for response to nCRT.

Keywords: Rectal neoplasms, Magnetic resonance imaging, Neoadjuvant therapy, Prognosis

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INTRODUCTION

To date, magnetic resonance imaging (MRI) plays a critical role in the management of rectal cancer, considering its accuracy and reproducibility in the evaluation of local staging of cancer, allowing to stratify recurrence probability and approaching the disease adequately, neither undertreating the patients nor overtreating (1).

The gold standard strategy for locally advanced rectal cancers management is to apply neoadjuvant chemoradiotherapy (nCRT) to reduce the tumor size and perform total mesorectum excision (TME), an approach that allows the preservation of the anal sphincter and prevents a life-long requirement for colostomy implementation as well as decreasing recurrence rate (2,3).

It has been well-documented that various MRI findings, including tumor (T) grading, lymph node (N) involvement, mesorectal fascia (MRF) involvement, extramural venous invasion (EMVI) and tumor regression grading (TRG), are associated with rectal cancer prognosis (4). Since a long time ago, the T and N classification has been applied to prognosticate the patients' outcomes after surgical approach for rectal cancer. Similarly, it has been considered for the response to neoadjuvant therapy with a similar context; however, the accuracy of this staging system remained a question due to tissue alterations because of chemoradiotherapy, such as fibrosis and edema (5, 6). EMVI defined as the presence of tumor cells in blood vessels outside the muscular layer, is associated with rectal cancer poor prognosis. Numerous investigations in the literature have represented that MRI findings compatible with EMVI grades 3 and 4 can prognosticate rectal cancer adverse outcomes (7). Response to nCRT can be assessed using TRG as another indicator representing that less regression following nCRT is compatible with poor prognosis (8).

One of the facts that might occur due to nCRT is tissue texture change that potentially can affect MRI findings; however, the knowledge about the influence of this tissue change on various MRI prognostic factors is limited (2, 9, 10). Accordingly, the current study aimed to assess the prognostic significance of pre-nCRT MRI and post-nCRT MRI findings in patients with rectal cancer.

MATERIALS AND METHODS

Study population:

The current cross-sectional study has been conducted on 50 patients with adenocarcinoma of the rectum who were candidates for neoadjuvant therapy for their underlying malignancies, referring to Alzahra or Seyed-o-shohada Hospitals affiliated with Isfahan University of Medical Sciences from March 2020 to April 2021.

The study was designed according to tenets of the Helsinki Declaration, proposed to the Ethics Committee of Isfahan University of Medical Sciences and approved via code number IR.MUI.MED.REC.1398.714. The trend of the study was entirely explained to the patients. They were reassured regarding their personal information confidentiality and signed written consent.

The patients with documented diagnoses of rectal cancer whose malignancy was in T3-T4 stages according to the baseline MRI and were candidates for neoadjuvant therapy were included. Those with distant metastasis (M1 based on TMN staging), who were reluctant to participate in the study, deceased during neoadjuvant therapy, had more than 20% defects in their medical records, failed to refer for follow-up visits, who did not have MRI at baseline and in post-neoadjuvant therapy settings and whose quality of MRI was inappropriate were excluded.

Due to the census design of the study, all the patients who met the criteria entered into the investigation through convenience sampling.

Study design:

Before neoadjuvant therapy, complete examination, including digital rectal examination, colonoscopy, biopsy, and biomarkers assessment (carcinoembryonic antigen [CEA] and CA 19-9) were performed for the patients. Besides, they underwent MRI assessments to determine the extension and grading of the tumor. Those who met the criteria for neoadjuvant therapy entered into the study (11). Accordingly, the studied population was treated with the standard therapeutic regimen of chemotherapy with capecitabin/5fu followed by 25-28 sessions of radiotherapy in 4500-5000 centigrade dose. The second MRI was performed for the patients at 6-8 weeks intervals after the end of the neoadjuvant protocols.

The gathered data included the patients' age, sex, colorectal biomarkers, including CEA and CA 19-9 measured at baseline and within 6-8 weeks after the neoadjuvant chemoradiotherapy and MRI-related parameters.

Imaging:

MRI was done twice for all the patients, once at the time of cancer diagnosis to assess the disease staging and within 6-8 weeks after neoadjuvant chemoradiotherapy for the second time.

The images were taken using a 1.5 Tesla MRI device (GE HealthCare, The United States) in T1, T2 and diffuse weighted imaging (DWI) modes. Then, an expert target radiologist who was blinded to the patients interpreted the images. In order to minimize the potential bias, both imaging performed at the time of disease diagnosis and after the end of neoadjuvant therapy were anonymous so as not to affect the radiologist's insight.

The recruited data from the MRIs included tumor signal (hypo-, iso- and hyperintense), tumor appearance in DWI (no lesion, scattered or mass-like), tumor staging based on TMN(12), lymph node involvement, mesorectal fascia invasion (MRF), extramural venous invasion (EMVI), peritoneal reflection involvement, and tumor size.

Tumor staging was done based on TMN staging system (12). Therefore, the patients in T3/T4 stages were included, and post-treatment T was presented by the radiologist. Lymph nodes were assessed, and the presence of nodes with diameters>5mm, irregular borders, or heterogenous signals was determined as node involvement. Tumor size was determined as the longest axis of the tumor. MRF invasion was defined as extramural node involvement or more than 1 mm extramural tumoral deposition (13). Scores of 3 and 4 based on Smith et al. MRI scoring system was indicated to EMVI (14). Eventually, mrTRG was determined based on the Patel staging system presented in table 1 (15).

Table 1. Tumor regression grading

Grade 1	No evidence of tumor
Grade 2	Dense (>75%) fibrosis with no obvious residual tumor
Grade 3	>50% fibrosis or mucin with a minority of visible tumor
Grade 4	<50% fibrosis of mucin with a majority of visible tumor
Grade 5	No post-treatment changes (same as before treatment)

In the post-neoadjuvant therapy assessments, response to treatment was defined as TRG grades 1-3 and TMN stages 1-2.

Statistical analysis:

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 15.0, SPSS Inc., Chicago, IL, USA) software. The categorical data were presented in absolute numbers and percentages. The continuous variables were reported in mean and standard deviation. The chi-square or Fisher's exact tests were applied to compare the categorical variables. The continuous data were compared using the independent t test. The logistic regression test was utilized to assess the predictive factors associated with the response to the neoadjuvant protocols. A P value of less than 0.05 was considered a significant level.

RESULTS

The current study was conducted on 50 patients with rectal cancer whose MRI characteristics were evaluated in advance to and after nCRT. The studied population had a mean age of 65.46±9.09 years, ranging from 45-85 years.

Table 2. The tumor-related parameters before and after neoadjuvant therapy

Variables		Pre-nCRT (n=50)	Post-nCRT (n=50)	P
Laboratory biomarkers				
CEA (ng/mL), mean±standard deviation		5.63±0.44	5.58±0.44	<0.001*
CA 19.9 (units/ml), mean±standard deviation		69.18±8.91	66.95±9.41	<0.001*
MRI parameters				
Tumor signal intensity, n (%)	Hyperintense	5 (10)	1 (2)	0.038**
	Isointense	16 (32)	11 (22)	
	Hypointense	29 (58)	38 (76)	
Tumor appearance in DWI, n (%)	No	4 (8)	28 (56)	<0.001**
	Scattered	4 (8)	12 (24)	
	Mass-like	42 (84)	10 (20)	
Tumor stage, n (%)	T1 & T2	0 (0)	34 (68)	<0.001**
	T3	21 (42)	10 (20)	
	T4, a & b	29 (58)	6 (12)	
Lymph node involvement, n (%)	N0	10 (20)	29 (58)	<0.001**
	N1 (a & c)	28 (56)	14 (28)	
	N2 (a & b)	12 (24)	7 (14)	
Mesorectal fascia invasion (yes), n (%)		28 (56)	11 (22)	<0.001#
Extramural venous invasion (yes), n (%)		27 (54)	11 (22)	<0.001#
Peritoneal reflection involvement (yes), n (%)		26 (52)	14 (28)	<0.001#
Tumor size (cm), mean±standard deviation		5.24±1.73	2.35±1.04	<0.001*

*Paired t-test
**Wilcoxon test
#McNemar test

The studied population predominantly consisted of 28 men (56%).

Table 2 demonstrates the changes in the assessed parameters before and after nCRT. Based on this table, tumor size (P<0.001), MRI signal intensity (P=0.038), tumor appearance in DWI planes (P<0.001), tumor stage (P<0.001), lymph node involvement (P<0.001), mesorectal (P<0.001) or vascular invasion (P<0.001), and peritoneal reflection involvement (P<0.001) remarkably improved in the patients.

Table 3. The comparison of cancer-related parameters between neoadjuvant responders and non-responders

Variables		TRG		P	TNM		P
		4&5 (n=13)	1&2&3 (n=37)		3&4 (n=16)	1&2 (n=34)	
Sex	Female	5 (38.5)	23 (62.2)	0.139	8 (50.0)	20 (58.8)	0.558**
	Male	8 (61.5)	14 (37.8)		8 (50.0)	14 (41.2)	
Lymph node involvement, n (%)	N0	7 (53.8)	3 (8.1)	<0.001	6 (37.5)	1 (11.8)	0.034**
	N1&2	6 (46.2)	34 (91.9)		10 (62.5)	30 (88.2)	
Tumor signal intensity n (%)	Hyperintense	0 (0)	5 (13.5)	0.351	0 (0)	5 (14.7)	0.782#
	Isointense	6 (46.2)	10 (27)		6 (37.5)	10 (29.4)	
	Hypointense	7 (53.8)	22 (59.5)		10 (62.5)	19 (55.9)	
Mesorectal fascia invasion, n (%)	-	8 (61.5)	14 (37.8)	0.139	9 (56.3)	13 (38.2)	0.231**
	+	5 (38.5)	23 (62.2)		7 (43.8)	21 (61.8)	
Lymphovascular invasiobn, n (%)	-	8 (61.5)	15 (40.5)	0.191	9 (56.3)	14 (41.2)	0.318**
	+	5 (38.5)	22 (59.5)		7 (43.8)	20 (58.8)	
Peritoneal reflation invasion, n (%)	-	8 (61.5)	16 (43.2)	0.256	8 (50.0)	16 (47.1)	0.846**
	+	5 (38.5)	21 (56.8)		8 (50.0)	18 (52.8)	
Tumor appearance in DWI, n (%)	No	2 (15.4)	2 (5.4)	0.558	3 (18.8)	2 (5.4)	0.209#
	Scattered	1 (7.7)	3 (8.1)		1 (6.3)	3 (8.1)	
	Mass-like	10 (76.9)	32 (86.5)		12 (75.0)	32 (86.5)	
Age (years), mean±standard deviation		64.64 (10.27)	67.76 (8.36)	0.333	67.93(10.24)	64.29 (9.67)	0.229##
Tumor size (cm), mean (std)		5.90 (1.36)	3.36 (1.23)	<0.001	3.88 (1.50)	5.88 (1.45)	<0.001##
CEA (ng/mL) *, mean±standard deviation		5.68 (0.43)	5.48 (0.47)	0.173	5.53 (0.59)	5.68 (0.35)	0.263##
CA 19.9 (units/mL), mean±standard deviation		70.30(9.41)	65.97(6.59)	0.133	66.96(6.26)	70.22(9.82)	0.232##

*ln(CEA)
**Chi-square test
#Fisher exact test
##Independent t-test

In the next step, logistic regression analysis was performed to determine the predicting factors for response to neoadjuvant therapy. Accordingly, each centimeter increase in tumor size was associated with 3.75 (95% CI: 1.61-8.72) and 2.64 (95% CI: 1.40-4.97) folds increased probability of response to treatment based on improved TRG and TNM, respectively. Similarly, lymph node involvement in advance to neoadjuvant therapy was associated with 77% (95%CI: 0.21-15.02) and 60% (95%CI: 0.21-11.96) increased probability of response to treatment based on post-neoadjuvant TRG and TNM assessments (table 4).

Table 4. Logistic regression analysis of predicting factors for response to neoadjuvant therapy in colorectal cancer

Variables		B	S.E.	Sig.	OR	95% Confidence interval	
						Lower	Upper
TRG	Lymph node involvement (n1&2)	.575	1.089	.598	1.777	.210	15.027
	Tumor size	1.323	.430	.002	3.756	1.616	8.727
	Constant	-5.405	1.730	.002	.004		
TNM	Lymph node involvement (n1&2)	.475	1.024	.642	1.609	.216	11.963
	Tumor size	.973	.322	.002	2.647	1.409	4.973
	Constant	-4.090	1.686	.015	.017		

DISCUSSION

The current study mainly aimed to investigate the effects of nCRT on rectal cancer-related factors in patients with rectal cancer and figure out the best MRI-associated parameters predicting response to nCRT. Accordingly, we found that nCRT for rectal cancer led to significantly improved parameters, including a decrease in CEA and CA 19.9, increased tumor signal intensity and decrease in the rate of mass-like lesions in DWI, declined tumor size, decrease in the rate of lymph node, MRF, EMVI invasion and peritoneal reflection involvement. Nevertheless, the logistic regression assessments showed that lymph node involvement and tumor size were the only predicting factors for response to neoadjuvant therapy in rectal cancer. Given that, each centimeter increase in tumor size was accompanied by 3.7 and 2.6 folds increased probability of achieving TRG and TMN grades compatible with response to the medication. Besides, those patients with lymph node involvement before nCRT had an increased probability of responding to the treatment for 77% based on TRG and 60% based on TMN.

To date, MRI plays a critical role in the management of rectal cancer regarding the accurate assessment of local staging and the selection of the most proper therapeutic strategy made by the multidisciplinary team (MDT). Nevertheless, the value of diverse MRI parameters after nCRT to predict response to treatment and approach the cancer in the next steps remained a matter of debate considering the effects of nCRT on the tissue textures (1,16).

Similar to our findings, Stanely and colleagues represented that tumor size above 5 cm was a predicting factor for response to nCRT (17). Besides, Sathyakumar and colleagues measured tumor volume at baseline, and then, after nCRT reporting, that more significant diminish in larger tumors volume was noted compared with smaller ones. They continued that the amount of decrease in tumor volume was the best predictive factor for response to treatment (18). The notion in these studies regarding the significance of larger tumor size refers to the fact that a low-size tumor may relatively lack organ mobility compared with larger rectal tumors. Hence, the probability of geographical miss during radiotherapy might be reduced, and the likelihood of receiving the appropriate volume and dose of radiation might increase (17). On the other hand, there are several studies indicating that tumors with less than 3 cm are better responders to nCRT (19-21). They have claimed that tumor size is a factor that affects other parameters such as MRI TRG or might determine the probability of pathologies such as EMVI and MRF invasions (22,23); however, these studies have measured the tumor size via different means, including endorectal ultrasound, digital rectal examination, and flexible endoscopy (19-21).

We also found that the patients with lymph node involvement were better responders to nCRT, considering their TRG outcomes. Nodal involvement in rectal cancer is a great concern for the physicians assessing the treatment

outcomes. In this regard, a decrease in the size and number of malignant lymph nodes is considered as one of the key points after nCRT (24), a characteristic that is in line with our findings; however, additionally, we found that the patients with more severe node involvement experienced higher rates of decrease in the number of malignant nodes. Similarly, Patel and colleagues insisted on the significance of nodal involvement in response to nCRT (15).

Although we found other MRI findings, including EMVI, MRF and peritoneal reflection involvement, unable to predict response to nCRT in rectal cancer, the major body of evidence in the literature emphasizes these parameters. EMVI has been factored in as a predictive factor prognosticating rectal cancer outcomes in regard to diverse variables, including response to nCRT, CRT, and distant metastasis probability (6,7). Besides, it should be noted that interobserver agreement for EMVI diagnosis was relatively high in the previous studies showing the value of this parameter in MRI studies of the patients (10, 25); however, EMVI source and the association of its source with response to nCRT remained a matter of debate (26).

MRF and peritoneal reflection invasion have been noticed to less content, probably due to the extent and significance of EMVI, but generally, the studies are in agreement regarding the negative impact of MRF and peritoneal reflection involvement on rectal cancer response to treatment, including nCRT or CRT. Besides, they have concluded that the probability of EMVI is higher among those with mesorectal or peritoneal reflection tumor invasion (4, 27, 28).

Tumor markers, including CEA, are of great interest as the determinant of response to nCRT. Accordingly, in contrastto our study, the majority of studies represent that CEA above 5 ng/mL is associated with poor response to nCRT (29-31); however, some authors believe that as smoking can increase CEA levels, it is not reliable enough (32). Nevertheless, similar to De la Pinta and others (33), we found no predicting role for this biomarker; however, we have not evaluated smoking in our patients, either.

One the other imaging parameters that has turned the attention in recent investigations is DWI of the tumors. In agreement with the majority of investigations, we found remarkable improvement in post-nCRT lesion patterns in DWI; however, it did not come out as one of the predictors of response to nCRT. Searching the literature showed that tumoral view in DWI is a valuable factor in predicting response to treatment (34) as well as a means to evaluate the manner of tumors in the future (18,35).

Despite the valuable findings of the current study, its cross-sectional design seems to be its most significant limitation. More generalizable outcomes can be achieved in further investigations with cohort design. The small sample population is the other limitation of this study. Besides, considering the requirement for an MDT to decide on the therapeutic approach in rectal cancer, a team of radiologists is required to blindly assess the pre- and post-nCRT MRIs, and the agreement between the interpretations should be evaluated. Another limitation is the lack of histopathological results (by re-biopsy or surgical specimen) as the gold standard of the study to validate the post-treatment MRI findings. This is the main drawback of this study that might affect all the results. Additionally, some data on the mucinous type of cancer was missed and forced us to neglect them, which restricts us from analyzing it and making a frequency in these cases.

CONCLUSION

We found that post-nCRT MRI can help assess response to treatment in patients with locally advanced rectal cancer despite the possibility of tissue texture damage and change due to chemoradiotherapy. Lymph node involvement and tumor size were the only predictive factors for response to neoadjuvant therapy in adenocarcinoma of the rectum. Patients with lymph node involvement prior to nCRT had a higher probability of responding to the treatment, with a 77% response rate based on TRG and a 60% response rate based on TMN. Lymph node involvement was also associated with better TRG outcomes after nCRT. EMVI, MRF and peritoneal reflection involvement were not able to predict response to nCRT in rectal cancer. Based on the findings of this study, nCRT could remarkably improve rectal cancer-related laboratory and imaging parameters; however, tumor size and lymph node involvement were the only predictive factors for response to nCRT.

Authors' Contribution

Conceptualization: Ali Akhavan, Mohsen Karimian
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Conflict of interest

The authors declare no conflict of interest related to this work.

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