RESEARCH ARTICLE

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Role of Intravoxel Incoherent Motion and Dynamic-Contrast-Enhanced Perfusion in Response Prediction of Patients with Colorectal Cancer after Neoadjuvant Chemotherapy

Hayder Jasim Taher[1,2]*, Arvin Arian[3], Mahdi Aghili[4], Amir Keshvari[5]

Abstract

Background: Colorectal cancer (CRC) is a complex malignancy requiring multimodal treatment strategies, including neoadjuvant chemoradiation therapy (Neo-CRT), to improve patient outcomes. However, the response to Neo-CRT varies among individuals, which necessitates the development of reliable predictors of treatment response. The present study aimed to investigate the role of intravoxel incoherent motion (IVIM) and dynamic contrast-enhanced (DCE) perfusion in predicting treatment response in CRC patients after Neo-CRT. **Methods:** This study was conducted on patients diagnosed with locally advanced CRC who received Neo-CRT. IVIM and DCE perfusion imaging were performed before and after CRT. Quantitative parameters, including perfusion fraction (f), diffusion coefficient (D), and transfer constant (Ktrans), were calculated from the imaging data. Treatment response was assessed based on the pathological response after surgery. Statistical data were analyzed in SPSS v. 26 using the t-test and the chi-square method. **Results:** A total of 51 patients (female: male = 22:29, mean age = 58.14±3.49) participated in the study. Among all the patients, 15 (29.4%) cases had good responses, while 36 (70.58%) cases did not respond to treatment. All DCE parameters showed higher sensitivity and specificity than IVIM D*. Ve, Kep, and DCE Ktrans indicated significant predictive power for treatment response. Ktrans was the most accurate parameter for predicting response to treatment. Overall sensitivity and specificity of DCE were 88.8% [95% CI: 80-95.6], and 80 % [95% CI: 65-90], and those of IVIM were 65.5% and 81%, respectively. Sensitivity and specificity for DCE + IVIM were 79.5% and 93.5%, and those of DCE + IVIM + standard magnetic resonance imaging were 80.2% and 86%, respectively. **Conclusion:** IVIM and DCE perfusion imaging could serve as promising tools for predicting treatment response in CRC patients after Neo-CRT.

Keywords: DCE-MRI- IVIM- prediction of response- rectal cancer.

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Introduction

Colorectal cancer (CRC) is the third most frequently tumor reported in the United States and the second leading reason for malignant deaths. The disease is lethal both in both men and women, accounting for the third highest cause of mortality, and more than 43,000 new cases of CRC are diagnosed each year [1]. While the annual decline in CRC incidence and death is 3%, it remains a major health problem [2]. To reduce the recurrence risk of locally advanced CRC, preoperative chemoradiation therapy (CRT) is extensively utilized. As a result of vascular changes and cell death, CRT may cause downstaging of the tumor and pathologic complete/partial response [3]. Ineffective preoperative CRT may induce unnecessary toxicity to the patient's health and cause a delay in correct therapy. However, there is substantial individual diversity in responsiveness to CRT.

Neoadjuvant chemoradiation therapy (Neo-CRT) before surgery has the benefit of reducing tumor size, leading to tumor downstaging. This approach results in a pathologic complete response in approximately 15-27% of the patients after a 6-8-week period between the CRT and the surgical procedure [4]. The response of tumors to CRT varies significantly, and the exact reasons for this variability remain unclear. Around 54-75% of CRC patients experience tumor downstaging, while the remaining do not show any response to the treatment [5]. In patients with locally advanced (T3-4) resectable CRC, distant metastases still dominate with a five-year cumulative incidence of 30% in a pooled analysis of five randomized control trials [6]. There is significant morbidity associated with locally advanced CRC treatment, and about a third of the patients will have

*[1]Department of Technology of Radiology and Radiotherapy, Allied Medical Science School, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Radiology, Hilla University College, Babylon, Iraq. [3]Radiology, TUMS (Cancer Institute-ADIR), Tehran University of Medical Sciences (TUMS), Tehran, Iran. [4]Radiation Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran. [5]Division of Colorectal Surgery, Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran. *For Correspondence: Haiderdr75@gmail.com*

a permanent colostomy as a result of surgery. At present, there is no accurate method of predicting response to CRT. Current prediction models need pathological staging, making them ineffective as a pre-treatment decision support tool [6, 7]. Non-invasive predictive biomarkers, such as magnetic resonance imaging (MRI), are required to guide individualization of patient treatment in order to maximize therapeutic outcomes and minimize treatment toxicity.

Early imaging prediction of CRT response is important for a therapeutic strategy, with the potential to increase therapeutic response and reduce treatment-related complications. The ability to predict a complete response to CRT prior to surgery could help the patients undergo the "watch-and-wait" strategy, therefore avoiding the morbidity of surgery. Accurate diagnosis of non-responsiveness to CRT allows these patients to avoid futile treatment and move towards dose-escalation techniques, systemic treatments or surgery [8].

Functional MRI as an important advance in imaging evaluation in oncology enables the assessment of different biological tumor characteristics. Tumors are biologically heterogeneous, and this feature can affect therapeutic response [9]. Other tumor characteristics influencing therapeutic response include cellularity, perfusion, hypoxia, and the tumor extracellular matrix microenvironment. MRI offers the capability of a comprehensive virtual tumor biopsy, facilitating the capture of data pertaining to intra-tumoral heterogeneity. This capacity holds promise for enhancing treatment personalization by leveraging insights derived from the unique characteristics of the patient's tumor [10].

Volumetric measurements based on standard morphologic MRI (T2-weighted) are not accurate enough to identify difference between individuals who respond and not respond to treatment because they detect small tumor deposits in areas where radiation has caused fibrosis. Changes in morphologic MRI in response to treatment also occur late, making it unsuitable for early stratification of management. Functional MRI biomarkers show higher promise than typical T2-weighted sequences for predicting treatment response in locally advanced CRC [11]. The clinical usefulness of these functional MRI indicators in CRC, together with a whole tumor heterogeneity analysis for treatment response prediction, needs further investigation.

MRI offers a significant advantage by allowing imaging of the entire tumor, which provides comprehensive information on its heterogeneity. This technique helps overcome sampling errors associated with biopsies. Tumors exhibit biological heterogeneity and understanding intratumoral heterogeneity could enhance the prediction of treatment response. Most published studies on MRI response prediction in CRC mainly focus on single summary parameters obtained from either diffusion or perfusion MRI. This study addresses an unmet clinical need by exploring non-invasive methods for predicting treatment response, which can aid clinicians in making informed treatment decisions. Successful identification of predictive biomarkers using intravoxel incoherent motion (IVIM) and dynamic contrast-enhanced (DCE) perfusion MRI could enable the stratification of patients into responders and non-responders before surgery, allowing for tailored treatment strategies. This personalized approach has the potential to improve treatment outcomes, minimize treatment-related morbidity and optimize resource utilization in the management of CRC. Therefore, the study seeks to contribute to the advancement of precision medicine in CRC care. The present study was undertaken to evaluate the diagnostic accuracy and prognostic relevance of IVIM and DCE perfusion in prediction response to CRT in patients with locally advanced CRC.

Materials and Methods

This prospective design cohort study investigated the efficacy of multi-parametric MRI in predicting response in CRC patients after CRT. The study was carried out in the Medical Imaging Center of the Imam Khomeini Hospital (Tehran, Iran), and the patients underwent regular treatment for their malignancy. The gold standard for patients with locally advanced CRC who were recommended for MRI was biopsy or "watch and wait." In this approach, patients undergo a period of close monitoring through regular clinical assessments, imaging studies, and possibly endoscopic evaluations, without undergoing immediate surgical resection.

Inclusion/exclusion criteria

This prospective trial was open to all the patients with locally advanced CRC who experienced Neo-CRT, followed by primary surgery. Patients with the following data were included: a very distant tumor, a T4 tumor, a T3 tumor with mesorectal involvement and/or N1 disease, a distant subcutaneous tumor, or a N2 status. However, patients with chronic renal impairment, active inflammatory bowel disease, prior malignancy, a history of allergy to contrast media, an implanted pacemaker or implantable defibrillator, or extreme claustrophobia were excluded from the study.

Patients and methods

We identified 51 patients with locally advanced CRC (29 men and 22 women; 18-86 years) who were referred to our institution for assessing their response to treatment. The patients were evaluated by conventional DCE perfusion MRI and compared with histopathology. All the patients received standard treatment, i.e. Neo-CRT, followed by primary surgery, and then received MRI before and after CRT (within one week prior to surgery). The schematic design of the study is represented in Figure 1.

DCE perfusion-weighted imaging

Fat-saturated volumetric interpolated breath-hold examination (VIBE) T1-weighted sequence was utilized with the following parameters: repetition time (TR) and echo time (TE) of 788/7.9 ms, field of view (FOV) of 250 × 250 mm, matrix size of 320 × 192, slice thickness and number of 4 mm and 40/60, respectively, and a Nexus 3 (NXT 3) system with flip angles of 2°, 8°, and

15°. Intravenous injection of 0.1 mL/kg of gadobenate dimeglumine (MultiHance, Bracco, Milan, Italy) was administered before and after image acquisition. The sequence was repeated on the axial plane at 30, 70, and 300 seconds post contrast administration. Magnetic resonance (MR) images were acquired during the hepato-specific phase approximately 1 hour following contrast administration.

IVIM-DWI (diffusion-weighted imaging)

The axial IVIM scanning was performed perpendicular to the lesion in the same direction as the axial TSE T2-weighted series using a single-shot EPI sequence with 12 b-values of 10, 20, 30, 50, 80, 100, 150, 200, 400, 600, 800, and 1000 s/mm2, slice thickness of 3.6 mm, TR/TE of 8000/74 ms, FOV of 250 mm × 250 mm, matrix size of 128 × 128, NEX range of 2-6. The scanning time of IVIM was approximately 6 minutes 30 s.

Image analysis

Images were processed before and after treatment by a radiologist with more than 20 years of experience in abdominal MRI. Image processing was performed using GE Function Tool post-processing software after scanning (Figures 2 and 3) and region of interest (ROI)-based measurement to calculate the mean f, D, and D* values within the ROI. The relative blood flow was also assumed as the multiplication of f and D*. The pseudo-color images were selected based on the IVIM-DWI quantitative parameters D, D*, and f of the double exponential model. Diffusion correlation coefficient (D) and perfusion correlation coefficient (D*, f) of water molecules was used to identify the diffusion movement of water molecules in vivo from microcirculation perfusion. The high signal lesion area was selected on the axial DWI image of b = 1000 s/mm2. The corresponding level of T2WI image was utilized as the anatomic structure reference, which requires that the blood vessels, tumor necrosis, and bleeding components should not be included, to avoid the influence of heterogeneous components on the measurement results. On the pseudo-color images of each parameter, the solid part of the tumor was selected to outline the ROI at the maximum level of the tumor and its upper and lower levels, and then the measurement results of the three-layer ROI were averaged.

DCE-MRI data were analyzed, and post-processing procedures encompassed initial motion correction and rigid registration of precontrast images acquired at multiple flip angles, facilitating the generation of a T1 map. Subsequently, registration with dynamic images was performed to convert signal intensities into gadolinium concentration. Any misalignment in the automatic registration of images was corrected. Based on a Toft and Kermode model, 30 maps of the tracer exchange between the compartments "Ktrans" and the extracellular volume fraction "Ve" were extracted. The arterial input function was automatically selected on the iliac arteries, and its curve was checked for adequate fit. A manual volume of interest (VOI) delineation was conducted along the tumor periphery utilizing high-resolution axial T2-weighted reference images. The following parameters were then gathered for Ktrans and Ve analysis. Using corresponding axial T2W images as reference, three irregular ROIs were placed to include most of the solid tumors on DCE-MR images (Figures 2 and 3). The mean value of each permeability parameter within a ROI on DCE-MR images was recorded.

Data analysis

All patients' MRI images were evaluated and analyzed by a committee of highly experienced radiologists, who were blind to abnormal outcomes, in a medical imaging center. Members of Pathology Department of our institution evaluated histopathology of tumors. The program used for data entry was SPSS version 24, and the data were analyzed by the t-test and the chi-square method. P-values less than 0.05 was regarded as significant in all outcomes. Based on sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, diagnostic indices for MR imaging techniques were computed.

Results

A total of 51 patients (female:male [22:29]; 58.14±3.49 years) were included in the study. Among all the patients, 15 (29.4%) cases showed a good respond to treatment, but 36 (70.58%) cases did not respond to treatment (Table 1). Scatter plots of parameters derived from DCE-MRI and IVIM-MRI indicated no significant correlation between any IVIM and DCE parameters after treatment (Figure 4).

Table 1. Demographic Variables of the Study Population

Population feature	Good response population (%)	Non-response population (%)
Male	11 (73.3%)	18 (50%)
Female	4 (26.6%)	18 (50%)
Age, median (IQR, year)	58 (19.5)	60 (17.75)
Tumour location, n		
Upper	9	14
Lower	3	8
Mid	3	14
Total	15	36
T Staging		
T3	2	10
T3a	8	15
T3b	1	4
T3c	0	2
T4	3	4
T4a	1	1
Total	15	36
N Staging		
N0	7	12
N1	6	14
N2	2	10
Total	15	36

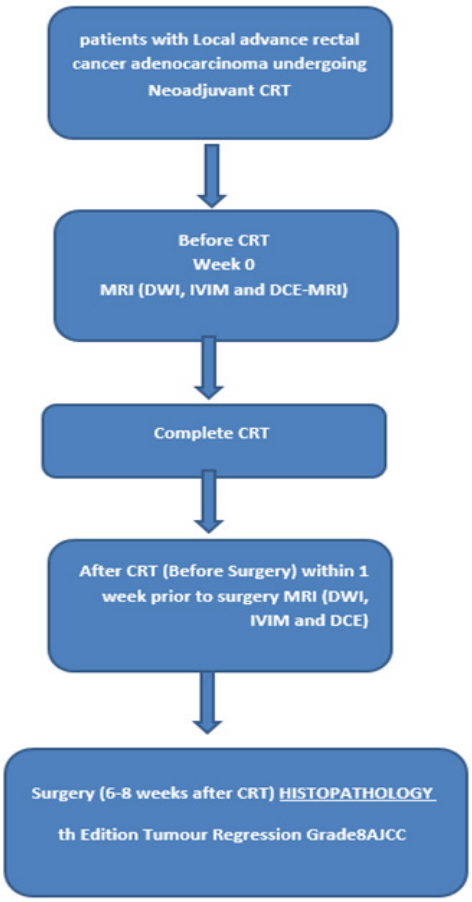

Figure 1. Schematic of Study Design

Exact Pearson's correlation coefficients and relevant p-values are reported in Tables 2 and 3.

Tables 4 and 5 show a significant difference between pre- and post-treatment DCE-Ve, DCE-Ke, DCE-Ktrans, and IVIM D* parameters. In post-treatment, these parameters were higher than in pre-treatment.

Table 2. Pearson Correlation Coefficient; Post-Treatment

	IVIM-MRI		
	D* ($10^{-3}mm^2/s$)	D ($10^{-3}mm^2/s$)	f (%)
DCE-MRI			
K^{trans} (min^{-1})	r =-0.261	r= -0.394	r= 0.286
	P = 0.43	p= 0.230	P = 0.392
k_{ep} (min^{-1})	r = 0.538	r = 0.379	r = -0.311
	P = 0.87	P = 0.250	P = 0.350
ve	r = -0.409	r = 0.293	r = 0.416
	P = 0.211	P = 0.381	P=0.202

r, Pearson Correlation Coefficient; p, P-value (significance level<0.05)

Table 3. Pearson Correlation Coefficient; Pre-Treatment

	IVIM-MRI		
	D* ($10^{-3}mm^2/s$)	D ($10^{-3}mm^2/s$)	f (%)
DCE-MRI			
Ktrans (min^{-1})	r =0.170	r= 0.153	r= -0.09
	P = 0.37	p= 0.420	P = 0.622
kep (min^{-1})	r = 0.128	r = 0.187	r = -0.029
	P = 0.50	P = 0.328	P = 0.871
ve	r = 0.181	r = 0.216	r = 0.158
	P = 0.33	P = 0.25	P=0.41

r, Pearson Correlation Coefficient; p,P-value (significance level<0.05)

Mann-Whitney test demonstrated that the Kep and Ve parameters of DCE-MRI and the D* parameter of IVIM-MRI in some of their relevant indicators (mean, standard deviation, kurtosis, and skewness) had statistically significant differences between good responders and non-responders to treatment.

The receiver operating characteristic (ROC) curve demonstrated the true positive rate (sensitivity) on the y-axis and the false positive rate (1-specificity) plotted

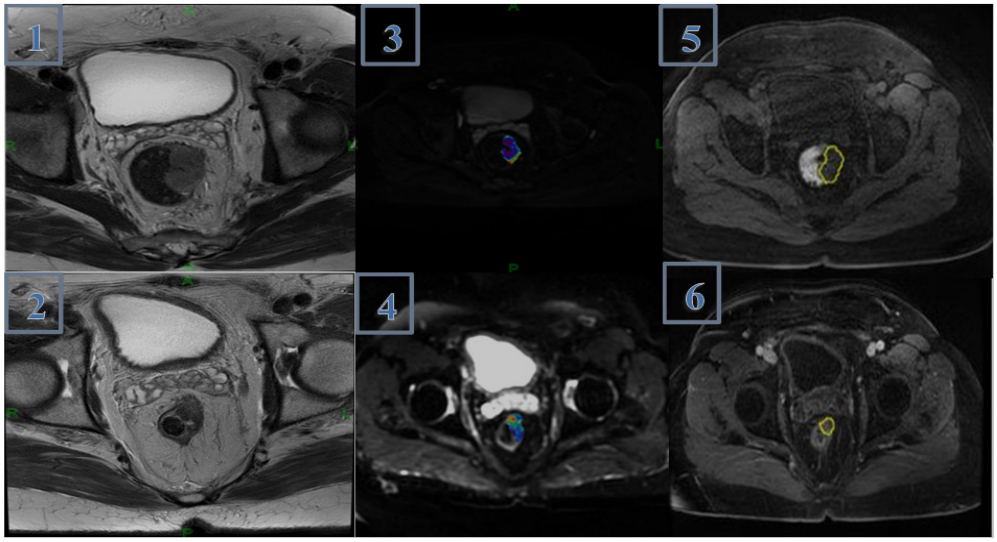

Figure 2. Good Response Case based on the Tumor Regression Grade (TRG) Criteria. A 63-year-old female with locally advanced colorectal cancer. Axial T2-weighted images of a T3c tumor on 1. The pre-CRT MR imaging. T2 images demonstrates the regressive change in the mass as a result of CRT (2. after CRT phase). The Ktrans shows relatively high Ktrans (2.37 min^{-1}) in 5. Pre-CRT phase.6. Ktrans significant drop after CRT MR imaging (f Ktrans 00.85 min^{-1}). After surgical resection, pathological examination revealed the complete remission status (ypT0 and TRG1), suggesting a good response due to downstage and TRG.

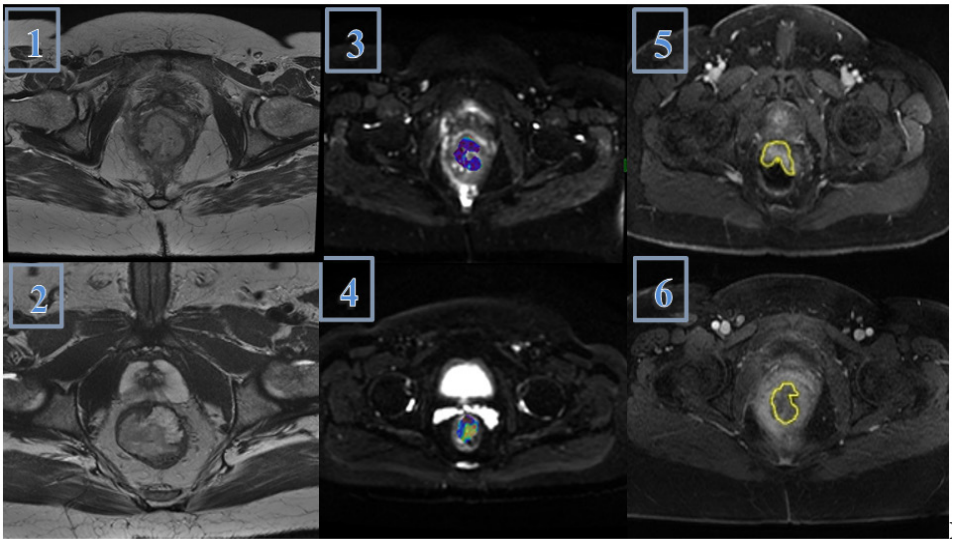

Figure 3. Non-Response Case based on the TRG Criteria. A 63-year-old male with locally advanced colorectal cancer. (1) Axial T2-weighted images of a T3 tumor with extramural fat infiltration. Pre-CRT phase. 2. After -CRT phase.

Table 4. Comparison of DCE and IVIM Parameters

pre-CRT		Good responder				Non-responder				Mann-Whitney's test
		Mean	Median	SD	N	Mean	Median	SD	n	p-Value
DCE Kep	Mean	1.918	1.938	0.708	9	0.871	0.886	0.39	20	0.0008 *
DCE Ve	Mean	0.672	0.723	0.13	9	0.239	0.271	0.134	20	0.001 *
DCE K_{trans}	Mean	1.416	1.103	0.402	9	0.387	0.401	0.154	20	0.0006 *
IVIM D*	Mean	63.36	61.67	4.01	5	36.47	43.61	16.7	11	0.0004 *
IVIM f	Mean	0.29	0.215	0.282	10	0.39	0.182	0.577	25	0.073
IVIM D	Mean	1.598	1.62	0.042	5	1.395	1.42	0.092	11	0.003 *

on the x-axis. Sensitivity measures the percentage of real positives that are correctly recognized, whereas specificity evaluates the percentage of true negatives (Figure5, 6). The area under curve, optimal cut-off value, the relevant specificity and sensitivity, positive and negative predictive values, and positive and negative likelihood ratios for all MRI parameters (DCE-Ve, Kep, DCE-Ktrans, and D*) were extracted from ROC curve. The results showed that all DCE parameters had higher sensitivity and specificity than IVIM D*, Ve, Kep, and DCE-Ktrans had meaningful predictive power for treatment response, and Ktrans was the most accurate parameter for predicting treatment response (Table 6).

We used a statistical technique as meta-analysis to aggregate the findings of two tests to obtain an overall estimate of the diagnostic accuracy. This strategy allowed us to compute combined sensitivity and specificity of the two diagnostic tests (Table 7).

Discussion

Advanced imaging techniques such as IVIM and DCE are becoming increasingly popular in predicting the response to Neo-CRT in CRC patients. IVIM is a DWI technique that separates microcirculation from molecular diffusion and seeks to measure the movement of water within the extracellular fluid and capillaries [12]. This method can also be used to estimate tissue perfusion, diffusivity, and cellular density. DCE-MRI is used to evaluate tumor perfusion and calculate treatment response in patients suffering from CRC and measures the passage of contrast agents through the tissue, reflecting tissue

Table 5. Comparison of DCE and IVIM Parameters in Post-Treatment

post-CRT		Good responder				Non-responder				Mann-Whitney's test
		Mean	Median	SD	n	Mean	Median	SD	n	p-Value
DCE Kep	Mean	0.681	0.662	0.118	4	0.566	0.622	0.236	7	0.527
DCE Ve	Mean	0.202	0.198	0.075	4	0.228	0.179	0.175	7	0.569
DCE K_{trans}	Mean	0.186	0.171	0.062	4	0.302	0.322	0.173	7	0.315
IVIM D*	Mean	57.257	67.95	22.29	10	49.367	51.65	15.39	25	0.014 *
IVIM f	Mean	0.258	0.23	0.038	5	0.59	0.23	0.615	11	0.69
IVIM D	Mean	1.618	0.915	2.064	10	0.922	0.93	0.2	25	1

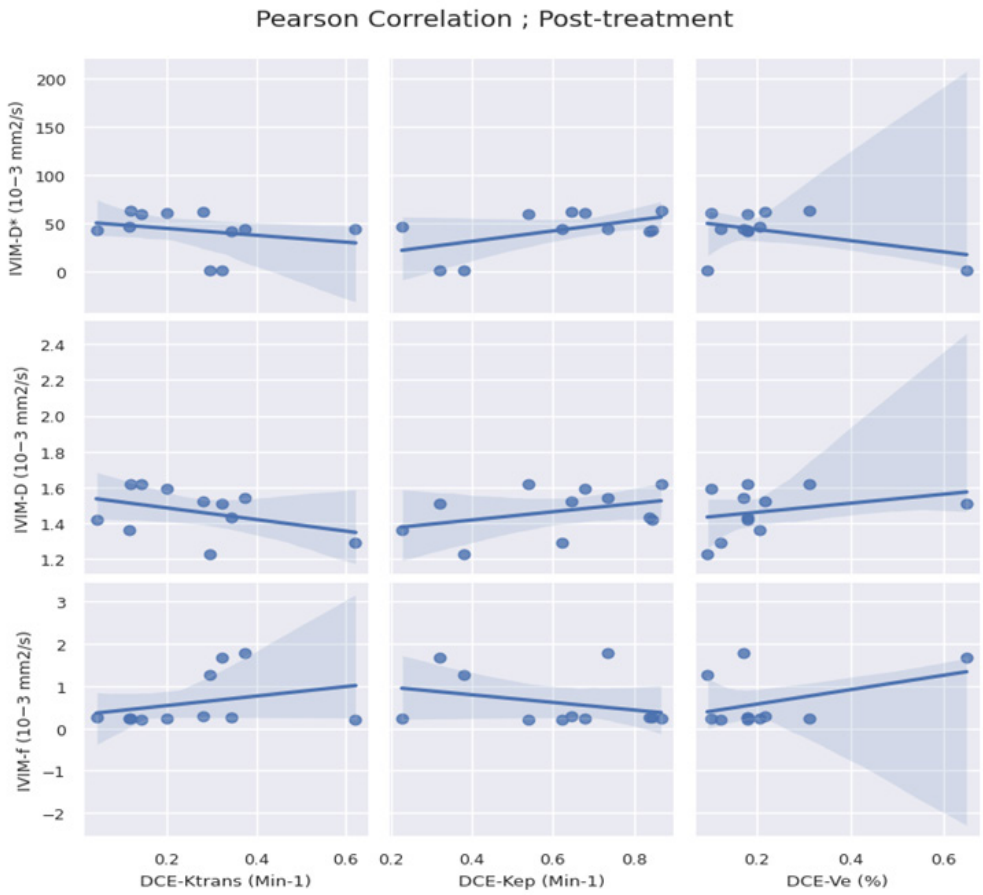

Figure 4. Pearson Correlation of DCE and IVIM Parameters Post Treatment.

perfusion and permeability [13]. Overall, both techniques are helpful in predicting the pathological response to Neo-CRT in CRC patients [14]. However, the sensitivity and specificity of each technique vary.

Our results demonstrated that in CRC patients, after receiving Neo-CRT, parameters such as ve, Kep, and ktrans had more sensitivity and specificity than IVIM D* at predicting the response to treatment. To better understand the meaning of these parameters to discuss, their detailed definition is necessary. DCE stands for DCE-MRI, which uses a contrast agent to assess tissue blood vessels and can provide information about perfusion and permeability in cancerous tissue [15]. Ve or volume of extravascular extracellular space is a DCE parameter that quantifies the extracellular fluid volumes. Kep or influx rate constant is a DCE parameter that measures the leakiness of capillaries. Ktrans, a ratio of kep and Ve is commonly used in DCE studies, which describes the rate of contrast

Table 6. Prediction Performance Parameters Derived from ROC Analysis in the Prediction Response Compared with Pathology

Pre and post CRT	Area under curve (AUC)	Optimal cut-off	Sensitivity	Specificity	positive predictive value (PPV)	negative predictive value (NPV)	positive likelihood ratio (LR+)	negative likelihood ratio (LR-)
DCE K_{trans}	0.961	0.838	0.88	0.82	0.611	0.853	4.933	0.137
DCE Ve	0.901	0.652	0.88	0.78	0.612	0.805	4.036	0.144
DCE Kep	0.894	1.672	0.88	0.81	1	0.851	4.674	0.138
IVIM D*	0.769	55.73	0.8	0.76	0.969	0.791	3.333	0.263
IVIM D	0.5	1.081	0.3	0.92	0.789	0.567	3.75	0.76
IVIM f	0.698	0.197	0.8	0.679	0.714	0.772	2.499	0.294
DCE K_{trans} post	0.75	0.778	0.84	0.72	0.394	0.585	3.001	0.44
DCE Ve post	0.864	0.852	0.79	0.88	0.537	0.936	6.58	0.227
DCE Kep post	0.807	1.753	0.712	0.83	0.44	0.92	4.18	0.32
IVIM D* post	0.667	51.29	0.641	0.71	0.34	0.91	2.21	0.61
IVIM D post	0.53	1.237	0.3	0.83	0.361	0.724	2.29	0.69
IVIM f post	0.412	0.312	0.52	0.579	0.27	0.527	1.27	0.9

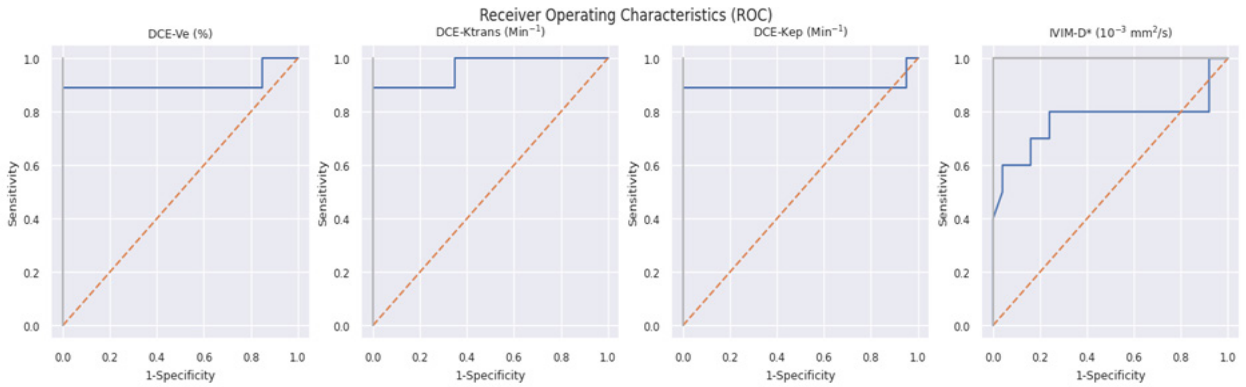

Figure 5. Receiver Operating Characteristics (ROC) of Predictive MRI Parameters.

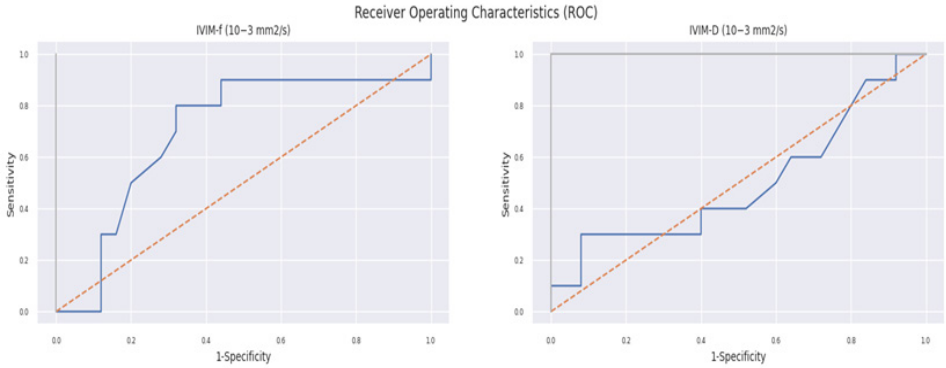

Figure 6. Receiver Operating Characteristics (ROC) of Non-Predictive MRI Parameters.

flowing from the blood vessel into the extravascular extracellular space [16]. The D* value is a parameter of IVIM and indicates the slow diffusion of water within capillaries [17]. The above statement implies that the DCE parameters are better predictors of therapeutic response in CRC patients than IVIM, specifically the D* value. The higher sensitivity and specificity of DCE parameters could be due to the ability to measure changes in blood flow and permeability, which are important indicators of tumor response to chemotherapy. On the other hand, IVIM measures changes in water diffusion, which might not necessarily depict differences in tumor characteristics post therapy [18]. Some studies contradict our claim regarding the sensitivity and specificity of the above-mentioned parameters. One such study conducted by Song et al. (2021) on patients with CRC demonstrated that both IVIM and DCE-MRI are sensitive imaging methods to detect rectal tumor response, but IVIM might be more specific in predicting the pathologic response of chemotherapy [19]. Hence, it seems that IVIM parameters may be better at detecting response to chemotherapy. Altogether, this area of research is still ongoing. While some studies have shown that DCE parameters may better predict therapeutic response in patients with CRC after Neo-CRT, other studies have recognized IVIM parameters as better predictors. Ultimately, combining different imaging techniques, including DCE and IVIM, might provide more comprehensive information about tumor response to chemotherapy, and further research is required to confirm this view. This information can be used to stratify patients based on their predicted response to treatment, which can help select the most appropriate therapy for each patient. For instance, patients with a predicted good response may benefit from less aggressive treatment. In contrast, patients with a predicted poor response may benefit from more aggressive treatment or a different treatment approach. More extensive prospective studies are needed to confirm our findings and evaluate the clinical utility of DCE in predicting the response to Neo-CRT in patients with rectal cancer.

Table 7. Combined Sensitivity and Specificity of Two Diagnostic Tests

	Sensitivity	Specificity
Pre-CRT		
DCE overall	0.888	0.8
IVIM overall	0.655	0.81
Combined DCE and IVIM	0.795	0.935
Standard MRI	0.83	0.53
Combined DCE + IVIM + Standard MRI	0.802	0.86
Post-CRT		
DCE overall	0.785	0.81
IVIM overall	0.48	0.72
Combined DCE and IVIM	0.64	0.76
Standard MRI	0.79	0.56
Combined DCE + IVIM + Standard MRI	0.69	0.7

In the present study, Ktrans parameter provided favorable results in predicting treatment response in patients with CRC after Neo-CRT. The results indicated that Ktrans was a reliable predictor of response, and using this parameter can help clinicians determine the most appropriate course of treatment for their patients. Ktrans measures the transfer rate of contrast agent between the blood and the tissue and is commonly used in imaging studies such as MRI [20]. Utilizing this parameter to forecast treatment response in CRC patients presupposes that regions exhibiting elevated Ktrans values might exhibit greater sensitivity to chemotherapy. Consequently, such areas are anticipated to demonstrate a more favorable response to treatment. In support of this statement, several studies have reported that Ktrans is a valuable predictor of response to Neo-CRT in CRC patients [21]. In an earlier study, the authors found that Ktrans values were significantly higher in patients who responded to chemotherapy than those who did not [22]. In another study, Ktrans was found to be an independent predictor of tumor response in CRC patients receiving Neo-CRT [23]. Reduction in Ktrans values after chemotherapy in responders indicates that the chemotherapy has reduced tumor vascularization, resulting in tumor size reduction. These findings suggest that Ktrans may be used as a biomarker to predict patients' responses to chemotherapy. While there is some disagreements among studies over the ability of Ktrans to predict treatment response in CRC patients, the majority of evidence affirms its utility in this context [24]. However, it is essential to note that although Ktrans could help predict treatment response, it should not be used in isolation, and other factors such as tumor volume, stage, and other imaging parameters should also be considered when making treatment decisions for individual patients.

N-acetylcysteine (NAC) can specifically target and damage rapidly dividing cells, including blood vessels that supply the tumor. As a result, tumor blood flow may decrease the transfer rate (Kep)of contrast agent. Due to the lower availability of the extravascular extracellular space due to injured blood vessels, this decrease in blood flow may also reduce Ve. NAC can also cause alterations in the cellular and interstitial characteristics of the tumor tissue. As a result, Kep and Ve levels may change depending on how permeable the tumor vasculature and extracellular space are. NAC often leads to a reduction in tumor size. Smaller tumors may have different microvascular characteristics than larger tumors, which can influence DCE-MRI parameters, including Ktrans [23]. Areas of necrosis and altered cellular structure can emerge from NAC-induced cell death within the tumor. This behavior may affect the parameters associated with perfusion (D* and f), as well as the diffusion of water molecules (D) [25]. Reductions in D* and f may manifest consequent to alterations in tissue microstructure induced by cellular necrosis and impairment of the tumor microvasculature. NAC can affect blood vessels supplying the tumor, thus reducing the blood flow. Lower values of D* and f may result from this decrease in blood flow due to decreased perfusion-related signals. Additionally, NAC frequently causes a decrease in tumor growth. D* and f values may change if smaller tumors exhibit different perfusion characteristics from larger ones. NAC-induced changes in the tumor microenvironment, such as changes in tissue architecture, blood vessel density, and tissue perfusion, can contribute to changes in IVIM parameters [25].

The study was limited by a small sample size, which may compromise the generalizability of the findings and increase the risk of bias. A larger, more diverse sample would provide more robust results and promote the reliability of the study. Conducting the study in a single medical center restricts the variability of patient characteristics and treatment protocols, potentially affecting the external validity of the findings. Multicenter studies involving different patient populations and treatment approaches would provide more comprehensive insights. Future research should focus on standardizing imaging protocols for IVIM and DCE perfusion MRI across institutions to ensure consistency in data acquisition and interpretation. This objective would facilitate comparison and validation of results across different studies and patient populations. Large-scale prospective studies are needed to validate the predictive value of DCE parameters, such as Ve, Kep, and Ktrans, in predicting response to Neo-CRT in CRC patients. Future studies should incorporate clinical and histopathological data to develop comprehensive predictive models for treatment response in CRC patients.

In conclusion, the findings of this study suggest that the quantitative factors, including those derived from IVIM and DCE, may enhance the diagnostic performance of conventional MRI and develop into hopeful markers of complete response in CRC. However, the findings have stayed erratic, and post-processing methods are comparatively difficult, laborious, and unreliable.

Author Contribution Statement

HJT designed the conception of the study; AA and MA conducted statical analysis; HJT and NA performed technical support and conceptual advice. All authors contributed to the drafted manuscript, revised it critically, and approved the final version.

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Ethical statement

This study was approved by the Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran (ethical code: IR.TUMS.SPH.REC.1398.228). All patients provided informed consent before participation in the study. The study was done according to the

References

1. Pak JN, Jung JH, Park JE, Hwang J, Lee HJ, Shim BS, et al. P53 dependent lgr5 inhibition and caspase 3 activation are critically involved in apoptotic effect of compound k and its combination therapy potential in hct116 cells. Phytother

Res. 2020;34(10):2745-55. https://doi.org/10.1002/ptr.6717.
2. MacLeod C, Wilson P, Watson AJM. Colon capsule endoscopy: An innovative method for detecting colorectal pathology during the covid-19 pandemic? Colorectal Dis. 2020;22(6):621-4. https://doi.org/10.1111/codi.15134.
3. Cecchin E, De Mattia E, Dreussi E, Montico M, Palazzari E, Navarria F, et al. Immunogenetic markers in il17f predict the risk of metastases spread and overall survival in rectal cancer patients treated with neoadjuvant chemoradiotherapy. Radiother Oncol. 2020;149:30-7. https://doi.org/10.1016/j.radonc.2020.04.055.
4. Hu H, Jiang H, Wang S, Jiang H, Zhao S, Pan W. 3.0 t mri ivim-dwi for predicting the efficacy of neoadjuvant chemoradiation for locally advanced rectal cancer. Abdom Radiol (NY). 2021;46(1):134-43. https://doi.org/10.1007/s00261-020-02594-4.
5. Liang HQ, Dong ZY, Liu ZJ, Luo J, Zeng Q, Liao PY, et al. Efficacy and safety of consolidation chemotherapy during the resting period in patients with local advanced rectal cancer. Oncol Lett. 2019;17(2):1655-63. https://doi.org/10.3892/ol.2018.9804.
6. Lin Z, Liu J, Peng L, Zhang D, Jin M, Wang J, et al. Complete pathological response following neoadjuvant folfox chemotherapy in brca2-mutant locally advanced rectal cancer: A case report. BMC Cancer. 2018;18(1):1253. https://doi.org/10.1186/s12885-018-5182-z.
7. Pham TT, Liney GP, Wong K, Barton MB. Functional mri for quantitative treatment response prediction in locally advanced rectal cancer. Br J Radiol. 2017;90(1072):20151078. https://doi.org/10.1259/bjr.20151078.
8. Kokaine L, Gardovskis A, Gardovskis J. Evaluation and predictive factors of complete response in rectal cancer after neoadjuvant chemoradiation therapy. Medicina (Kaunas). 2021;57(10):1044. https://doi.org/10.3390/medicina57101044.
9. Guimaraes MD, Schuch A, Hochhegger B, Gross JL, Chojniak R, Marchiori E. Functional magnetic resonance imaging in oncology: State of the art. Radiol Bras. 2014;47(2):101-11. https://doi.org/10.1590/S0100-39842014000200013.
10. Wang F, Cheng M, Du B, Li LM, Huang WP, Gao JB. Use of radiomics containing an effective peritumoral area to predict early recurrence of solitary hepatocellular carcinoma </=5 cm in diameter. Front Oncol. 2022;12:1032115. https://doi.org/10.3389/fonc.2022.1032115.
11. van der Paardt MP, Zagers MB, Beets-Tan RG, Stoker J, Bipat S. Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic mr imaging: A systematic review and meta-analysis. Radiology. 2013;269(1):101-12. https://doi.org/10.1148/radiol.13122833.
12. Kim Y, Kim SH, Lee HW, Song BJ, Kang BJ, Lee A, et al. Intravoxel incoherent motion diffusion-weighted mri for predicting response to neoadjuvant chemotherapy in breast cancer. Magn Reson Imaging. 2018;48:27-33. https://doi.org/10.1016/j.mri.2017.12.018.
13. Martens MH, Subhani S, Heijnen LA, Lambregts DM, Buijsen J, Maas M, et al. Can perfusion mri predict response to preoperative treatment in rectal cancer? Radiother Oncol. 2015;114(2):218-23. https://doi.org/10.1016/j.radonc.2014.11.044.
14. Fusco R, Sansone M, Granata V, Grimm R, Pace U, Delrio P, et al. Diffusion and perfusion mr parameters to assess preoperative short-course radiotherapy response in locally advanced rectal cancer: A comparative explorative study among standardized index of shape by dce-mri, intravoxel incoherent motion- and diffusion kurtosis imaging-derived parameters. Abdom Radiol (NY). 2019;44(11):3683-700. https://doi.org/10.1007/s00261-018-1801-z.
15. Gollub MJ, Tong T, Weiser M, Zheng J, Gonen M, Zakian KL. Limited accuracy of dce-mri in identification of pathological complete responders after chemoradiotherapy treatment for rectal cancer. Eur Radiol. 2017;27(4):1605-12. https://doi.org/10.1007/s00330-016-4493-1.
16. Khalifa F, Soliman A, El-Baz A, Abou El-Ghar M, El-Diasty T, Gimel'farb G, et al. Models and methods for analyzing dce-mri: A review. Med Phys. 2014;41(12):124301. https://doi.org/10.1118/1.4898202.
17. Hansen FY, Taub H. Decomposition of molecular motions into translational, rotational, and intramolecular parts by a projection operator technique. Commun Comput Phys. 2009;6(2):231.
18. Kim JH, Joo I, Kim TY, Han SW, Kim YJ, Lee JM, et al. Diffusion-related mri parameters for assessing early treatment response of liver metastases to cytotoxic therapy in colorectal cancer. AJR Am J Roentgenol. 2016;207(3):W26-32. https://doi.org/10.2214/AJR.15.15683.
19. Song T, Yao Q, Qu J, Zhang H, Zhao Y, Qin J, et al. The value of intravoxel incoherent motion diffusion-weighted imaging in predicting the pathologic response to neoadjuvant chemotherapy in locally advanced esophageal squamous cell carcinoma. Eur Radiol. 2021;31(3):1391-400. https://doi.org/10.1007/s00330-020-07248-z.
20. Amarnath J, Sangeeta T, Mehta SB. Role of quantitative pharmacokinetic parameter (transfer constant: K(trans)) in the characterization of breast lesions on mri. Indian J Radiol Imaging. 2013;23(1):19-25. https://doi.org/10.4103/0971-3026.113614.
21. Gollub MJ, Gultekin DH, Akin O, Do RK, Fuqua JL, 3rd, Gonen M, et al. Dynamic contrast enhanced-mri for the detection of pathological complete response to neoadjuvant chemotherapy for locally advanced rectal cancer. Eur Radiol. 2012;22(4):821-31. https://doi.org/10.1007/s00330-011-2321-1.
22. Molinari C, Matteucci F, Caroli P, Passardi A. Biomarkers and molecular imaging as predictors of response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. Clin colorectal cancer. 2015;14(4):227-38. https://doi.org/10.1016/j.clcc.2015.05.014.
23. Dijkhoff RAP, Beets-Tan RGH, Lambregts DMJ, Beets GL, Maas M. Value of dce-mri for staging and response evaluation in rectal cancer: A systematic review. Eur J Radiol. 2017;95:155-68. https://doi.org/10.1016/j.ejrad.2017.08.009.
24. Padhani AR, Hayes C, Assersohn L, Powles T, Makris A, Suckling J, et al. Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced mr imaging: Initial clinical results. Radiology. 2006;239(2):361-74. https://doi.org/10.1148/radiol.2392021099.
25. Zuo H. The Value of Intravoxel Incoherent Motion (IVIM) magnetic resonance imaging in the evaluation of the osteosarcoma response to preoperative neoadjuvant chemotherapy in teens. Concepts in Magnetic Resonance Part A, Bridging Education and Research. 2019;2019(5):1-8. https://doi.org/10.1155/2019/2918763.