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Role of diffusion-weighted MRI in diagnosis and post therapeutic follow-up of colorectal cancer



Mina Sameh Sabry¹, Amany Emad Eldeen Rady², Gamal Eldeen Mohamed Niazi² and Susan Adil Ali^{2*}

Abstract

Background: The colorectal cancer (CRC) is one of the deadliest cancers in the world. Local tumor stage, vascular or lymphatic invasion, and tumor grade are essential for accurate management. The main imaging modality for initial assessment and therapeutic response evaluation of CRC is magnetic resonance imaging (MRI). The purpose of this prospective study was to illustrate the role of diffusion-weighted MRI (DWI) and apparent diffusion coefficient (ADC) value in initial assessment and grading of colorectal carcinoma as well as evaluation of its response to chemotherapy or combined chemoradiation.

Results: Restricted diffusion in DWI was found in 37 out of 40 patients with sensitivity of about 92.5%. In the studied group, the median ADC value was 1.21 (min 0.80, max 1.31) and the average ADC value was 1.14 ± 0.161 . The mean ADC value in poorly differentiated tumors was 0.979×10^{-3} mm²/s. The mean ADC value in moderately differentiated tumors was 1.112×10^{-3} mm²/s. The mean ADC value in well-differentiated tumors was 1.273×10^{-3} mm²/s. The sensitivity, specificity, PPV, NPV, and accuracy were higher with addition of DWI and ADC value to conventional MRI reaching 100%, 80%, 83.3%, 100%, and 90%, respectively.

Conclusion: Adding DW imaging with ADC value to conventional MRI yields better diagnostic accuracy than using conventional MR imaging alone in detection, correlation with tumor histologic grade, initial staging, and response evaluation to neoadjuvant chemoradiotherapy in patients with locally advanced colorectal cancer.

Keywords: DWI, ADC value, MRI, Colorectal cancer

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Background

The colorectal cancer (CRC) is one of the deadliest cancers in the world. The risk increases with age as most cases seen in people aged 65 or more. Other risk factors include obesity, family history, cigarette smoking, and chronic inflammatory bowel disease. Over half of all CRCs arise from the sigmoid colon or the rectum with overall 5-year survival of about 50%. Local tumor stage, vascular or lymphatic invasion, tumor grade, and preoperative carcinoembryonic antigen serum level (CEA) are the main prognostic factors [1]. The main treatment for CRC is surgical excision, but it is more difficult in the rectum to get adequate marginal clearance to prevent local tumor recurrence without significant complications. Chemoradiotherapy has been used to reduce local recurrence in later-stage disease [2].

Among the imaging modalities for initial assessment and therapeutic response evaluation of different tumors, functional imaging with diffusion-weighted MRI (DWI) is considered critical in decision making for CRC patients [3–5]. It is able to discriminate between different

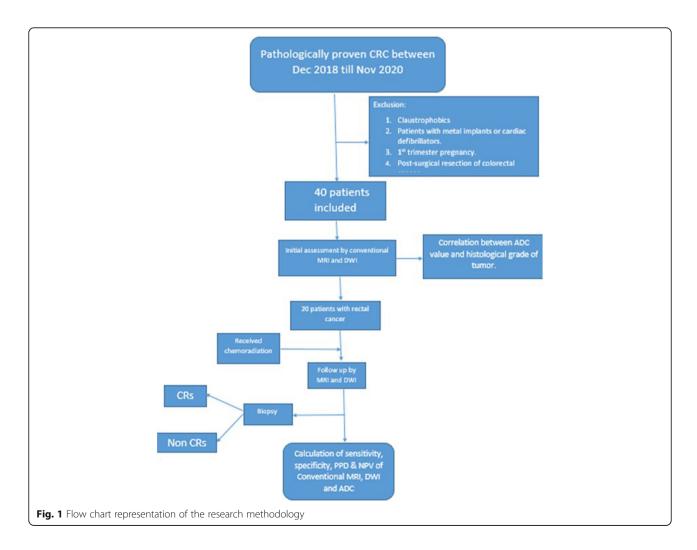
tissues of varying cellularity using differences in the extracellular movement of water protons. They diffuse freely in tissues with normal cellularity resulting in loss of signal on DWI, while restricted diffusion in tissues with high cellularity (as in tumors) resulting in high signal on DWI [6]. Apparent diffusion coefficient (ADC) can be correlated also to treatment response [7].

The purpose of this work was to illustrate the role of DWI in initial assessment and grading of colorectal carcinoma as well as evaluation of its response to chemotherapy or combined chemoradiation.

Methods

Patients

This was a prospective study conducted in the period between December 2018 and November 2020. Forty patients with histopathologically proven primary colorectal cancer at any age ranging between 20 and 80 years with no sex predilection were enrolled in this study. The diagnosis of colorectal carcinoma in these patients was



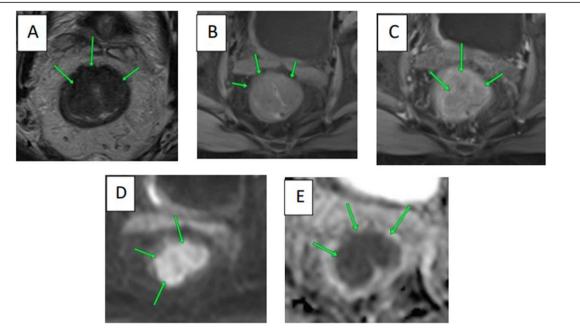


Fig. 2 Sixty-three-year-old male presented with bleeding per rectum. Colonoscopy and biopsy revealed rectal moderately differentiated adenocarcinoma. A middle third horseshoe shaped rectal mass (measured $4.2 \times 3.4 \times 3.6$ cm) sparing the posterior wall with no invasion to the mesorectal fat was noted. It displayed intermediate signal in both T2- (**A**) and T1 (**B**)-weighted images with mild homogenous enhancement in post contrast images (**C**). The lesion appeared bright in DWIs (**D**) and turned dark in the ADC map (**E**), with ADC value 0.95×10^{-3} mm²/s, indicating restricted diffusion

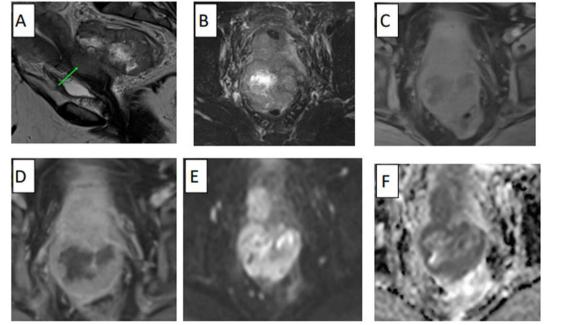


Fig. 3 Fifty-four-year-old female presented with constipation and bleeding per rectum. Colonoscopy and biopsy revealed rectal moderately differentiated adenocarcinoma. A Large lobulated circumferential soft tissue mass (measured $9 \times 5 \times 6.7$ cm) was seen infiltrating the upper and middle thirds of rectum with anteriorly exophytic component invading the posterior wall of uterine cervix, best appreciated in sagittal T2-weighted image (**A**). It displayed heterogeneous high signal in T2WI (**B**) and intermediate signal in T1WI (**C**), with heterogeneous enhancement in post contrast images (**D**). The lesion appeared bright in DWIs (**E**) and turned dark in the ADC map (**F**), with ADC value 1.0×10^{-3} mm²/s, indicating restricted diffusion

established based on their symptomatology, clinical examination, colonoscopy, and biopsy.

Patients with claustrophobia, metal implants (as cochlear implants), cardiac defibrillators and pacemakers, first trimesteric pregnancy, or post-surgical resection of colorectal cancer were excluded from this study. Approval of the institutional review board and written informed consents from all patients were obtained before the start of this study.

Technique of magnetic resonance imaging

1.5-Tesla MRI machine (Siemens Magnetom Sempra) was used for the examination using pelvic 8-channel phased array coil. The patients were advised to have an enema 1–2 h prior to the examination. The patient was lying on the examination couch in lateral decubitus and foly's catheter was inserted with luminal distention by about 150–200 ml warm gel. The patient then return to the supine feet first position, the pelvic phased array coil is connected, and ear blugs and immobilization foam pads were applied. Buscopan (20 ml) was administrated intravenously to control the peristalsis, and sagittal scout images are obtained parallel to the coil. The imaging sequences included T2-weighted fast spin-echo axial images (T2WIs) with fat suppression [using echo time (TE) 89.2 ms, repetition

time (TR) 2100 ms, slice thickness, 4.0 mm, field of view (FOV) 34.0 cm, matrix 256 × 224], non-contrast T1-weighted axial images (T1WIs) with fat suppression [using TE 1.78 ms, TR 3.73 ms, slice thickness 5 mm, FOV 310-370 mm, flip angle 13°, bandwidth 31.25 kHz, asset factor 2, NEX 1, matrix 288×160], suppressed dynamic contrast-enhanced weighted images [using TE 1.7 ms, TR 210 ms, bandwidth 31.25 kHz, FOV 34.0 cm, flip angle 80°], and DWIs for the rectum or the colon [using TE 63.5 ms, $TR \times 7 \text{ ms}$, RR interval 7, b = 0 , 400 and 800 s/mm2, trigger window 20%, minimum trigger delay, minimum inter-sequence delay, FOV 34.0 cm, slice thickness 5 mm, spacing 1 mm, asset factor 2, NEX 8, matrix 128 × 128]. Reconstruction of all axial images to 256 × 256 matrix after scanning was done. For each lesion, mean ADC was calculated by manually drawing a region of interest smaller in size than the lesion not including adjacent normal tissue.

Neoadjuvant chemoradiotherapy

Forty-five grays per 25 fractions preoperative pelvic radiation therapy (1.8 Gy per day) over the course of 51/2 or 6 weeks. Subsequent 5.4 Gy per three fractions boost was delivered to the primary neoplasia. Concurrent intravenous injection of two cycles of 5-fluorouracil (500 mg/

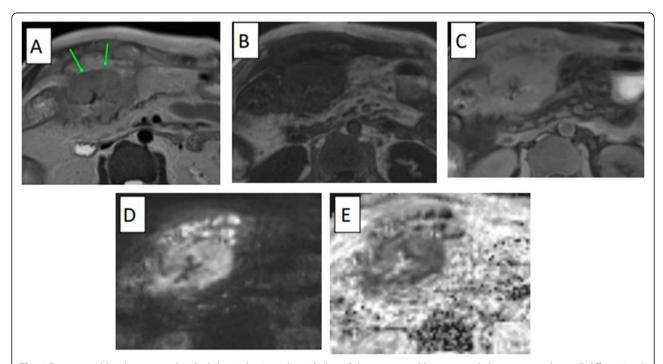
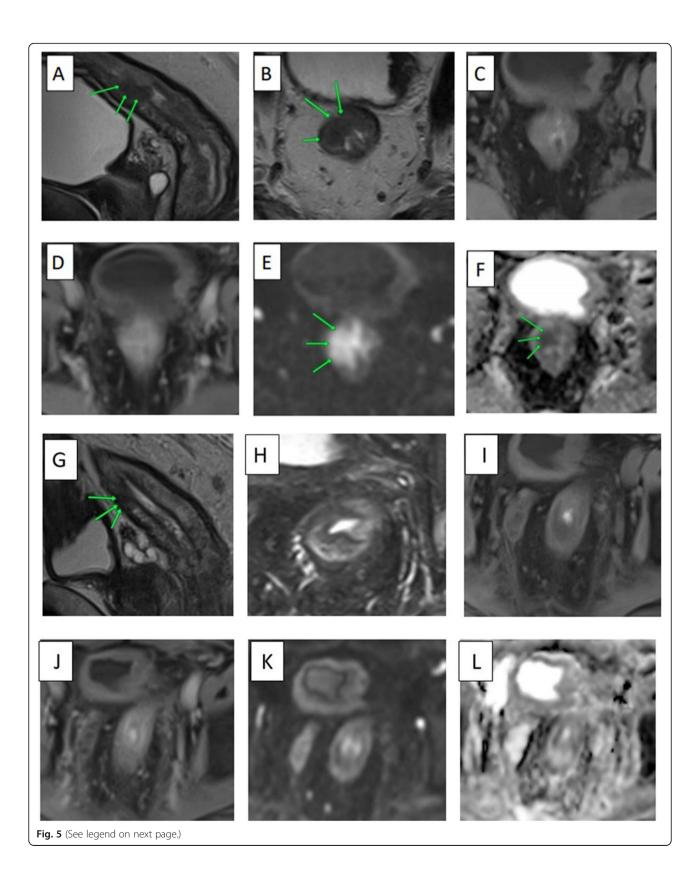


Fig. 4 Forty-year-old male presented with abdominal pain and weight loss. Colonoscopy and biopsy revealed transverse colon well-differentiated adenocarcinoma. Large lobulated circumferential soft tissue mass was seen infiltrating the right side of the transverse colon reaching the serosa with minimal extension into the surrounding fat. It displayed high to intermediate signal in T2WI (**A**) and low signal in T1WI (**B**), with heterogeneous enhancement in post contrast images (**C**). The lesion appeared bright in DWIs (**D**) and turned dark in the ADC map (**E**), with ADC value 1.1×10^{-3} mm²/s, indicating restricted diffusion



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Fig. 5 A 54-year-old male presented with bleeding per rectum (colonoscopy and biopsy revealed rectal poorly differentiated adenocarcinoma). *Pretreatment study* (**A** to **F**) revealed upper third rectal mass at the right anterolateral wall with no invasion to the mesorectal fat (measured $2 \times 1 \times 1.9$ cm). It displayed intermediate signal in sagittal and axial T2-weighted images (**A**, **B**) and intermediate signal in T1-weighted images (**C**) with mild homogenous enhancement in post contrast images (**D**). The lesion appeared bright in DWIs (**E**) and turned dark in the ADC map (**F**), with ADC value 0.63×10^{-3} mm²/s, indicating restricted diffusion. *Posttreatment study after chemo and radiotherapy* (**G** to **L**) revealed minimal low signal at the previous tumor site in sagittal, axial T2WIs (**G**, **H**) and axial T1WI (**I**) with no enhancement in post contrast images (**J**). There is no detectable altered signal at the site of abnormality in DWIs (**K**) and ADC map (**L**), with ADC value 1.5×10^{-3} mm²/s. Colonoscopy and biopsy revealed presence of fibrosis at the rectal wall with no evidence of residual tumor cells (complete response)

m2/d) with radiation therapy for 3 days during the 1st and 5th weeks of radiation therapy was also given to the patients.

Follow-up by MRI

Twenty patients out of forty were examined by MRI with diffusion after completion of chemoradiotherapy. The tumor in all the followed up twenty patients was in the rectum.

Image interpretation

The MRI images were interpreted by two consultant radiologists of 6- and 13-year experience in pelviab-dominal MRI. They reported the findings after reviewing conventional MRI alone and after reviewing conventional MRI with DWI and ADC value calculation.

In follow-up studies, CR was reported in conventional MRI when there is no mass or mural thickening seen and non-CR was reported when there is visualized residual tumor tissue. When DWI added to the conventional images, CR was reported when there was no high signal in the site of corresponding tumor and non-CR was reported when there is residual high signal in the site of corresponding tumor. After calculation of ADC value, a cutoff value of 1.20×10^{-3} mm²/s was used to discriminate CR from non CR. This value was used considering the results of previous study done by Kim et al. [2].

Biopsy after chemoradiotherapy

The primary tumor response to the chemoradiotherapy was graded as follows: "pathologic complete response" (which means no residual tumor cells found in the sample) or "pathologic non-complete response/residual tumor" varying from limited tumor cells to a solid residual tumor mass. Post-therapeutic pathological staging was compared to the MRI staging.

Statistical analysis

A post hoc power analysis was done using the G*Power software version 3.1.9.4, with a sample of size 20, considering an effect size equal to 0.5, an alpha level of 0.05, and the resulting power 69.5%. Software

(SPSS for Windows, version 10.0.1, 1999; SPSS, Chicago, III) was used for statistical analysis. The results were expressed as mean ± standard deviation or number (%). Comparison between mean values of ADC in the studied groups was performed using the one-way ANOVA test, followed by the Tukey test for multiple comparisons whenever a statistical significance was detected by the ANOVA. The standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (diagnostic efficacy) were calculated as described by Galen (1980). *P* value less or equal to 0.05 was considered significant and less than 0.01 was considered highly significant. A summary of study methodology is shown in Fig. 1.

Results

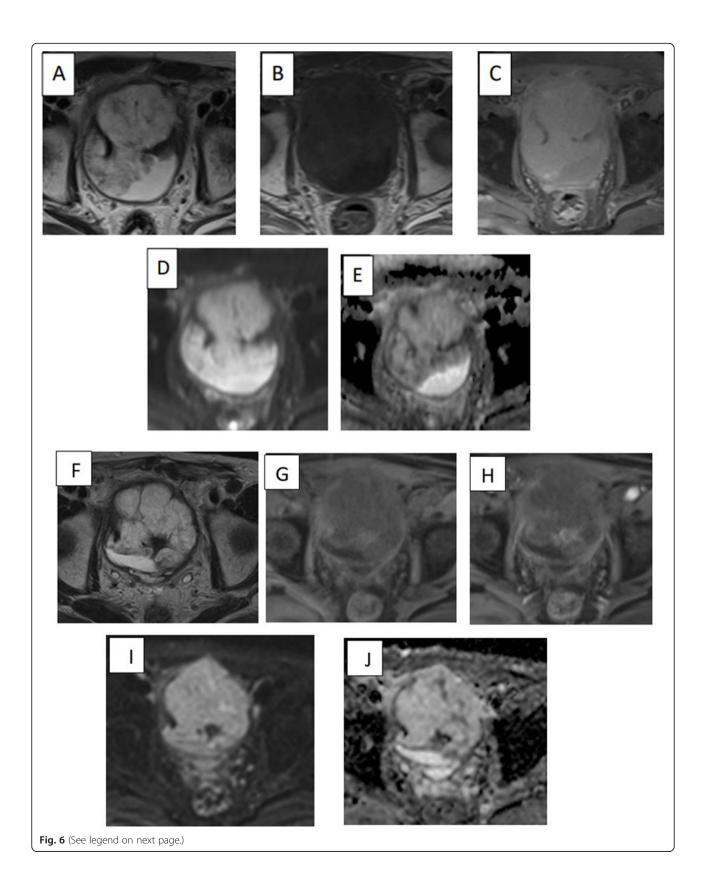
This study included 40 patients, 22 males (55%) and 18 females (45%), ranged in age from 27 to 76 years (with mean age of 51.3 ± 15.16 years).

Of the 40 cases (Figs. 2, 3, 4, 5, and 6), 30 cases (75%) were in the rectum (Figs. 2, 3, and 5), 5 cases (12.5%) in the sigmoid colon (Fig. 6), one case (2.5%) in the descending colon, 2 cases (5%) in the transverse colon (Fig. 4), one case (2.5%) in the ascending colon, and 1 case (2.5%) in the cecum.

There were 40 patients pathologically proven to be colorectal adenocarcinoma, 2 of them are mucinous type adenocarcinoma (5%) and 38 are tubular type adenocarcinoma (95%). Out of the 40 patients, 7 (17.5%) were poorly differentiated, 20 (50%) were moderately differentiated, and 13 (32.5%) were well differentiated histologically.

Out of the 38 cases of tubular adenocarcinoma, there was apparent diffusion restriction in 37 cases (97.3%) being high signal on DWI and low signal on ADC. The two cases of mucinous adenocarcinoma show no apparent diffusion restriction. They show high signal on both DWI and ADC map due to T2 shine through.

So, restricted diffusion in DWI was found in 37 out of 40 patients with sensitivity about 92.5%. In the studied group, the median ADC value was 1.21 (min 0.80, max 1.31) and the average ADC value was 1.14 ± 0.161 .



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Fig. 6 A 69-year-old male presented with constipation, bleeding per rectum, and hematuria (colonoscopy and biopsy revealed sigmoid colon mucinous type adenocarcinoma). *Pretreatment study* (**A** to **E**) revealed large lobulated soft tissue mass infiltrating the sigmoid colon with large exophytic component invading the urinary bladder (measured $10 \times 7.9 \times 13.3$ cm). It displayed heterogeneous high signal in T2WI (**A**) and low to intermediate signal in T1WI (**B**), with heterogeneous enhancement in post contrast images (**C**). The lesion appeared bright in DWIs (**D**) and relatively bright in the ADC map (**E**), with ADC value 1.6×10^{-3} mm²/s, indicating predominantly facilitated diffusion. *Posttreatment study after chemo and radiotherapy* (**F** to **J**) revealed stationary course regarding the size and signal of the mass and displayed heterogeneous high signal in T2WI (**F**) and low to intermediate signal in T1WI (**G**), with less prominent enhancement centrally in post contrast images (**H**). The lesion appeared bright in DWIs (**I**) and predominantly bright in the ADC map (**J**), with ADC value 1.8×10^{-3} mm²/s, indicating facilitated diffusion. Colonoscopy and biopsy revealed residual tumor cells of mucinous adenocarcinoma

The mean ADC value in poorly differentiated tumors was $0.979 \times 10^{-3} \text{mm}^2/\text{s}$. The mean ADC value in moderately differentiated tumors was $1.112 \times 10^{-3} \text{mm}^2/\text{s}$. The mean ADC value in well-differentiated tumors was $1.273 \times 10^{-3} \text{mm}^2/\text{s}$ (Table 1).

Twenty out of 30 patients with rectal cancer received chemoradiation for down staging. Fifteen patients proceed to surgery and the other five are followed up by repetitive sigmoidoscopy and biopsy to ensure recurrence free.

At histology, 10 patients have pathologic complete response (CR) and 10 patients have residual tumor (ranging from limited tumor cells to a solid residual tumor mass).

The agreement of the conventional MRI with the pathology was as follows: in complete responders (CRs), the true-negative results were found in 6 patients and the false-negative results were found in 2 patients, while in non-complete responders (non-CRs) true-positive results were found in 8 patients and the false-positive results were found in 4 patients (Table 2).

The agreement of the DWI with the pathology was as follows: in CRs, true-negative results were found in 8 patients and false-negative results were found in one patient, while in non CRs true-positive results were found in 9 patients, and false-positive results were found in 2 patients (Table 3).

When an ADC of 1.20×10^{-3} mm²/s was used as the cut-off value for discrimination between the CR and

Table 1 Tumor characteristics and MRI findings during initial assessment of the studied 40 patients with colorectal cancer

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Tumor characteristics	No. and MRI findings		
Histopathologic type			
Tubular adenocarcinoma	38 (37 show diffusion restriction in DWI)		
Mucinous adenocarcinoma	2 (show no diffusion restriction in DWI)		
Histopathologic grade			
Well-differentiated adenocarcinoma	13 (mean ADC value± SD 0.979 ± 0.183 \times 10 ⁻³ mm ² /s, <i>P</i> -value < 0.0001*)		
Moderately differentiated adenocarcinoma	20 (mean ADC value± SD 1.112 ± 0.141 \times 10 ⁻³ mm ² /s, <i>P</i> -value < 0.0001*)		
Poorly differentiated adenocarcinoma	7 (mean ADC value± SD 1.273 ± 0.017 × 10 ⁻³ mm ² /s. <i>P</i> -value < 0.0001*)		

^{*}statistically significant P-value ≤ 0.05

non-CR groups, the agreement of ADC value compared to the pathology was as follows: in CRs true-negative results were found in 8 patients and there was no false-negative results, while in non-CRs the true-positive results were found in 10 patients and false-positive results were found in 2 patients (Table 4).

The sensitivity, specificity, PPV, NPV, and accuracy of conventional MRI, DWI, and ADC in the studied group are shown in Table 5.

Discussion

Different cross-sectional imaging tools as CT (computed tomography), PET/CT (positron emission tomography/computed tomography), and MRI (magnetic resonance imaging) are usually used for initial assessment, staging, and follow-up of therapeutic response of cancers [8-11]. Contrast enhanced magnetic resonance imaging is considered a routine tool used in colorectal cancer local staging, yet it is invasive, time consuming, and adequate cooperation in breath hold technique which is required in addition to contrast media contraindications and adverse effects. Diffusion-weighted MRI is an imaging tool that can be used to assess the diffusion process in vivo that varies in different tissues and ADCs are the quantitative expressions of the diffusion characteristics that decreased with increased tissue cellularity indicative of tumor aggressiveness [12]. The recently developed MRI systems with high gradient amplitude have greatly improved the DWI diagnostic performance [13]. However, the choice of b values in application of DWI is a compromise. Low b values lead to increased ADC values due to contamination of

Table 2 Conventional MRI versus pathology in the studied group

Characteristics		Pathology		<i>P</i> -value
			Non-CRs (No. = 10)	· I
Conventional MRI	CRs (No. = 8)	6 (60%) TN	2 (20%) FN	0.001**
	Non-CRs (No. = 12)	4 (40%) FP	8 (80%) TP	

^{**}P-value < 0.01 highly significant

TN true negative, FN false negative, FP false positive, TP true positive

Table 3 DW MRI versus pathology in the studied group

Characteristics		Pathology		<i>P</i> -value
		CRs (No. = 10)	Non-CRs (No. = 10)	
Diffusion MRI	CRs (No. = 9)	8 (80%) TN	1 (10%) FN	0.001**
	Non-CRs (No. = 11)	2 (20%) FP	9 (90%) TP	

**P-value < 0.01 highly significant

TN true negative, FN false negative, FP false positive, TP true positive

other forms of intravoxel incoherent motion, while high b values lead to decrease in signal-to-noise ratio (SNR) but require long acquisition times [14]. In our DWI study, the used b values were 0, 500, and $1000 \, \mathrm{s/mm^2}$; with application of breath triggering technique and parallel imaging, a satisfying image quality with acceptable acquisition time has been achievable on a 1.5-T scanner.

In the first part of this study, our aim was to depict the sensitivity of MRI DWI in detection of colorectal cancer and the correlation between the ADC value of the tumor and its histological grade. We found that the sensitivity of DWI in detecting colorectal cancer was 92.5% (37/40). This matched with a study conducted by Ichikawa et al. that reported 91% sensitivity of MRI DWI to detect rectal cancer (30/33) [12].

Our study also showed significant correlation between the ADC value and the histological grade of the tumor. The ADC value is significantly lower in the poorly differentiated tumors. These results matched the results of the studies done by Gu et al. and Curvo-Semedo et al. [15, 16].

In this study, the value of adding post- neoadjuvant chemoradiotherapy DWMR imaging to conventional MR rectal imaging were evaluated to determine if there was a complete response (CR) to neoadjuvant CRT in the examined patients with locally advanced rectal cancer. The results showed that diagnostic accuracy for evaluating CR increased significantly when adding DWMR imaging to the conventional MR imaging.

Previous studies found that using conventional MRI alone (as a morphologic imaging modality) cannot accurately differentiate fibrotic changes from residual tumor tissue [17, 18].

In our study, when using cut-off ADC value of 1.20×10^{-3} mm²/s for discrimination of complete responders (CR) from non-complete responders (non-CR), the NPV was 100% (8 of 8 cases) supporting the use of ADC value for accurate differentiation of responders from non-responders. Our results are typical with those of a previous study conducted by Kim et al. that reported 100% negative predictive value (23 of 23 cases) when using an ADC of 1.20×10^{-3} mm²/s as the threshold value in the differentiation of CR group from the non-CR group [9].

ADC measurement is helpful in determining complete response in cases with mucinous adenocarcinomas because this entity has higher ADC values than other adenocarcinomas. Also, it is challenging to accurately detect disease activity in patients with mucinous tumors by conventional MRI due to difficulty in differentiating inactive mucin pools from residual tumors. Although DW MRI can be accurately used to differentiate complete from poor responders to neoadjuvant CRT, yet it has many limitations. First, it is not absolutely accurate in the differentiating CR from near CR as well as discriminating inactive mucin pools from residual tumor tissue in the mucinous type. Also, it cannot overcome the heterogeneity of the tumor response to neoadjuvant CRT as even ADC mapping reconstructed with highspatial-resolution based on small voxels cannot

Table 4 ADC versus pathology in the studied group

Characteristics		Pathology		<i>P-</i> value
		CRs (No. = 10)	Non-CRs (No. = 10)	
ADC	CRs (No. = 8)	8 (80%) TN	0 (0%) FN	0.001**
	Non-CRs (No. = 12)	2 (20%) FP	10 (100%) TP	

^{**}P-value < 0.01 highly significant

Table 5 Diagnostic indices (sensitivity, specificity, PPV, NPV, and accuracy) of MRI (conventional, DWI, and ADC) in the studied group

	Sensitivity	Specificity	PPV	NPV	Accuracy
Conventional	8/10 (80%)	6/10 (60%)	8/12 (66.7%)	6/8 (75%)	14/20 (70%)
DWI	9/10 (90%)	8/10 (80%)	9/11 (81.8%)	8/9 (88.9%)	17/20 (85%)
ADC	10/10 (100%)	8/10 (80%)	10/12 (83.3%)	8/8 (100%)	18/20 (90%)

PPV positive predictive value, NPV negative predictive value

assess the tumor response at each individual cellular level. In addition, DW MRI has limited spatial resolution and the relatively low signal-to-noise ratio at high b value [9].

Our study has some limitations. First, the relatively small study population and our results need to be confirmed by larger clinical studies. Also, our study does not include negative cases; thus, the specificity of DWI in detecting colorectal cancer cannot be measured. Third, the ADC measurements obtained in this study by measuring three ROIs that may not be adequately representative for the overall tumor profile, yet we chose this approach because it is very time-consuming to outline the whole tumor volume and is difficult to be performed in the daily clinical practice. We tried to perform what is happening in the daily clinical work, where a quicker and simpler way to obtain ADC values were used.

Conclusion

Adding DW imaging with ADC value to conventional MRI yields better diagnostic accuracy than using conventional MR imaging alone in detection, correlation with tumor histologic grade, initial staging, and response evaluation to neoadjuvant CRT in patients with locally advanced colorectal cancer.

Abbreviations

MRI: Magnetic resonance imaging; DWI: Diffusion-weighted images; ADC: Apparent diffusion coefficient; CRC: Colorectal carcinoma; CEA: Carcinoembryonic antigen; FOV: Field of view; ROI: Region of interest; CRs: Complete responders; TN: True negative; FN: False negative; FP: False positive; TP: True positive; PPV: Positive predictive value; NPV: Negative predictive value

Acknowledgements

Not applicable

Authors' contributions

MS carried out the MRI studies and collected the data. SA, GM, and AE participated in the design of the study. MS and SA performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee (REC) of Ain Shams University, Faculty of Medicine (FMASU M D 219/ 2018), and written informed consent was obtained from all patients to participate in the study.

Consent for publication

Written informed consent was obtained from all patients for publication of the study.

Competing interests

The authors declare that they have no competing interests.

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