The Role of Diffusion weighted Magnetic Resonance Imaging in Restaging Of Cancer Rectum After Neo-adjuvant Therapy

Mohamed Fouad Osman[1], Medhat Mohamed Madbouly[2], Shimaa H.I Desoukey[2], Mona H. Hassan[2], Amir Hanna[2], Asmaa Monir Ali[2], Dina Mostafa Hamzawy[2], Fatma Ali[3], Bahaa Eldeen Mahmoud Hussain[1], Amr Farouk Ibraheem[4], Shaimaa Fatouh Alkhouly[1]

Abstract

Background: Neo-adjuvant chemotherapy and radiation has been shown to reduce tumour size and the risk of local recurrence in individuals with advanced rectal cancer. Apparent diffusion coefficient (ADC) is measured by diffusion-weighted magnetic resonance imaging (DWI), which is sensitive to inter-tumoral alterations generated by CRT and gives biological information pertaining to tumor cellularity and the integrity of cell membranes.

Aim: The purpose of this research was to evaluate the use of diffusion-weighted magnetic resonance imaging (DW-MRI) in restaging rectal cancer following neoadjuvant treatment, and to compare these results to those obtained using traditional histological methods.

Patients and Methods: Colonoscopy confirmed the presence of rectal cancer in 38 of the participants in our research. After 6-8 weeks of CRT, participants underwent a restaging MRI. Comparing the pre-CRT baseline DWI with the post-CRT DWI allowed us to assess the effect.

Results: Twenty T2 and sixteen T3 patients showed full response on standard MRI without DWI. Two patients correctly staged as T0 (full response) by MRI, six correctly staged as T2, and twelve correctly staged as T3 when compared to histological data. This yields just two false negatives and eighteen positives, for a sensitivity of 63%, a specificity of 35%, and an overall diagnostic accuracy of 49%. Eight patients (14 T2 and 16 T3) who had DWI had a full response.There were 8 correctly staged as T0 (full response), 8 correctly staged as T2, and 14 correctly staged as T3 based on the correlation with histopathology data. By histological examination, 8 LNs were found to be malignant (false negative), whereas MRI with DWI failed to pick up on 4 LNs at all.This yields a sensitivity of 83%, a specificity of 83%, and an accuracy of 83% overall. The diagnostic accuracy did not improve significantly, but more LN were found thanks to the method's ability to highlight them. However, distinguishing benign from malignant nodes remains challenging.

Conclusion: In cases of locally advanced rectal cancers, DWI greatly improved the diagnostic accuracy of MR imaging by assessing tumour response to chemotherapy and radiation. Therefore, DWI plays an increasingly important role in rectal cancer staging and assessing recovery after chemotherapy and radiation.

Keywords: Diffusion Magnetic Resonance, Cancer Rectum, Neo-adjuvant Therapy

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Corresponding author: Shimaa Hamed Ibrahim Desoukey
E-mail: sh.hamed85@gmail.com
Mohamed Fouad Osman, E-mail:fouadradio@hotmail.com, [1]Department: Radiology department, faculty of medicine Cairo university, Cairo, Egypt
Medhat Mohamed Madbouly, E-mail:medhat.madbouly@yahoo.com, [2]Department: Radiology department, Theodor Bilhariz research institute, Giza, Egypt
Shimaa H.I Desoukey, E-mail:sh.hamed85@gmail.com, [2]Department: Radiology department, Theodor Bilhariz research institute, Giza, Egypt
Mona H. Hassan ,E-mail:mhussein097@gmail.com, [2]Department: Radiology department, Theodor Bilhariz research institute, Giza, Egypt
Amir Hanna ,E-mail:amirelhamy84@gmail.com, [2]Department of : Radiology department, Theodor Bilhariz research institute, Giza, Egypt
Asmaa Monir Ali ,E-mail:asmaa_monir@hotmail.com, [2]Department of : Radiology department, Theodor Bilhariz research institute, Giza, egypt
Dina Mostafa Hamzawy, E-mail:dinahamzawy@gmail.com, [2]Department of :Radiology department, Theodor Bilhariz research institute, Giza, Egyp
Fatma Ali, Ministry of health, Egypt
Bahaa Eldeen Mahmoud Hussain, Department: Radiology department, faculty of medicine Cairo university, Cairo, Egypt
Amr Farouk Ibraheem, National cancer institute, Cairo, Egypt
Shaimaa FatouhAlkhouly, E-mail:shaimafatooh@yahoo.com, [1]Department of : Radiology department, faculty of medicine Cairo university, Cairo, Egypt

Introduction

In terms of overall incidence, colorectal cancer ranks third. **(1).**

Preoperative combination radiation therapy with chemotherapy (CRT) has largely replaced surgery with adjuvant radiation therapy for the treatment of locally advanced rectal cancer (LARC) due to its superior local control and less acute and late toxic effects.**(2).**

Tumor reduction and a reduced risk of local recurrence in individuals with advanced rectal cancer are two established effects of neo-adjuvant chemotherapy and radiation therapy. **(2).**

To select the most appropriate therapeutic strategy (possibly a less invasive organ-sparing surgical approach) and to determine the feasibility of non-operative management, which is typically reserved for those with a complete clinical response to neo-adjuvant therapy, an accurate assessment of therapeutic response would be of great clinical value. **(3).**

The use of MRI for the staging and treatment planning of primary rectal tumours has been widely acknowledged as critical for quite some time. Additionally, MRI is now routinely used in the clinic to evaluate tumour response and restaging following CRT. Historically, initial staging results were the most important factor in determining surgical approach; however, restaging MRI results are now widely utilized to direct subsequent therapy. As a result, current recommendations advise using MRI for restaging rectal cancer following CRT on a regular basis. **(4).**

Diffusion-weighted magnetic resonance imaging (DWI), which measures apparent diffusion coefficient (ADC), is sensitive to inter-tumoral alterations generated by CRT and gives biological information relating to tumor cellularity and the integrity of cell membranes. DWI's potential relevance in predicting tumor response during and after therapy has been demonstrated. **(5).**

Most studies compared pre- and post-CRT DWIs to determine patient response. **(6).**

One major benefit of mrTRG is that it does not need evaluating tissue samples removed after surgery. Before any surgery is performed, the degree of tumour regression can be evaluated using magnetic resonance imaging (MRI), which may provide a window of opportunity to consider salvage pre-operative treatments if satisfactory tumour regression is not achieved with standard therapy, or to adopt a non-operative management strategy if a complete response with no active residual cancer is diagnosed. **(7).**

We aimed at this work to assess the role of magnetic resonance imaging with diffusion weighted MRI in restaging of rectal carcinoma after neo- adjuvant therapy with correlation to histopathological finding

PAtients and Methods

The study included 38 patients with pathologically proved rectal carcinoma referred from the General Surgery departments, National cancer institute to the MRI unit at the national cancer institute, for MRI pelvis examination in the period between 2019 and 2021.

The diagnosis of rectal carcinoma in these patients was established based on their symptomatology, clinical examination, proctoscopy and biopsy.

Written informed consent was taken from all patients including procedure description and benefits.

The study is IRB approved.

Inclusion criteria:

Patients with pathologically proven rectal cancer undergoing chemo &/ radiotherapy and are candidates for MR imaging.

Exclusion criteria

Patients who had absolute contraindications to MRI screening were not included, and neither were patients who had a history of operational intervention or who had had chemotherapy or radiation therapy without a baseline MRI.

Magnetic resonance imaging

Instruments:

1. ***The MRI machine:***

MRI scan was performed ona1.5Tesla magnet (Philips Achieva).

2. ***Pelvic phased array coil:***

The pelvic phased array is receiving only surface coil which consist of two sections. The bottom section is stationary and the top section is movable.

Patient position and preparation

Position is supine and the aim of the patient preparation is to familiarize the patient with the procedure, to make the procedure as comfortable as possible and to stress the importance of minimizing the motion.

The patient was advised to have a warm water enema 1-2 hour prior to the examination so that an excess amount of rectal feces would not be present.

The patient lies in the lateral decubitus and folly's catheter was inserted and luminal distention by ultrasound warm gel about 150-200ml.

Fasting for 6 hours prior to the examination when IV contrast will be used.

MRI protocol including:

- An array of multi-planar scout pictures is generated by scanning the coil at an angle.
- After determining the tumor's axis in sagittal MRI, all axial sequences were taken at the same, uniform angle that was perpendicular to that axis.

The tumor axis was aligned with the T2W coronal sequence.

1- T1 weighted (T1W) image in axial plane:

Repetition time (TR)= 438msec, echo time (TE)=10msec, matrix256x512, no of slices =25, slice thickness 3 mm, slice gap 1-2 mm, and FOV:250mm, Scan duration=1.18 min. Flip angle=90

2- T2 weighted (T2W-TSE) images (Turbo spin echo): (in axial, sagittal, and coronal plans):

TR =7000msec, TE=120msec, matrix 256x256 with FOV= 250 mm, slice thickness 3 mm, slice gap 2mm. Scan duration=1.17min, Flip angle=90.

3- Diffusion weighted imaging:

To improve sensitivity to cellular packing, DW imaging was done in the transverse plane with tri-directional diffusion gradients utilizing b values of 0,300 and 600sec/mm2.

The other parameters were as follows:

Scan length was 1.58 minutes; repetition time (TR) was 1.4 seconds; echo time (TE) was 60 milliseconds; number of excitations (NEX) was 3; matrix size was 256 by 256; field of view was 270 millimetres; slice thickness was 3 millimetres; slice gap was 1-2 millimetres. ADC maps were created by manually copying and pasting sections of interest from DW pictures. The operating system mechanically produced grayscale maps of the apparent diffusion coefficient based on a mono-exponential decay model that incorporated all three b-values.

1- ADC calculation:

Three manually set round/oval areas of interest (ROIs) inside solid tumor sections of three separate tumor-containing slices were used to determine the mean ADC. The regions of interest (ROIs) were designed to encompass the largest feasible percentage of the solid tumor..

*2- **T1 (Post contrast fat suppression) :(in axial planes):***

Completed after an antecubital vein bolus injection of 0.1 mmol/kg of body weight of (Gd-DTPA Schering-Germany) at a rate of 2 ml/s, followed by a flush of 20 ml of sterile 0.9% saline solution. Both the contrast media and the saline solution injections were administered by hand. Patient was instructed to pause at the point of full exhalation.

The parameters were as follows:

TR =492ms, TE=10msec, matrix 384x240 with a field of view: 250, slice thickness 7mm, slice gap 0mm and flip angle of 90 degrees. Images are usually acquired in the axial planes.

Follow up:

Typically, MR exams are performed between three and six months following neo-adjuvant treatment.

For such tumors, RECIST criteria were used to analyze subsequent examinations to determine how well patients were responding to treatmentand classified into: regressive disease (>30% regression), stationary disease (between -30%and+20%) and progressive disease (>20% progression).

Imaging evaluation:

Site, extension, maximal tumor thickness, signal characteristics, and enhancement pattern are all examples of the morphological MRI features.

All these criteria were independently reviewed by two experienced radiologists for the documentation of these findings.

Interpretation of diffusion-weighted images and ADC calculation:

Correlation of ADC maps with high-signal and low-signal lesions was used to rule out the T2 shine through effect and T2 black out, respectively, and this was evaluated qualitatively.

When doing a quantitative study of DWI, we first created an ADC map before choosing the ROI by hand. Minimum and average ADC values were computed mechanically by the workstation.
In each instance, a representative measurement was taken. Next, ADC calculations were done on the matched set of follow-up MRI scans to see how well they compared to the initial set.

Qualitative interpretation of diffusion weighted images with qualitative and quantitative interpretation of ADC map and average ADC value

- Diffusion limitation is diagnosed when a lesion has strong signal on DWI but poor signal on an ADC map.
- Diffusion facilitation is diagnosed when a lesion has a high area on the ADC map but a low signal on DWI.
- T2 black out effect is diagnosed when a lesion has poor signal on both the DWI and the ADC map.

When a lesion has a strong signal in both the DWI and the ADC map, this is known as T2 shine through effect.

Statistical analysis:

Social Science Statistical Package (SPSS) version 26 was used for data coding and entry (IBM Corp., Armonk, NY, USA). In the case of numerical data, we used measures of central tendency and dispersion; in the case of categorical data, we used measures of frequency (count) and relative frequency (percentage). The non-parametric Kruskal-Wallis and Mann-Whitney tests were used to compare quantitative variables. The Chi-square (2) test was used to analyse the differences between sets of discrete categories. When the anticipated frequency was less than 5, an exact test was employed instead. Statistical significance was defined as a probability value (P) less than 0.05.

Results

This study included (38) patients, their ages were ranged from26 to 84 years with the mean age was 49.32years.Our study was included 38 patients, 17 patients were male (44.7%) are male and 21 patients were female (55.3%).

Table 1: Age and sex of studied patients

		Mean	SD	Median	Minimum	Maximum
Age		49.32	14.47	49.00	26.00	84.00
		Count		%		
Sex	M	17		44.7%		
	F	21		55.3%		

Histopathological Findings

All cases in our study were pathologically proven adenocarcinoma.

Table (2): Demonstrates histopathological findings:

		Count	%
Pathology	adenocarcinoma	38	100.0%
	Lymphoma	0	0.0%
	Sarcoma	0	0.0%

Tumor thickness:

Thickness of the tumor pre-neo-adjuvant treatment ranged from 10to26mm with the mean thickness was 16.24 mm and post neo-adjuvant ranged from2to18mm with mean thickness was 10.6 mm.

Table (3): Demonstrates thickness of tumor pre and post CRT.

	Mean	Standard Deviation	Median	Minimum	Maximum
Thickness pre (mm)	16.24	4.83	15.00	10.00	26.00
Thickness (post) (mm)	10.63	3.54	10.00	2.00	18.00

Response evaluation criteria by solid tumor (RECIST)by thickness

Initial MRI signal and post neo-adjuvant therapy

The initial MRI signal before CRT in all patients was low/intermediate T2signal.

The T2 signal after CRT shows 2 patients elicit low T2 signal (5.4 %) while 36 patients elicit heterogeneous low/intermediate signal (94.6 %).

All patients are restricted in DWI in initial MRI (Pre CRT) while post CRT, 28 patients are restricted (73.6 %) and 10 patients are non – restricted (26.4 %)

Table (4): T2 and DWI pre and post CRT illustrated:

		Count	%
T2 (Pre)	**low /intermediate**	38	100%
	high	0	0%
T2 (Post)	**low**	2	5.4 %
	Heterogeneous(low/intermediate)	36	94.6 %
DWI pre	**restricted**	38	100 %
	Non restricted	0	0 %
DWI post	**restricted**	28	73.6 %
	Non restricted	10	26.4 %

Pathological findings after neo adjuvant therapy:

The patients were distributed into 3groups: the tumor regression grade (TRG1) (Complete response) includes 8 patients (2.1 %), the TRG2 (Fibrosis25-99%) includes 20 patients (52.6%) and the TRG3 (No regression) includes 10 patients (26.3 %).

Table (5): Pathological findings after neo adjuvant therapy:

		Count	%
Pathology after neo-adjuvant	**TRG1 (Complete regression)**	8	2.1 %
	TRG2 (Fibrosis25-99%)	20	52.6 %
	TRG3 (Fibrosis<25% or no regression)	10	26.3 %

Relation between pathology and ADC

In our study, the main clue of detecting the response of the tumor to the treatment was the ADC value that was illustrated in the following comparison showing P value <0.001.

Table (6): Relation between pathology and ADC:

		Pathology after neo-adjuvant			
		TRG1 complete regression	**TRG2 fibrosis25-99%**	**TRG3 fibrosis<25% or no regression**	**P value**
ADC post	**Mean**	1.5	1.0	0.8	< 0.001
	Standard Deviation	0.20	0.27	0.30	
	Median	1.40	1.25	1.50	
	Minimum	1.3	0.9	0.8	
	Maximum	1.7	1	0.8	
Percentage of ADC	**Mean**	140.48	28.04	4.73	< 0.001
	Standard Deviation	95.92	21.15	17.56	
	Median	100.00	25.00	7.11	
	Minimum	71.43	-20.00	-35.00	
	Maximum	250.00	70.00	22.22	

T stage by MRI without and with DWI after CRT

Twenty T2 and sixteen T3 patients showed full response on standard MRI without DWI. Two patients correctly classified as T0 (complete response) by MRI, six patients staged as T2, and twelve patients staged as T3 when compared with histological data.

An overall diagnosis accuracy of 63% is achieved, with only 2 false negatives and 18 positives produced.

Table (7): T stage by MRI without DWI after CRT

T stage by MRI without DWI after CRT		**Pathological stage**		
		T0	**T2**	**T3**
T0	2	2	0	0
T2	20	8	6	6
T3	16	0	4	12
Total (cases)	38	10	10	18

Statistic	**Value**	95%CI
Sensitivity	63 %	57 % to 66 %
Specificity	35%	24 % to 39 %
Accuracy	49%	45 % to 55 %

Complete responses were seen in 8 individuals when DWI was implemented, including 14 T2 and 16 T3 stages. Based on the correlation with histological findings, 8 patients were correctly staged as T0 (total response), 8 patients were correctly staged as T2, and 14 patients were correctly staged as T3.

Table (8): T stage by MRI with DWI after CRT

T stage by MRI with DWI after CRT		**Pathological stage**		
		T0	**T2**	**T3**
T0	8	8	0	0
T2	14	2	8	4
T3	16	0	2	14
Total (cases)	38	10	10	18

Statistic	**Value**	95%CI
Sensitivity	88 %	84 % to92 %
Specificity	82%	76.5 % to 85 %
Accuracy	85 %	73.5 % to 87.5 %

This yields a sensitivity of 88%, a specificity of 82%, and a total accuracy of 86%, with 8 false negatives and 22 positives. Complete response to neo-adjuvant chemo-radiotherapy in patients with locally advanced rectal cancer may be evaluated with greater diagnostic accuracy using DWI in addition to traditional MR imaging.

Nodal staging by conventional MRI without diffusion

Concerning nodal staging following chemoradiotherapy, 64 LNs were found by standard MRI without diffusion, with 26 LNs thought to be benign and 38 LNs suggested to be malignant.

The histological investigation of 12 LNs that were not discovered by conventional MRI were malignant, whereas 4 of the 38 LNs that were first suspected to be malignant based on conventional MRI without diffusion turned out to be benign (4 false positives). Those numbers break down to 77% sensitivity, 80% specificity, and 78% accuracy.

Table (9): Rectal MRI without DWI vs. histology for nodal staging.

N stage by MRI without DWI		Pathological stage	
		Benign	**Malignant**
Benign LN	26	16	10
Malignant LN	38	4	34

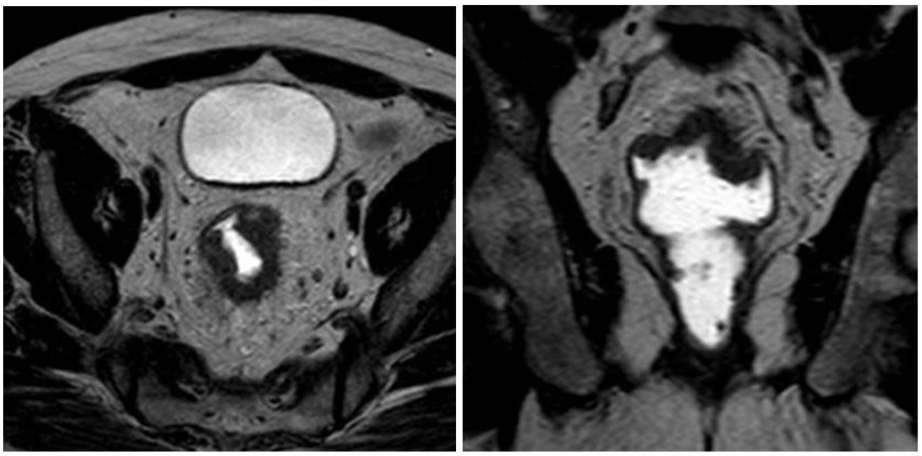
Nodal staging by conventional MRI with diffusion

A total of 72 LNs were found after incorporating DWI and ADC examination; 28 LNs had indications of being benign and 44 LNs had indications of being malignant.

Four of the 44 LNs that DWI suggested were malignant were found to be benign upon histopathological evaluation (false positive), while eight of the 28 LNs that DWI suggested were benign were found to be malignant upon histopathological evaluation (false negative). Four LNs were not detected by MRI with DWI. This yields a sensitivity of 83%, a specificity of 83%, and an accuracy of 83% overall. The diagnostic accuracy did not improve significantly, but more LN were found thanks to the method's ability to highlight them. However, distinguishing benign from malignant nodes remains challenging.

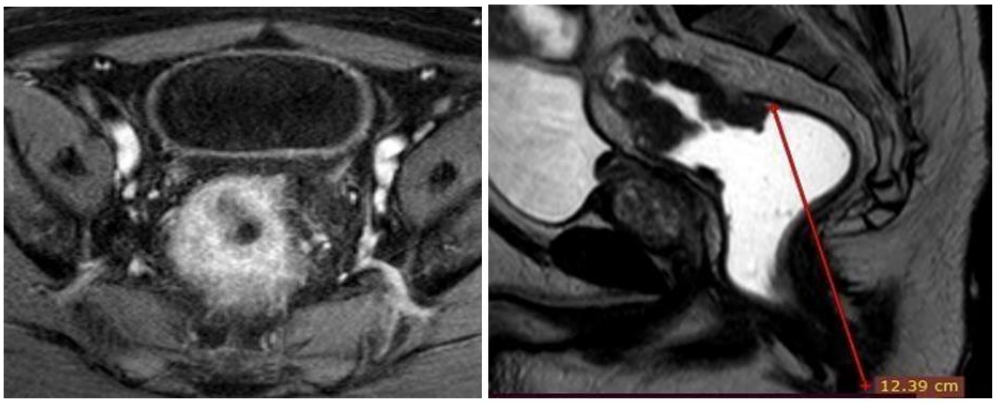
Table (10): Comparison of DWI to rectal MRI for nodal staging vs histology.

N stage by MRI with DWI		Pathological stage	
		Benign	**Malignant**
Benign LN	28	20	8
Malignant LN	44	4	40



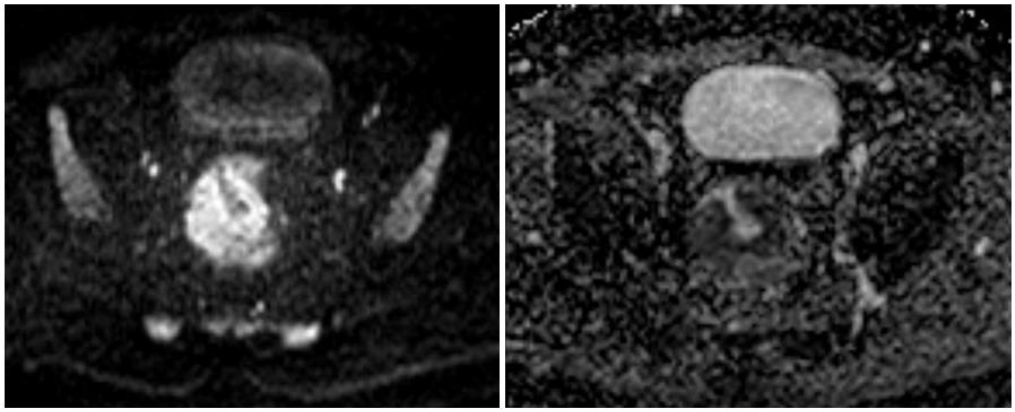
(a) (b)

Figure 1: 67 years old male patient complaining from bleeding per rectum for 2 months. Underwent colonoscopy. Pathology result was adenocarcinoma. MRI study was done pre and post combined chemo-radiotherapy (CCRT).1st pre CCRT conventional MRI:(a) An axial oblique T2 FSE picture reveals focused infiltration of the mesorectal fat and irregular thickening of the mural mucosa and submucosa in the upper rectum. (b) Rectal mass is shown in full on the coronal oblique T2 FSE picture, and neither the levator muscle nor the anal sphincter complex are involved.



(a) (b)

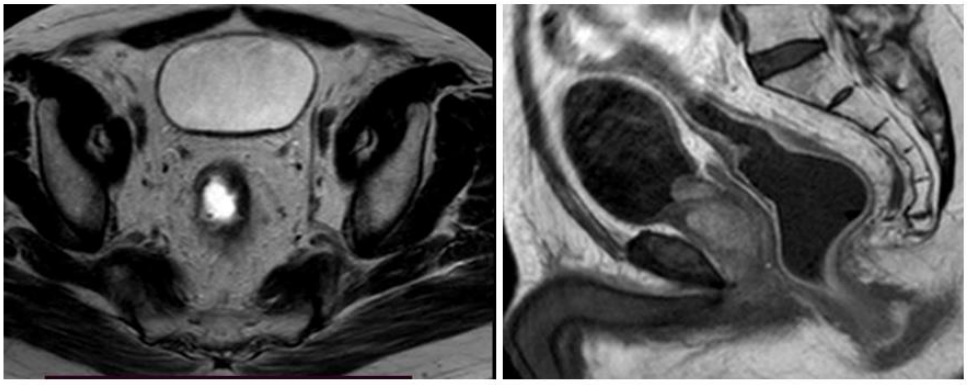
Figure 2: 1st pre CCRT conventional MRI:(a) Heterogeneously increasing mass is shown on an axial oblique T1 postcontrast image after fat reduction. (b) The distance to the anal verge, as shown on sagittal T2WI.



(a) (b)

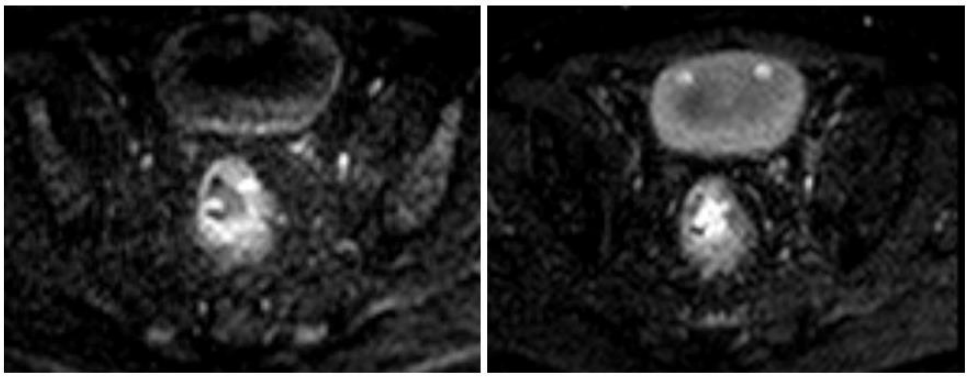
Figure 3: Diffusion weighted imaging findings: (a) Photographs with a diffusion weighting, (b) mean ADC for the mass is 0.6 103 mm2/sec, while the regional LN shows a high degree of diffusion limitation in the relevant area on the map, yielding low ADC values. MRI-based staging: T3bN1 was simulated for this example.

Post CCRT



(a) (b)

Figure 4: Second-stage MRI scans taken after adjuvant treatment demonstrate complete regression of the tumour (as shown on axial oblique T2 FSE and sagittal T1-post-contrast fat suppression scans) and the development of hypo-intense diffuse wall thickening in the absence of any residual mass.



(a) (b)

Figure 5: After receiving adjuvant treatment, the next step is an MRI. (a) In the past rectal mass diffusion weighted pictures(b) High ADC values, with a mean ADC for the mass of 1 103 mm2/sec indicating excellent response to therapy yet with persistent tumoral tissue within the limits of the wall, both reveal removal of the microscopic perirectal LNs with thin ring of diffusion restriction inside the mural boundaries. According to MRI criteria for restaging: After receiving adjuvant treatment, the patient's restaging results were T2N0. T2N0 stage pathology shows a favorable response (adding DWI distinguishes residual tissue from post therapeutic fibrosis).)

Discussion

Preoperative imaging determines the T-stage, nodal involvement, and location of the tumour, which in turn determines the kind of preoperative therapy. MRI has been shown to be the most reliable staging modality for primary rectal cancer over the past decade(8). Unfortunately, without the insertion of an endo rectal coil, MRI has not been able to reliably predict T-stage.**(9).**

In the evaluation of cancerous tumours, DWI is gaining prominence. Diffusion-weighted imaging (DWI) allows for the noninvasive evaluation of biologic tissues based on their water diffusion characteristics. **(5).**

In this study, we assess the use of diffusion-weighted imaging (DWI) MRI for re-staging locally advanced rectal cancers for the purpose of gauging the efficacy of chemotherapy and radiation (CRT).

Due to the high rate of metastasis and local recurrence, the prognosis for locally advanced rectal cancer is dismal. Patients with rectal cancer whose anal sphincter or circumferential resection margin (CRM) is threatened or implicated on preoperative high-resolution pelvic MR imaging undergo concurrent chemotherapy and radiation treatment (CCRT).**(2).**

Tumor response with CCRT is characterised postoperatively via pathologic examination of tumour tissues as TRG1 full response (no residual tumour), TRG2 partial response (fibrosis 25-99 percent), or TRG3 no response.

When it comes to primary tumour staging in rectal cancer, conventional MRI is the gold standard; however, this modality has inherent limitations when it comes to distinguishing viable tumour from surrounding fibrosis following neoadjuvant CRT. Following medical intervention, the rectal wall becomes thicker due to the presence of fibrous tissue.Due to the inability to see each rectal wall layer, MR imaging is unable to reliably distinguish between tumours in the T0, T1, and T2 stages.**(10).**

Through our research, we found that T2-weighted images are unreliable for staging tumours based on morphological characteristics, as they result in over-staging due to the inability to distinguish fibrosis from microscopic residual tumours tissue within the desmoplastic reaction generated by neo-adjuvant treatment.

Restaging using conventional MRI without DWI gives 63 % sensitivity and specificity 35 % with overall accuracy 49 %. *While the* restaging using DWI with the calculation of ADC values gives 88% sensitivity and specificity 82 % with overall accuracy 85 %.

Chen et al.(11) found that conventional MR imaging had accuracy of 52% only for tumor restaging of irradiated rectal cancer

.Kuo et al (12)also reported similar results of conventional MRimaging showing low accuracy for tumor restaging after CRT was 47% only.

Marouf et al.(13) resulted in findings that were consistent with our own. Restaging with conventional MRI without DWI has a sensitivity of 60%, specificity of 33%, and overall accuracy of 46.5%, whereas restaging with DWI and the determination of ADC values yields a sensitivity of 87%, specificity of 80%, and overall accuracy of 83.5 %.

Fusco et al.(14) discovered that DWI's sensitivity was 76% and specificity was 79%.**Paardt et al.(15)** DWI was reported to increase the sensitivity of MRI for tumour staging following CRT from 50% to 84%.

DWI has been shown to have several potential benefits for the assessment of tumor localization and re- staging **(16).**

Since anti-tumor therapy reduces tumour cellularity, and ADC values obtained from DWI measurements reflect tumour cellularity, CRT should raise the ADC value.

Using a threshold value of 1.2 to differentiate residual tumour from fibrosis, our study found that the ADC values significantly increased both before and after CRT, with the mean ADC values before treatment being 0.7 and after treatments being 1.5.

Results from a number of studies suggest that elevated ADC readings following CRT are consistent with tumour necrosis and decreased cell density.

In our study, A statistically significant rise in ADC value was seen following NCRT in all patients (pCR patients, and non-pCR patients), and the difference between pre- and post-treatment was also noteworthy.***Chen et al.(11)***found similar findings that increase of the ADC value after NCRT in all patients and that is statistically significant.

After CCRT, morphologic criteria make it challenging to tell the difference between a metastatic lymph node and an irradiated lymph node alteration on MR imaging. In specifically, lymph node over staging occurs when there is a change in a lymph node, with or without metastases, after CCRT.

Higher ADCs are a documented consequence of necrosis in irradiated cancer lymph nodes. Lymph nodes have a high cellular density, so they typically show restricted diffusion and are easily detected on DWI. This is why DWI is so useful for lymph node evaluation; it increases the number of detected nodes by making them stand out against the suppressed background signal of surrounding tissues.

Consistent with their findings, we found that the use of DWI significantly enhanced the detection rate of the implicated LN, from 38 to 72 on standard MRI.

The research has certain caveats. A number of factors limit the study's applicability to the wider population. Second, the volume of the tumour was not taken into account while doing the textural analysis; rather, just the biggest diameter was used. Rectal cancer tends to spread along the rectal wall in an uneven pattern, therefore ROIs drawn using a single slice may not be a good representation of the true tumour shape.

Conclusion:

In cases of locally advanced rectal cancers, DWI greatly improved the diagnostic accuracy of MR imaging by assessing tumour response to chemotherapy and radiation. The use of DWI to

assess progress after chemotherapy and radiation for rectal cancer is expanding.

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