MRI for Response Evaluation after Chemoradiotherapy for Locally Advanced Rectal Cancer

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Abstract:

Background: Standard treatment for T3 or T4 and/or node-positive rectal cancer is preoperative chemoradiotherapy (CRT) followed by total mesorectal resection (TME). After surgery, 10–24% of patients have no remaining tumor. Complete pathologic response (pCR) after CRT has led to nonoperative treatment for carefully chosen patients with a complete clinical response (CR). 5-year overall survival (OS) and disease free survival (DFS) were 93% and 85%. DWI can evaluate chemoradiotherapy response (8-10), adding DWI to regular MRI increased radiologists' ability to select full responders.

Aim: The purpose of our study is to evaluate the accuracy of MRI for selection of complete responders after chemoradiotherapy for locally advanced rectal cancer.

Subject and Methods: This is a retrospective study. Baseline, post treatment MRI scans, Clinical assessment including digital rectal examination, and endoscopy are needed for each patient.

Results: ADC after chemoradiotherapy in the study population ranged from 0.43 to 1.53. T2WI volumetry after CRT in the study population ranged from 3.1 to 8.7. Number of patients with good MRI - TRG in the study population was 20 (67%).

Conclusion: Pathological and MRI evaluation agree well. DWI patterns and T2W MRI-based MR-TRG improve MRI's diagnostic effectiveness for predicting pathological response. Improves interobserver agreement and radiologist trust. Further studies are needed to investigate MRI-capacity TRG's to identify pathological complete responders for nonoperative therapy and to give complementary prognostic information to pathological TRG for risk-stratification following surgery.

Key words: MRI, Rectal Cancer, Chemoradiotherapy

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Introduction:

For patients with T3 or T4 and/or node-positive rectal cancer, the current standard of care is to provide preoperative concurrent chemotherapy and radiation therapy (CRT), which is followed by complete mesorectal excision (TME). [1] In 10–24% of patients, no residual tumor is found at histology after surgery [2].

Recently, a more conservative treatment is advocated in patients who show a good or complete response to neoadjuvant treatment. Results at 5-year follow-up were favorable for the nonsurgical group, with an overall and disease-free survival of 93% and 85%, respectively [3].

As of late, a watch and wait strategy retains oncologic outcomes while avoiding the morbidity linked to drastic surgery. When chemoradiotherapy yields a full clinical response in patients with locally advanced rectal cancer, it may be taken into consideration as a therapeutic option. [4].

Prior to surgical resection, high-resolution magnetic resonance imaging (MRI) has been utilized to evaluate tumor response. It was discovered that the MRI-assessed TRG (mrTRG) is an independent predictor of DFS and overall survival (OS). [5].

A nonoperative strategy has been suggested as an alternative treatment for carefully chosen patients who have achieved a complete clinical response (CR)

following complete pathologic response (pCR) following CRT. Results from 99 patients with a clinical CR who received just observational treatment were published by Habr-Gama et al. [6].

According to a recent study, MRI-assessed complete tumor response can be utilized as a surrogate marker to predict the lack of live tumor cells because it has a good correlation with pathologic complete response. [7].

Our study's goal is to assess how well MRI can identify a favorable response following chemotherapy and radiation treatment for locally advanced rectal cancer.

Patients and Methods:

This was a retrospective study

Number of patients included in this study was 60 patients

Age of patients: Patients over the age of eighteen.

Patient inclusion:

Patients who have locally advanced rectal adenocarcinoma (T3c-T4 N any, CRM+ M0) and are receiving neoadjuvant chemotherapy and radiation therapy must have baseline and post-treatment MRI scans, as well as a clinical evaluation that includes an endoscopy and digital rectal examination.

Exclusion criteria:

Patient who is not fit for preoperative CRT

MRI protocols:

This study was conducted by 1.5 T MRI machines using a phased array body coil. The MRI protocol consisted of

a-Standard T2-wighted fast spin echo sequences with an in plane resolution ranging from 0.42-2.56 mm2, and slice thickness of 4-5 mm.

2- Diffusion-weighted image echo planner imaging sequences was acquired with b-0 value as the lowest and b-1000 s/mm2 as the highest b-factor, in a plane resolution of 7.8 – 9.6 mm2 with slice thickness of 4-5 mm

This technique was applied pre & post chemoradiation.

Imaging analysis:

Initial assessment includes: Tumor site, size, volume, extension, T2, DWI signal intensity. Extramural tumor spread, mrT stage, LNS, and peritoneal deposits. Secondary assessment after chemo-radiotherapy includes: the same as pre therapy assessment in addition to Magnetic tumor regression grade (TRG5-TRG1) mr Volumetric analyses T2, DWI signal intensity changes.

Biopsy:

Endoscopic biopsy was obtained from all study population before chemoradiation followed by histopathological examination of the post operative specimen

Ethical considerations:

Danger-benefit analysis: During this trial, no patient will be at danger of any type. Confidentiality: All patient data was kept private and kept in a secure location. In addition, ethical considerations dictated that only individuals with scientific training and qualifications would perform the research. and the procedure included has been already used in hospitals and centers in and outside Egypt.

Statistical Analysis:

All data were collected, tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median.

Results:

Table (1) showed the demographic characteristics of the studied group. Table (2): showed response (pathology) among the studied group. Table 3 showed the results of the t test which compares the means of the parameters values to determine the statistical difference.

Table (1): Demographic data of studied group

Characteristics		**Patients**		**Mean ± SD**
		N	%	
Age (Ranged from 26-57)		60	100	40.77 ± 7.427
Gender	Male	26	43.3	
	Female	34	56.7	
Pathology	signet ring cell adenocarcinoma	23	38.3%	
	moderately differentiated adenocarcinoma	30	50%	
	mucoid carcinoma	6	10%	
	Malignant Melanoma	1	1.7	

Table (2): Response (pathology) among the studied group.

Response assessment after neoadjuvant treatment				
Response	Tumor regression grade	DWI findings	Number of patients	Percentage
Complete or near complete	1.Normalized wall. thin fibrosis. No tumor signal 2. Dense fibrosis. No tumor signal	No focal diffusion restriction	20	33%
Good	3. Predominant fibrosis, scattered or focal areas with tumor signal (heterogenous fibrosis)	Scattered spots or small focus of diffusion restriction	26	43%
Poor	4.Predominant tumor signal, minimal fibrosis 5. Solid Tumor only, no fibrosis	Mass – like diffusion restriction	14	23 %

Table (3): The difference between the means of the study group parameters before and after CRT

	N	**Mean**	**St. Dev.**	**t**	**P**
Tumor size staging before CRT (in cm)	60	2.85	0.502	5.957	<.001*
tumor size staging after CRT (in cm)	60	1.17	0.551		
Regional LNs size before CRT (cm at the largest SAD)	60	1.94	0.526	7.974	<.001*
Regional LNs size after CRT (cm at the largest SAD)	60	0.73	0.548		
Regional LNs number before CRT	60	1.17	0.526	7.974	<.001*
Regional LNs number after CRT	60	0.73	0.548		
T2WI volumetry before CRT (**cm^3**)	60	**20.675**	14.684	13.761	<.001*
T2WI volumetry after CRT (**cm^3**)	60	5.282	1.4246		
ADC VALUE Before **(x 10^{-3} mm^{-2} /s)**	60	0.967	0.119	4.583	<.001*****
ADC VALUE AFTER **(x 10^{-3} mm^{-2} /s)**	60	1.470	0.253		

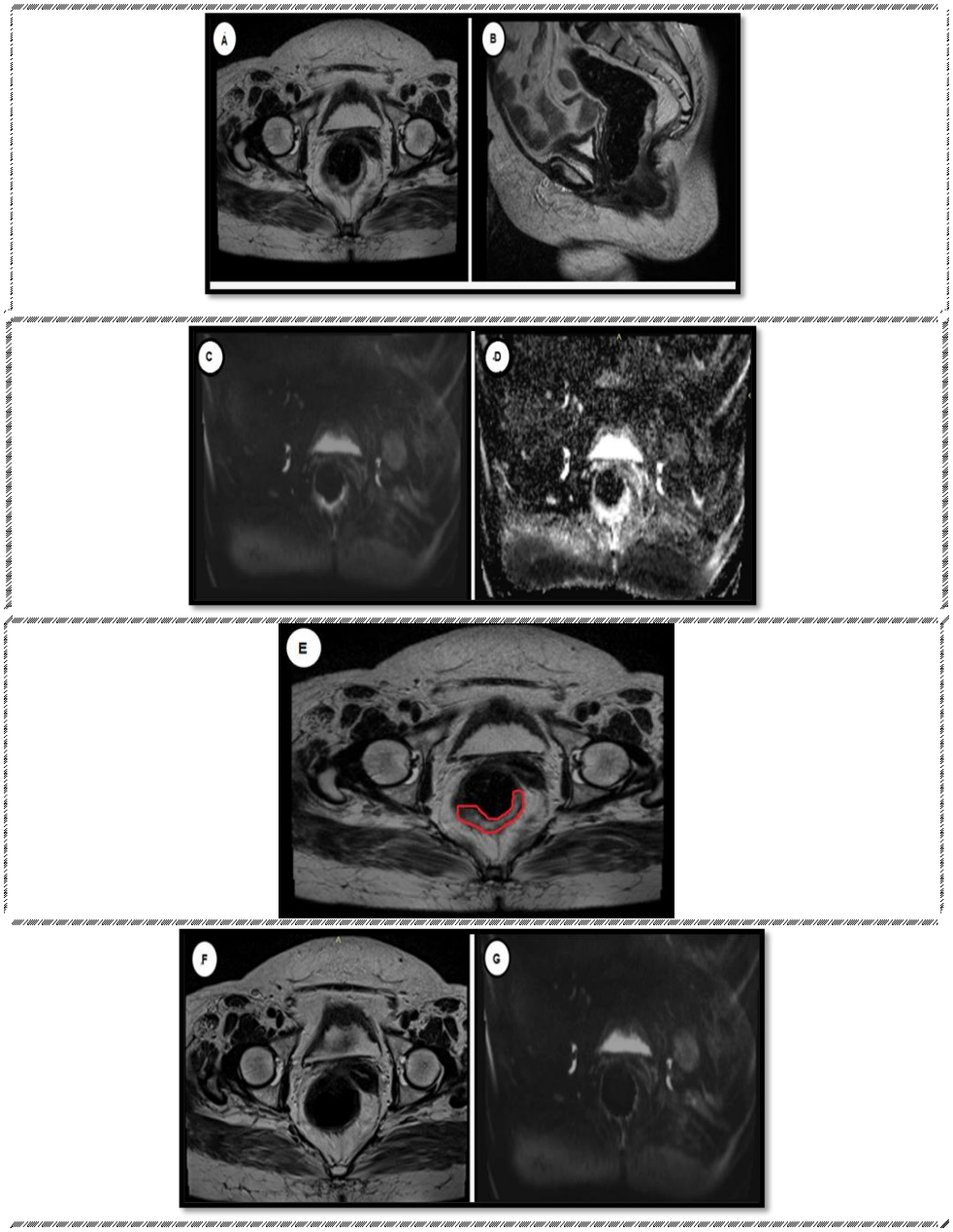


Figure (1) pathologically proven moderately differentiated adenocarcinoma of the rectum , pre-CRT A : Axial T2WI through the pelvis shows tumor that is involving posterior & lateral rectal walls with mesorectal fascia invasion of intermediate signal intensity B: Sagittal T2WI carried through the pelvis with tumor confined to the rectal wall No detected mesorectal tumor invaded LNs C : Prechemoradiotherapy therapy axial diffusion-weighted MRI (b – value , 1000 s mm $^{-2}$) shows hyper-intense signal in the corresponding tumor , D : diffusion coefficient (ADC) mapping shows hypointense signal with ADC_{1000} value of 0.75 x10 $^{-3}$ mm2 s^{-1} in the corresponding tumor E : Gross tumor volume (GTV) of rectal tumor that are well-defined is calculated. The sum of the cross-sectional volumes was used to automatically determine the GTV following the manual tracing of the lesion's outer edge on each image (red line). A well-defined rectal tumor with pathological evidence is seen on axial T2-weighted MR imaging. T2N0 disease GTV was 8.35 cm^3

Post CRT, (F) axial T2WI through pelvis show significant decrease in the size of the tumor size seen only confined to 3 to 6 O'clock . (G) no residual hyperintense signal at diffusion – weighted axial images , patient was pathologically proven (ypT0N0, pathological complete response).

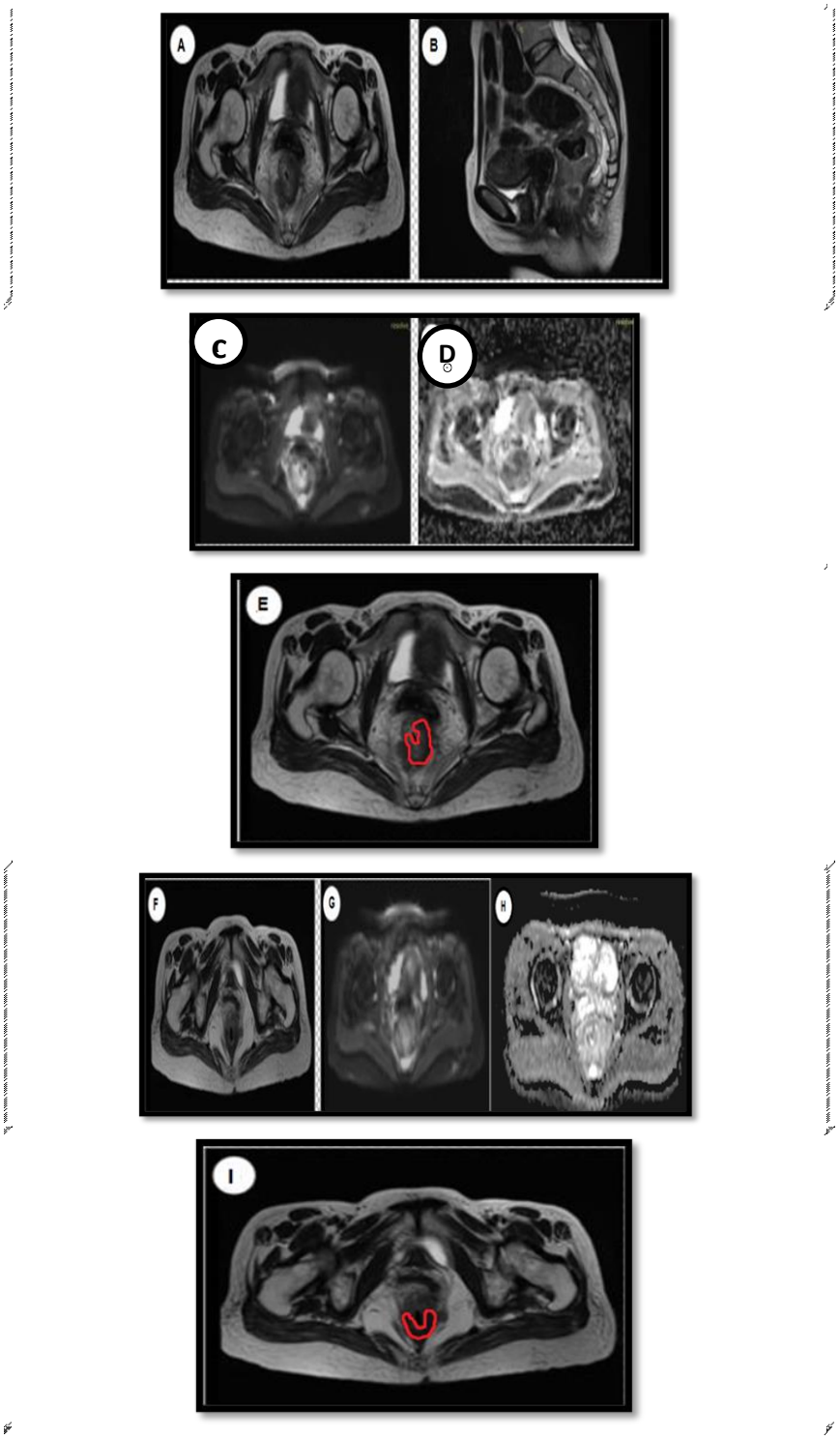
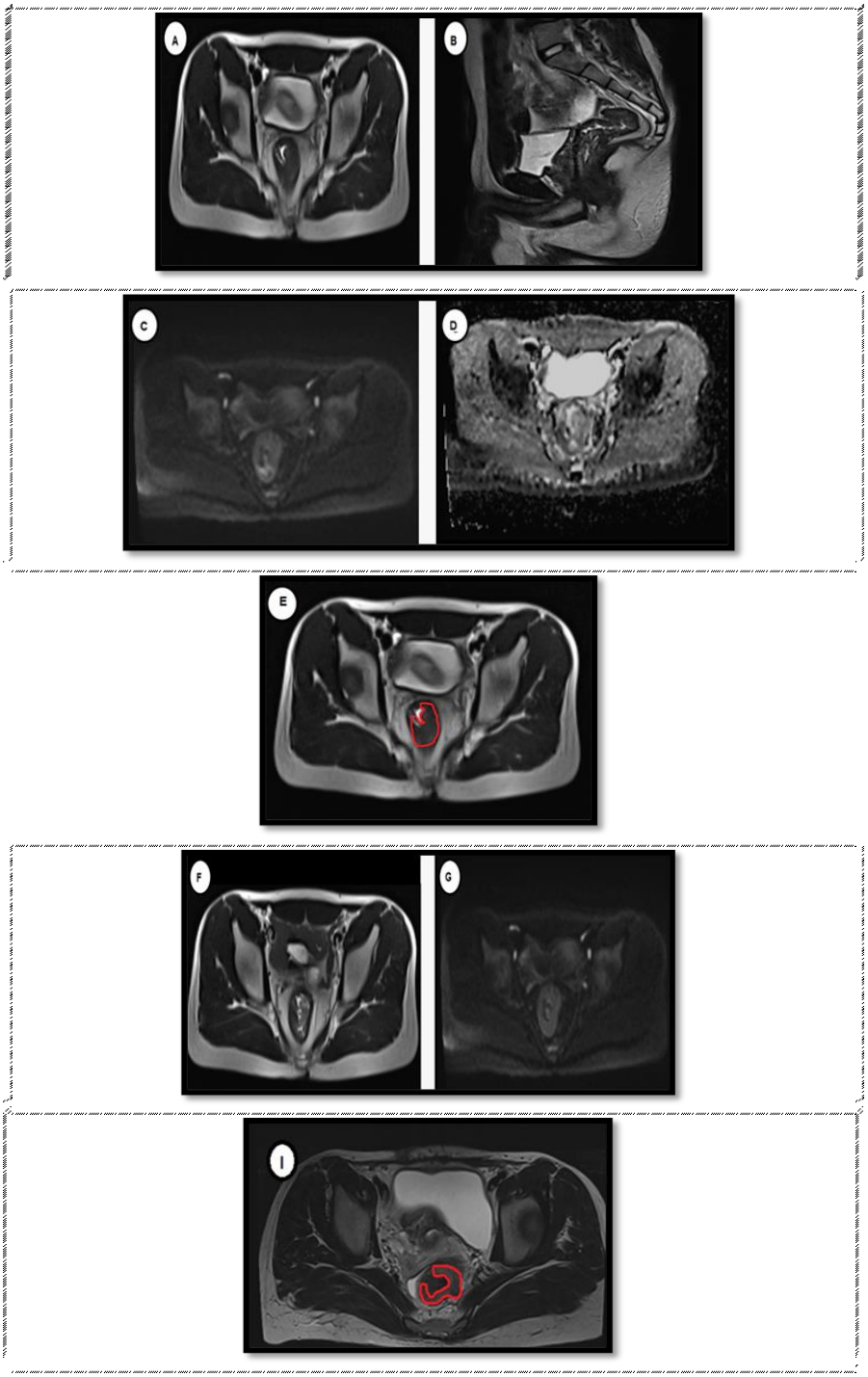


Figure (2) pathologically proven moderately differentiated adenocarcinomaA : Pre-chemoradiotherapy Axial T2WI through the pelvis shows annular tumor that is confined to the rectal wall of low to intermediate signal intensity B: Sagittal T2WI carried through the pelvis . PRE-CRT TNM classification: T2N1M0 . C : Prechemoradiotherapy therapy axial diffusion-weighted MRI (b – value , 1000 s mm -2) shows hyper-intense signal in the corresponding tumor , D : apparent diffusion coefficient (ADC) mapping shows hypointense signal with ADC $_{1000}$ value of 0.69 x10^{-3} mm^2 s^{-1} in the corresponding tumor

E : Calculation of gross tumor volume (GTV) of well-defined rectal tumors. After manual tracing of lesion outer edge on each image (red line), GTV was automatically calculated as sum of cross-sectional volumes. axial T2-weighted MR show well-defined rectal tumor with pathologically proven T2N1 disease GTV was 27.1 cm

Post CRT , (F) axial T2WI through pelvis show significant decrease in the size of the tumor size. (G) decrease hyperintense signal at diffusion – weighted axial images , (H) Post-CRT apparent diffusion coefficient (ADC) mapping shows residual hypointense signal with ADC value of 1.394 x10^{-3} mm^2 s^{-1} in the corresponding tumor Post –CRT TNM classification : T2N0M0

(I): following chemotherapy and radiation Gross tumor volume (GTV) of rectal tumors that are well-defined is calculated. The sum of the cross-sectional volumes was used to automatically determine the GTV following the manual tracing of the lesion's outer edge on each image (red line). Axial T2-weighted MR indicates a reduced volume following CRT., GTV was 8.7 cm^3



Figure(3) pathologically proven grade II adenocarcinoma A : Pre-chemoradiotherapy Axial T2WI through the pelvis shows annular tumor that is confined to the rectal wall of low signal intensity B: Sagittal T2WI carried through the pelvis . Pre CRT TNM classification: T3N2M0

C: Prechemoradiotherapy therapy axial diffusion-weighted MRI (b – value , 1000 s mm -2) shows hyper-intense signal in the corresponding tumor , D :apparent diffusion coefficient (ADC) mapping shows hypointense signal with ADC value of 0.81 x10 -3 mm2 s-1 in the corresponding tumor

E: Calculation of gross tumor volume (GTV) of well-defined rectal tumors. After manual tracing of lesion outer edge on each image (red line), GTV was automatically calculated as sum of cross-sectional volumes. axial T2-weighted MR show well-defined rectal tumor with pathologically proven T2N1 disease GTV was 26.1 cm3

Post CRT , (F) axial T2WI through pelvis show significant decrease in the size of the tumor size . (G) decrease hyperintense signal at diffusion – weighted axial images , (H) Post-CRT apparent diffusion coefficient (ADC) mapping shows residual hypointense signal with ADC value of1.034 x10 -3 mm2 s-1 in the corresponding tumor Post CRT TNM : T2N1M0

(I): Post chemoradiotherapy Calculation of gross tumor volume (GTV) of well-defined rectal tumors. After manual tracing of lesion outer edge on each image (red line), GTV was automatically calculated as sum of cross-sectional volumes. axial T2-weighted MR show decreased volume post CRT , GTV was 9.5 cm3

Discussion:

The current gold standard for patients with locally advanced rectal tumors is neoadjuvant chemoradiotherapy (CRT), which improves local control and surgical resectability [8]. Furthermore, following CRT, between 10% and 30% of patients with rectal cancer experience pathological complete remission (pCR).[8, 9].

These patients carry a very low risk of lymph node metastasis, with excellent overall and disease-free survival (DFS) [10]. A more conservative policy, such as "wait-and-see," has been proposed as a possible method of treatment in clinical complete responders [10].

While restaging following CRT is mandated to undergo magnetic resonance imaging (MRI), there was disagreement about the reliability of pCR prediction [11]. The characteristic of CRT-induced fibrosis that is most well recognized is the hypointense region surrounding the primary tumor in T2-weighted MRI. However, eye inspection is not a reliable way to differentiate between the signal intensity (SI) of viable tumors and fibrosis. [12].

As a result, the importance of morphological assessments, functional imaging research, and quantitative analysis has grown. T2 MRI volumetry is one such technique that has been introduced; however, T2 volumetry's diagnostic performance varies: areas under the curve (AUC) for pCR have been reported to range from 0.700 to 0.792 in some studies, while no significant difference was found in post-treated tumor volume between pCR and non-pCR individuals ($p = 0.451$) in another study [13, 14].

The entire treated tumor was assessed in these trials, however it is assumed that measuring the entire treated tumor volume without taking into account SI variations between the components (fibrotic component vs. viable tumor) is what leads to decreased diagnostic performance. [15].

The main aim of this study was to evaluate the accuracy of MRI for selection of patients with of the good response after chemoradiotherapy for locally advanced rectal cancer.

This retrospective cross-sectional study was conducted in Radiology department, South Egypt Cancer Institute, Assiut University. This study was conducted on 60 patients with locally advanced rectal adenocarcinoma (T3c-T4 N any, CRM+ M0) treated with neoadjuvant chemoradiotherapy.

Regarding the demographics of the study population, we discovered that there were 22 (37%) male patients. In the study population, the number of female patients was 38 (63%). Age in the study population ranged from 26 to 57 with mean ± SD = 38.17 ± 6.91.

However, the vast majority of literature showed that of patients with Rectal Cancer were males aged more than 50 years. Curvo-Semedo et al., [14] enrolled 50 patients (74% male, 26% female) with median age was 70 years (range, 49–88 years). Also, Sclafani et al., [16] showed that enrolled 191 patients (56.5% male, 43.5% female) with median age was 63 years (range, 31–80 years). As well, Fayaz et al., [7] reported that the median age was 53 years, and 60% of patients were male.

Furthermore, the systematic review and meta-analysis by van der Paardt et al., [17] enrolled 29 studies with 1556 patients Mean patient age was 62.1 years (range, 53–71; 28 studies). Male-to-female ratio was 1.9:1.

Furthermore, Chandramohan et al., [18] in their study found no association between age or sex with Pathological complete response of neoadjuvant chemoradiotherapy.

Regarding Pathological diagnosis among the study population, our results showed that the number of patients that had Signet ring cell adenocarcinoma as pathological diagnosis in the study population was 18 (30%). Number of patients that had Moderately differentiated adenocarcinoma as pathological diagnosis in the study population was 34 (57%). Number of patients that had Mucoid carcinoma as pathological diagnosis in the study population was 6 (10%). Number of patients that had Malignant Melanoma as pathological diagnosis in the study population was 2 (3%).

In line with our results Yi et al., [19] showed that the most common Pathological diagnosis was Well/moderately differentiated adenocarcinoma followed by Poor differentiated Adenocarcinoma then Mucinous carcinomas.

Also, Chen et al., [20] reported that the most common Pathological diagnosis was Adenocarcinoma (92.3%) followed by Mucinous adenocarcinoma (7.7%).

Regarding the tumor size staging among the study population, we found that the number of patients with Tumor size staging (2) in the study population was 42 (70%). Number of patients with Tumor size staging (3) in the study population was 18 (30%).

Also, regarding regional LNs staging among the study population, we found that the number of patients with Regional LNs staging (0) in the study population was 12 (20%). Number of patients with Regional LNs staging (1) in the study population was 42 (70%). Number of patients with Regional LNs staging (2) in the study population was 6 (10%).

However, Sclafani et al., [16] reported that the mean Length of tumour was 54.4±15.8 mm, the majority of cases were T-stage 3 (75%), but one-third of cases were N-stage 0, 1 and 2 each.

Also, Yi et al., [19] showed that the most common T-stage was stage 2 and the most common N-stage was stage 1.

As well, Chen et al., [20] reported that the most common T-stage was stage 3 (61%) and clinical node classification N1-N2 was present in 82% of patients.

Also, Wan et al., [21] showed that the most common T-stage was stage 3 (52%) followed by stage 2 in (27%) and the most common N-stage was stage 0 (67%) followed by stage 1 (26%).

Furthermore, Chandramohan et al., [18] in their study found no association between T-stage on pretreatment staging MRI with Pathological complete response of neoadjuvant chemoradiotherapy.

The current study showed that all patients in the study population had no distant Metastasis.

Regarding T2WI volumetry before and after CRT among the study population, we found that T2WI volumetry before CRT in the study population ranged from 0.1 to 49 with mean ± SD = 21.98 ± 14.31.T2WI volumetry after CRT in the study population ranged from 3.1 to 8.7 with mean ± SD = 5.74 ± 1.45.

More aggressive tumor profiles were linked to lower ADC readings. There were notable associations discovered between the radiological MRF status, N stage, differentiation grade, and mean ADC values. ADC may develop as an imaging biomarker for the aggressiveness profile of tumors. [12]. In this study, as regard ADC value before and after CRT among the study population, we found that ADC value before in the study population ranged from 0.43 to 0.96 with mean ± SD = 0.68 ± 0.12.ADC value after in the study population ranged from 0.43 to 1.53 with mean ± SD = 1.05 ± 0.25.

This was supported by Kim et al., [22] who revealed that the post-CRT ADC (1.43±0.10) (×10−3 mm^2/s) and the percentage change (70.0±23.5%) in the CRT (n=11) were significantly higher than those in the non-CR (n=65) (1.14±0.18, 30.2±21.7%, respectively) (both, P<0.0001).

As well, regarding the pre-and post-CRT—DWI among the study population, we found that pre-CRT—DWI in the study population ranged from 5.8 to 55.6 with mean ± SD = 23.34 ± 12.26. Post-CRT—DWI in the study population ranged from 0.01 to 1.77 with mean ± SD = 0.63 ± 0.45.

It is important to mention that the DWI & ADC value are directly correlated to the cellularity of the tissue (tumor), restricted diffusion with lower ADC values indicates high tumor cellularity. The higher the ADC value in ADC mapping the lower the tissue (tumor) cellularity

In the current study regarding MRI-TRG (tumor regression grade) among the study population. Number of patients with good MRI-TRG in the study population was 20 (67%). Number of patients with poor MRI-TRG in the study population was 10 (33%).

Comparing the pathological and MRI tumor regression grade we found that there was a good agreement between the findings of both examinations. This comes in agreement with Chandramohan et al., [18] who reported that there was a substantial agreement (k = 0.765) between DWI patterns and pathological TRG and excellent agreement (k = 0.811) between the combined approach (T2 HR MRI + DWI) and pathological TRG. They concluded that complete response to neoadjuvant chemoradiotherapy can be determined with excellent accuracy, substantial interobserver agreement and high level of confidence by combined interpretation of DWI and T2 high resolution MRI.

This finding was also supported by previous work by Lee et al., [23] which showed good correlation (ρ = 0.700) between DWI incorporated MR-TRG and pathological TRG.

Also, Fayaz et al., [7] concluded that MRI-assessed complete tumor response was strongly correlated with pathological complete response (pCR) and, therefore, can be used as a surrogate marker to predict absence of viable tumor cells.

Furthermore, Chen et al., [20] reported that based on tumor regression grade (TRG), 66.6% patients were classified as having a histopathologic good response (GR; TRG 0-1) and 33.3% as non-GR (TRG 2-3). Tumor downstaging (T-downstaging) occurred in 64% patients. The study concluded that Pre-CRT MRI, post-CRT MRI, and delta radiomic-based models have the potential to predict tumor response after nCRT in LARC.

A decision about organ preservation can be made more effectively and with greater relevance to the surgical pathology when post-CRT MRI is used to straightaway represent the tumor's state following nCRT. In order to protect the anal sphincter and lower morbidity, some patients with LARC may be considered for local excision instead of the curative total mesorectal excision (TME) when considerable clinical downstaging follows nCRT. Therefore, while choosing an operating technique, the radiomic feature performance for T-downstaging is also a clinical concern. [24].

This study has a few limitations related to its retrospective nature and also limited by small sample size.

Conclusion:

Pathological and MRI response assessment show excellent agreement and a significant correlation. When DWI patterns and T2W MRI-based MR-TRG are combined, MRI's diagnostic ability for predicting the complete pathogenic response is improved. Additionally, it raises the degree of confidence among radiologists who interpret data and increases interobserver agreement. More research is required to determine whether MRI-TRG can detect pathological complete responders for the implementation of nonoperative management techniques and whether it can supplement pathological TRG with prognostic data to improve risk-stratification following surgery.

List of abbreviations

CRT : chemoradiotherapy
pCR : pathological complete response
CR : clinical complete response
OS : overall survival
DFS : disease free survival
TRG : tumor regression grade
mrTRG : MRI based tumor regression grade
MRF : mesorectal fascia
GTV: gross tumor volume

Author's contributions:

All authors made substantial contributions to the conception or design of the work, acquisition, analysis, or interpretation of data.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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