

Dynamic contrast-enhanced MRI combined with intravoxel incoherent motion in quantitative evaluation for preoperative risk stratification of resectable rectal adenocarcinoma

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Abstract. Rectal adenocarcinoma is a common malignant tumor of the digestive tract. However, it is difficult to obtain tumor microstructural information using conventional magnetic resonance imaging (MRI). Dynamic contrast-enhanced (DCE)-MRI and intravoxel incoherent motion (IVIM) have been used in tumor research. The present study aimed to explore the application of DCE-MRI and IVIM in the risk stratification of resectable rectal adenocarcinoma. To achieve this, 75 patients with rectal adenocarcinoma confirmed via postoperative pathological examination who underwent high-resolution MRI, IVIM and DCE-diffusion-weighted imaging before surgery were retrospectively enrolled and divided into very low-risk (19 cases), low-risk (29 cases) and medium-risk (27 cases) groups. The quantitative parameters of DCE-MRI and IVIM were obtained using the GenIQ and Medical Imaging Interaction Toolkit software, respectively. One-way analysis of variance or the Kruskal-Wallis H test were used to analyze the differences in the measured parameters between the different risk groups. Receiver operating characteristic curves were used to analyze the diagnostic efficacy of each parameter. The differences in rate constant (K_{ep}), perfusion fraction (f) and false diffusion coefficient (D^*) between the different risk stratification groups were statistically significant ($P < 0.05$). When the very low- and low-risk groups were compared, $f + D^*$ had the highest diagnostic efficiency [area under the curve (AUC)=0.719], with a sensitivity and specificity of 100 and 51.70%, respectively. When the low- and medium-risk groups were compared, K_{ep} had the

highest diagnostic efficiency (AUC=0.602), with a sensitivity and specificity of 72.41 and 55.56%, respectively. When the very low-risk and medium-risk groups were compared, $K_{ep} + f + D^*$ had the highest diagnostic efficiency (AUC=0.887), with a sensitivity and specificity of 100 and 70.4%, respectively. Thus, DCE-MRI and IVIM can aid the prognostic risk stratification of resectable rectal adenocarcinoma, and K_{ep} , f and D^* are potential quantitative imaging parameters for the risk stratification of rectal adenocarcinoma.

Introduction

Colorectal cancer (CRC), including colon cancer and rectal cancer, is one of the major cancers that threaten the life and health of Chinese residents, causing a heavy social burden. According to the national cancer statistics released by China National Cancer Center in March 2024, from 2000 to 2018, the incidence rate of male CRC in China will increase by 2.7% annually, the incidence rate of female CRC will increase by 1.1% annually, the male mortality rate will increase by 1.2% annually, and the female mortality rate will be basically flat, indicating that the overall incidence rate and mortality rate of CRC in China will show a significant upward trend (1). According to the clinical practice guidelines of the European Society for Medical Oncology (ESMO) (2), rectal cancer can be classified into very low-, low-, medium-, high- and very high-risk groups according to the tumor-node (TN) stage, depth of submucosal invasion (SM), tumor location, mesenteric fascia (MRF) involvement, external vascular invasion (EMVI) and lymph node metastasis. Different treatment methods are used for the different risk groups. The very low-risk and low-risk groups are mainly treated with trans-anal endoscopic microsurgery and total mesorectal excision (TME), respectively. Direct TME surgery is the standard treatment for the medium-risk group, which may be followed by radiotherapy or chemotherapy based on the TME surgery quality and local recurrence rate. Patients with high-risk rectal cancer require short- or long-term radiation therapy or chemotherapy before undergoing surgery. Long-term neoadjuvant chemoradiotherapy is required before surgery in patients with very high-risk rectal cancer (2,3). Therefore, accurate risk

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stratification of rectal cancer before surgery is essential for selecting appropriate clinical treatment methods. At present, there have been some studies on preoperative evaluation of lymph node metastasis, tumor infiltration depth, and EMVI using magnetic resonance imaging (MRI), but the results vary and its benefit is controversial (4-6).

MRI is commonly used for the preoperative evaluation of rectal cancer and as an additional biomarker that reflects the tumor microstructure (5). Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient can be used to evaluate benign or malignant tumors, tumor composition and biological behavior (6). Intravoxel incoherent motion (IVIM) is a form of DWI that simultaneously quantifies both pure water molecular- and perfusion-related diffusion information with multiple b-values (the b-value is a factor that reflects the strength and timing of the gradients used to generate diffusion-weighted images) (7). Dynamic contrast-enhanced MRI (DCE-MRI) is a novel imaging technique used to assess tumor vascular status, provide data on tumor aggressiveness and the degree of angiogenesis, and aid the restaging of rectal cancer (8). DCE-MRI is used to assess the morphological and hemodynamic information of tumors and to indirectly reflect the formation of blood vessels in tumor cells (9). Functional MRI, including IVIM and DCE-MRI, are the focus of recent research, with a small number of studies on rectal cancer (10,11). The accuracy of high-resolution T2 weighted imaging (WI) combined with DCE-MRI in evaluating the mrT staging (magnetic resonance T staging) of rectal cancer after neoadjuvant therapy (80.60%) is higher than that of high-resolution T2 weighted imaging and high-resolution T2 weighted imaging combined with DWI, which is highly consistent with pathological T staging (12). A histogram of DCE-MRI parameters can facilitate the preoperative identification of EMVI in rectal cancer (13). IVIM and diffusion kurtosis imaging (DKI) can provide microstructural information of cancer, such as blood vessels and cells, and have the potential to accurately grade cancer (14). Furthermore, IVIM can be used to evaluate the efficacy of chemoradiotherapy in rectal cancer (15).

However, the use of IVIM and DCE-MRI for preoperative risk stratification of rectal adenocarcinoma has been limited to a small number of isolated studies (16,17), and a consistent conclusion has not been reached. Therefore, the present study aimed to combine the quantitative parameters of DCE-MRI and IVIM for preoperative risk stratification of rectal adenocarcinoma and to analyze the diagnostic potential of the parameters.

Materials and methods

Participants. A total of 120 patients with rectal adenocarcinoma who were admitted to Xinxiang Central Hospital (Xinxiang, China) between January 2021 and May 2023 were retrospectively enrolled in the present study. The inclusion criteria were as follows: i) Patients with rectal adenocarcinoma confirmed via operation and pathological examination; ii) patients who did not receive any radiotherapy, chemotherapy or surgical treatment before the examination; and iii) patients with complete clinical and imaging data, with complete pathological information. The exclusion criteria were as follows: i) Patients with lesions that were too small to be accurately measured using IVIM and DCE-MRI (n=5);

ii) patients who did not complete the whole process and those with an incomplete scan sequence (n=13); and iii) patients who underwent preoperative chemoradiotherapy (n=27). Finally, 75 patients were enrolled (Fig. 1). The present study was approved by the Xinxiang Central Hospital Ethics Committee (approval no. 2020-098; Xinxiang, China) and all patients provided written informed consent.

MRI technique and methods. The patients were provided with a liquid diet the day before the examination, and their intestines were cleared as required on the examination day. The patients were administered 20 mg of raceanisodamine hydrochloride (Suicheng Pharmaceutical Co., Ltd.) intramuscularly 5-10 min before the examination to suppress intestinal movement. The 3.0T MR scanner (SIGNA™ Pioneer; GE Healthcare) with a 16-channel phased coil was used. The patients were placed in a supine position with the head in front and the magnetic field center was at the superior margin of the pubis. The scanning sequences included periodically rotated overlapping parallel lines with enhanced reconstruction (propeller) T2WI, T1WI, DWI, IVIM and DCE-MRI. The oblique-axis scanning plane was perpendicular to the long axis of the bowel, where the tumor was located. For IVIM, 11 groups of b-values (0, 30, 50, 80, 100, 200, 400, 600, 800, 1,200 and 2,000 sec/mm²) were selected (18-20). The liver acceleration volume acquisition sequence was used for the DCE-MRI. First, the image was scanned as a mask, and in five phases, gadolinium diethylenetriamine pentaacetic acid was injected through the elbow vein at a flow rate of 3.5 ml/sec at a dose of 0.1 mmol/kg. Finally, 20 ml of normal saline was flushed into the tube. The detailed sequence parameters are listed in Table I.

Image analysis and index measurement. The original DCE-MRI images were transferred to a post-processing workstation (GenIQ, version AW 4.7; GE Healthcare) to obtain pseudocolor maps of the volume transfer constant (K^{trans}), rate constant (K_{ep}) and extravascular extracellular volume fraction (V_e). K^{trans} reflects the local microvascular blood flow state and its surface penetration area, K_{ep} reflects the rate constant between the plasma and extravascular extracellular space (EES) and V_e reflects the volume fraction of the EES contrast agent (21); thus, $K_{ep} = K^{trans}/V_e$.

After the original IVIM images were transferred to the Medical Imaging Interaction Toolkit software (version 2023.04; German Cancer Research Center), pseudocolor maps of the true diffusion coefficient (D), false diffusion coefficient (D^*) and perfusion fraction (f) were obtained. The linear fitting equation was as follows: $S_b/S_0 = (1-f) \exp^{(-b \times D)} + f \exp^{(-b \times D^*)}$, where S_b is the MRI signal intensity with the diffusion gradient, S_0 is the MRI signal intensity without a diffusion gradient and exp is the exponential function.

Measurements were taken in the largest plane of the tumor (22) by two double-blinded radiologists (YXC, 7 years of work experience; YCN, 18 years of work experience). In total, three different regions were selected to manually draw three regions of interest (ROI) with similar areas, avoiding the areas of liquefaction, bleeding and necrosis. The ROIs were drawn on the D and K^{trans} images and copied to the other two corresponding parameter graphs. Each group of data was measured three times and the mean value was obtained.

Table I. MRI acquisition parameters.

Parameters	Propeller T2WI	Propeller T1WI	DWI	IVIM	DCE-MRI
TR/TE, msec	4,729/92.1	4,709/91.0	4421/70	5,000/70	2.9/1.2
Field of view, mm ²	200x200	200x200	240x240	260x260	380x380
Slice thickness, mm	3.5	3.5	3.5	3.5	3.5
b-values, sec/mm ²	N/A	N/A	1,000	0, 30, 50, 80, 100, 200, 400, 600, 800, 1,200 and 2,000	N/A
Fat suppression	No	No	No	No	Yes

WI, weighted image; MRI, magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced MRI; IVIM, intravoxel incoherent motion; DWI, diffusion-weighted imaging; N/A, not applicable.

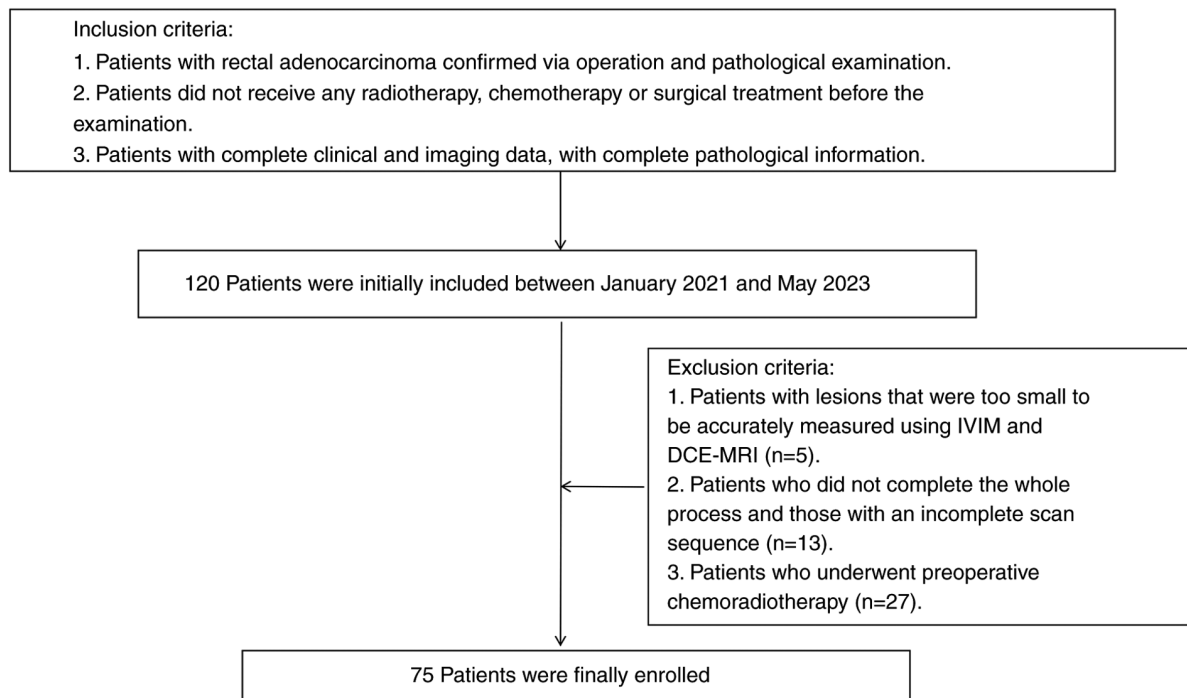


Figure 1. Flowchart of patient selection.

Pathological grouping. Detailed pathological reports were obtained for all surgical specimens according to protocols published by the College of American Pathologists (23), and all sections including the degree of differentiation, tumor location, MRF, EMVI, lymph node metastasis and subdivision of T1 cancer according to submucosal invasion depth (SM; SM1, upper 1/3; SM2, middle 1/3; SM3, lower 1/3) were reviewed by a gastrointestinal pathologist (XYS, 8 years of work experience; SL, 10 years of work experience), and in case of any dispute, assisted by a more experienced gastrointestinal pathologist (LY, 18 years of work experience). In accordance with the clinical practice guidelines of the ESMO (2), all included tissue specimens were divided into the following groups: Very low-risk (pathological T1 staging, SM1 and pathological N0 staging), low-risk [pathological T1-T2 staging, medium/high (distance between tumor and anal margin: <5 cm low, 5-10 cm medium, >10 cm high) T3a/b, pathological N0 staging or high pathological N1 staging, MRF- and EMVI-] and medium-risk

(low/medium/high pathological T3a/b staging, without involvement of the levator ani muscle, pathological N1-N2 staging, not extranodal, MRF- and EMVI-) groups. Due to the fact that patients in high- and very high-risk groups need to receive routine radiotherapy and chemotherapy before surgery, this study used it as an exclusion criterion and only included patients with rectal adenocarcinoma who can be directly resected.

Statistical analysis. SPSS (version 25.0; IBM Corp.) and MedCalc (version 15.2; MedCalc Software, Ltd.) statistical software were used for analysis. The interclass correlation coefficient was used to evaluate the consistency of measurement results of the two radiologists ($r \geq 0.75$, excellent; $0.60 \leq r < 0.75$, good; $0.40 \leq r < 0.60$, moderate; $r < 0.40$, poor). The measurement data consistent with a normal distribution and homogeneity of variance were expressed as the mean $\pm$ standard deviation, while data that were inconsistent were

Table II. Comparison of age and sex distribution differences among different risk stratification groups.

Groups	Age		Sex	
	Mean difference (I-J)	P	Mean difference (I-J)	P
Very low- vs. low-risk	3.412	0.355	0.098	0.494
Low- vs. medium-risk	-1.888	0.572	-0.117	0.366
Very low- vs. medium-risk	-1.524	0.683	-0.019	0.893
F	0.449		0.466	
P	0.640		0.629	

Mean difference (I-J), LSD test shows the difference in mean values between the two groups; F value, test result of the ANOVA.

expressed as the median (interquartile range). The differences in DCE-MRI and IVIM parameters between the different risk-stratification groups were analyzed using analysis of variance or the Kruskal-Wallis H-test, followed by multiple comparisons using the least-significant difference (LSD) or Bonferroni tests. Spearman's or Pearson's tests (Pearson's test was used for variables with a normal distribution and Spearman's test was used for variables without a normal distribution) were used to analyze the correlations between all parameters and rectal adenocarcinoma risk stratification groups. Receiver operating characteristic (ROC) curves were used to analyze diagnostic efficiency, and the Delong test was used to compare the difference in the area under the curve (AUC) between the different risk stratification groups.

Results

Patient clinical and pathological characteristics. The study included 19 cases (25.33%), 29 cases (38.67%) and 27 cases (36.00%) in the very low-risk, low-risk and medium-risk groups, respectively. There were 49 males and 26 females, aged 36-92 years, with a mean age of 66.03 ± 12.33 years. In the very low-risk group, 6 patients were female (31.57%) and 13 were male (68.42%), aged 48-91 years, with a mean age of 67.89 ± 10.91 years. In the low-risk group, 12 patients were female (41.38%) and 17 were male (58.62%), aged 36-92 years, with a mean age of 64.48 ± 14.19 years. In the medium-risk group, 8 patients were female (29.63%) and 19 were male (70.37%), aged 38-88 years, with a mean age of 66.37 ± 11.31 years. There was no significant difference in the distribution of age and sex (Table II). The clinical features, TN stages, EMVI, MRF, SM and distance are summarized in Table III. Typical cases from different risk groups are shown in Figs. 2-4. A 72 year-old-male patient with rectal adenocarcinoma, pT3aN1, medium-risk group, is presented in Fig. 2. A 72 year-old-male patient with rectal adenocarcinoma, pT2N0, low-risk group, is shown in Fig. 3. A 54-year-old male patient with rectal adenocarcinoma, pT1N0, very low-risk group, is presented in Fig. 4.

Intraclass correlation coefficient test results. The V_e , K_{ep} , K^{trans} , f , D and D^* -values measured by two radiologists showed excellent consistency, with values of 0.981, 0.968, 0.920, 0.917, 0.912, and 0.862, respectively (Table IV). The data obtained by senior physicians were used in the present study.

Table III. Clinical and pathologic characteristics of the study participants.

Characteristic	Value
Sex	
Male	49 (65.33)
Female	26 (34.67)
Age, years	
Mean $\pm$ standard deviation	66.03 ± 12.33
Range	36-92
Pathology	
Rectal adenocarcinoma	75 (100.00)
T stage	
T1	20 (26.67)
T2	28 (37.33)
T3a/b	27 (36.00)
N stage	
N0	41 (54.67)
N1	19 (25.33)
N2	15 (20.00)
EMVI-	75 (100.00)
MRF-	75 (100.00)
SM (T1)	
Upper 1/3	19 (95.00)
Middle 1/3	0 (0.00)
Lower 1/3	1 (5.00)
Distance	
Very low	13 (17.33)
Medium	46 (61.33)
High	16 (21.33)

Values are expressed as n (%) unless otherwise indicated. -, negative; T, tumor; N, node; SM, subdivision of T1 cancer according to submucosal invasion depth; EMVI, external vascular invasion; MRF, mesenteric fascia.

Comparison of DCE-MRI parameters among the risk stratification groups. The differences in K_{ep} -values among the

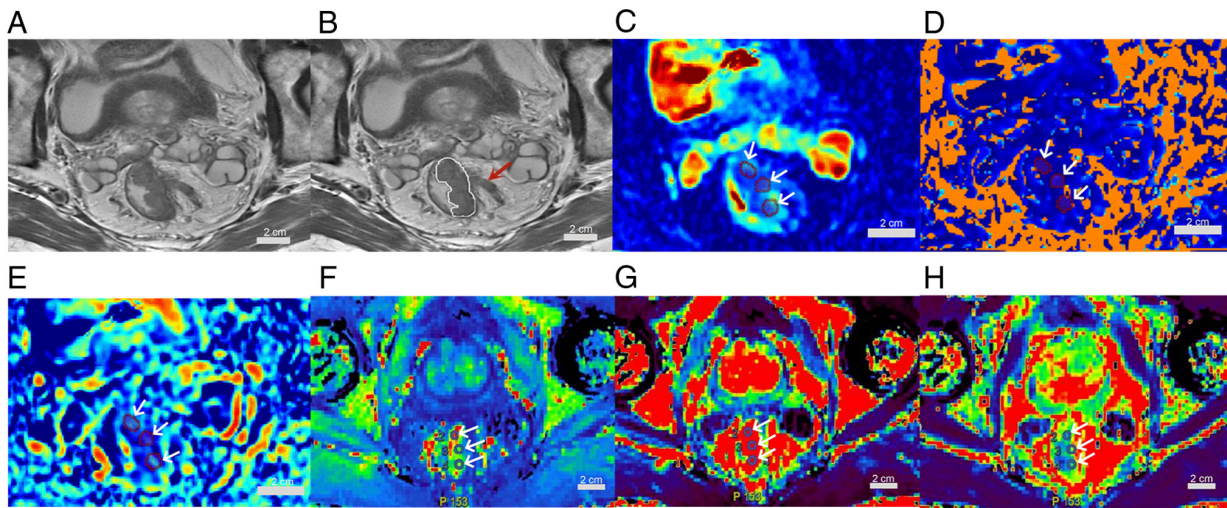


Figure 2. A 72-year-old male patient with rectal adenocarcinoma, pT3aN1, medium-risk group. (A) Oblique axial T2-weighted image shows a mass with slightly high intensity signal in the rectum. (B) The white line indicates the tumor area; the lesion breaks through the musculi propria and burrs into the surrounding adipose space (red arrow). (C) D, (D) D* and (E) f maps show the mass with mean values of $0.98 \times 10^{-3} \text{ mm}^2/\text{sec}$, $8.39 \times 10^{-3} \text{ mm}^2/\text{sec}$ and 0.23, respectively. (F) K_{ep} , (G) K^{trans} and (H) V_e maps show the mass with mean values of 1.73 1/min, 1.46 1/min and 0.98, respectively (scale bars, 2 cm; white arrows indicate regions of interest). K^{trans} , volume transfer constant; K_{ep} , rate constant; V_e , extravascular extracellular volume fraction; D, true diffusion coefficient; D*, false diffusion coefficient; f, perfusion fraction; EMVI, external vascular invasion; -, negative.

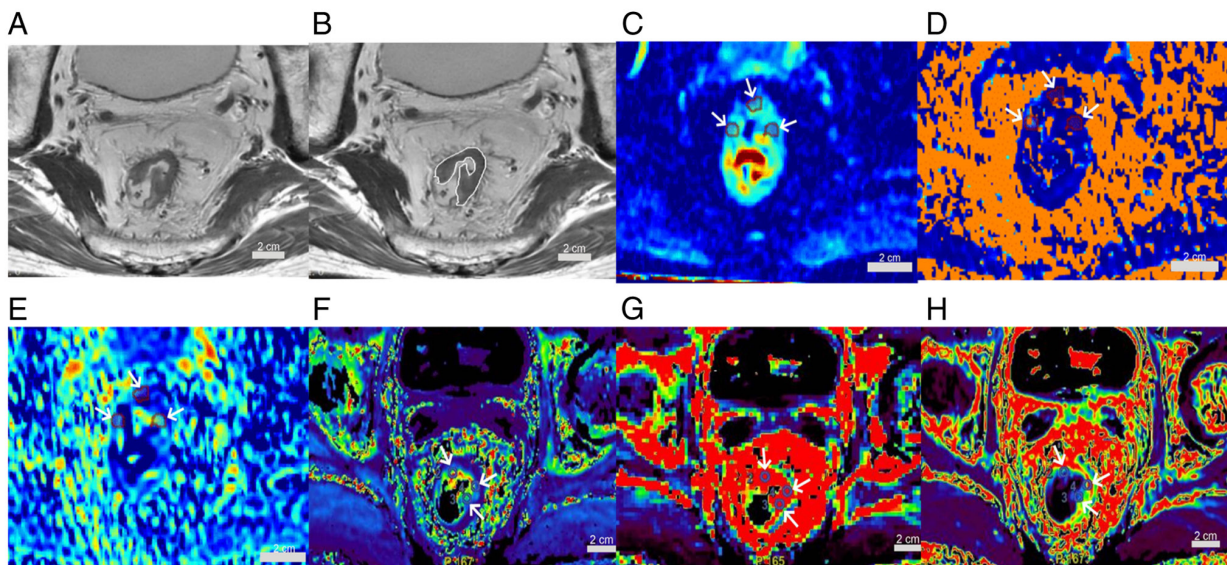


Figure 3. A 72-year-old male patient with rectal adenocarcinoma, pT2N0, low-risk group. (A) Oblique axial T2-weighted image shows a mass with slightly high intensity signal in the rectum. (B) The white line indicates the tumor area. (C) D, (D) D* and (E) f maps show the mass with mean values of $0.51 \times 10^{-3} \text{ mm}^2/\text{sec}$, $7.53 \times 10^{-3} \text{ mm}^2/\text{sec}$ and 0.11, respectively. (F) K_{ep} , (G) K^{trans} and (H) V_e maps show the mass with mean values of 1.41 1/min, 0.83 1/min and 0.37, respectively (scale bars, 2 cm; white arrows indicate regions of interest). K^{trans} , volume transfer constant; K_{ep} , rate constant; V_e , extravascular extracellular volume fraction; D, true diffusion coefficient; D*, false diffusion coefficient; f, perfusion fraction.

very low-risk, low-risk and medium-risk groups were statistically significant ($P=0.037$, $P<0.05$), whereas there were no significant differences in V_e and K^{trans} -values (Table V).

The K_{ep} -value differences between the very low- and medium-risk groups were statistically significant ($P=0.01$, $P<0.05$) according to an LSD pairwise comparison, whereas the differences between the other groups were not statistically significant.

Comparison of IVIM parameters among different risk stratification groups. The differences in D* and f-values among the

three groups were statistically significant ($P=0.014$, 0.042 , $P<0.05$, respectively), and the values increased with an increase in the risk grade. There were no statistically significant differences in D-values among the different risk groups ($P=0.929$, $P>0.05$) (Table VI).

The f-values between the very low- and medium-risk groups ($P=0.044$, $P<0.05$), the D* values between the very low- and low-risk groups ($P=0.0038$, $P<0.05$) and D*-values between the very low- and medium-risk groups ($P=0.004$, $P<0.05$) were significantly different according to Bonferroni's pairwise comparison. However, the

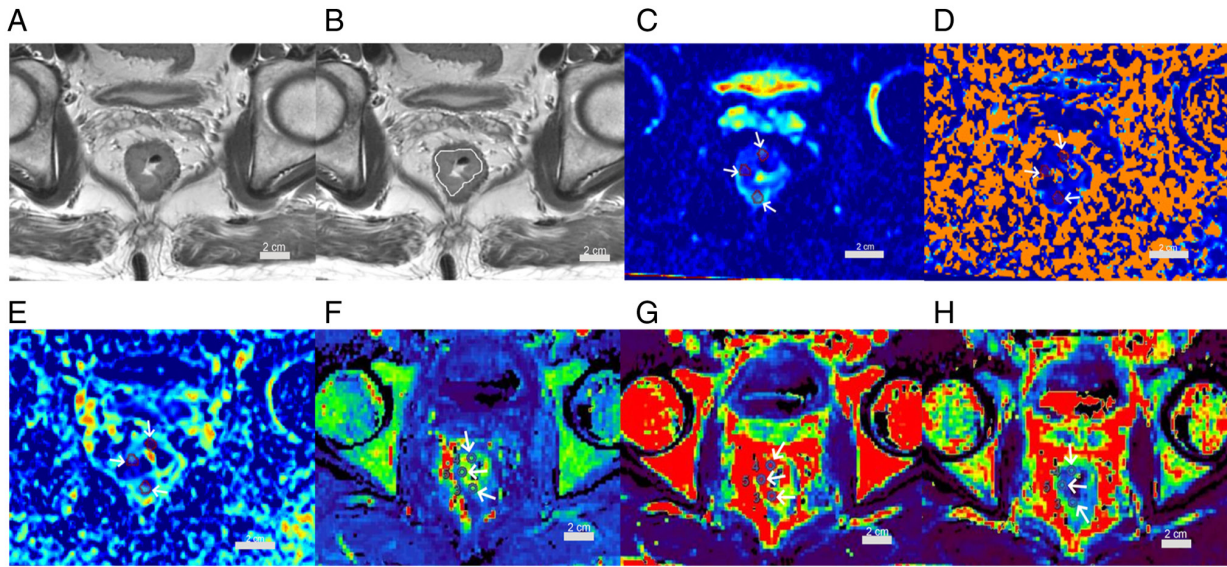


Figure 4. A 54-year-old male patient with rectal adenocarcinoma, pT1N0, very low-risk group. (A) Oblique axial T2-weighted image shows a mass with slightly high intensity signal in the rectum. (B) The white line indicates the tumor area. (C) D, (D) D^* and (E) f maps show the mass with mean values of $0.48 \times 10^{-3} \text{ mm}^2/\text{sec}$, $4.99 \times 10^{-3} \text{ mm}^2/\text{sec}$ and 0.09, respectively. (F) K_{ep} , (G) K^{trans} and (H) V_e maps show the mass with mean values of 0.77 1/min, 0.25 1/min and 0.33, respectively (scale bars, 2 cm; white arrows indicate regions of interest). K^{trans} , volume transfer constant; K_{ep} , rate constant; V_e , extravascular extracellular volume fraction; D, true diffusion coefficient; D^* , false diffusion coefficient; f , perfusion fraction.

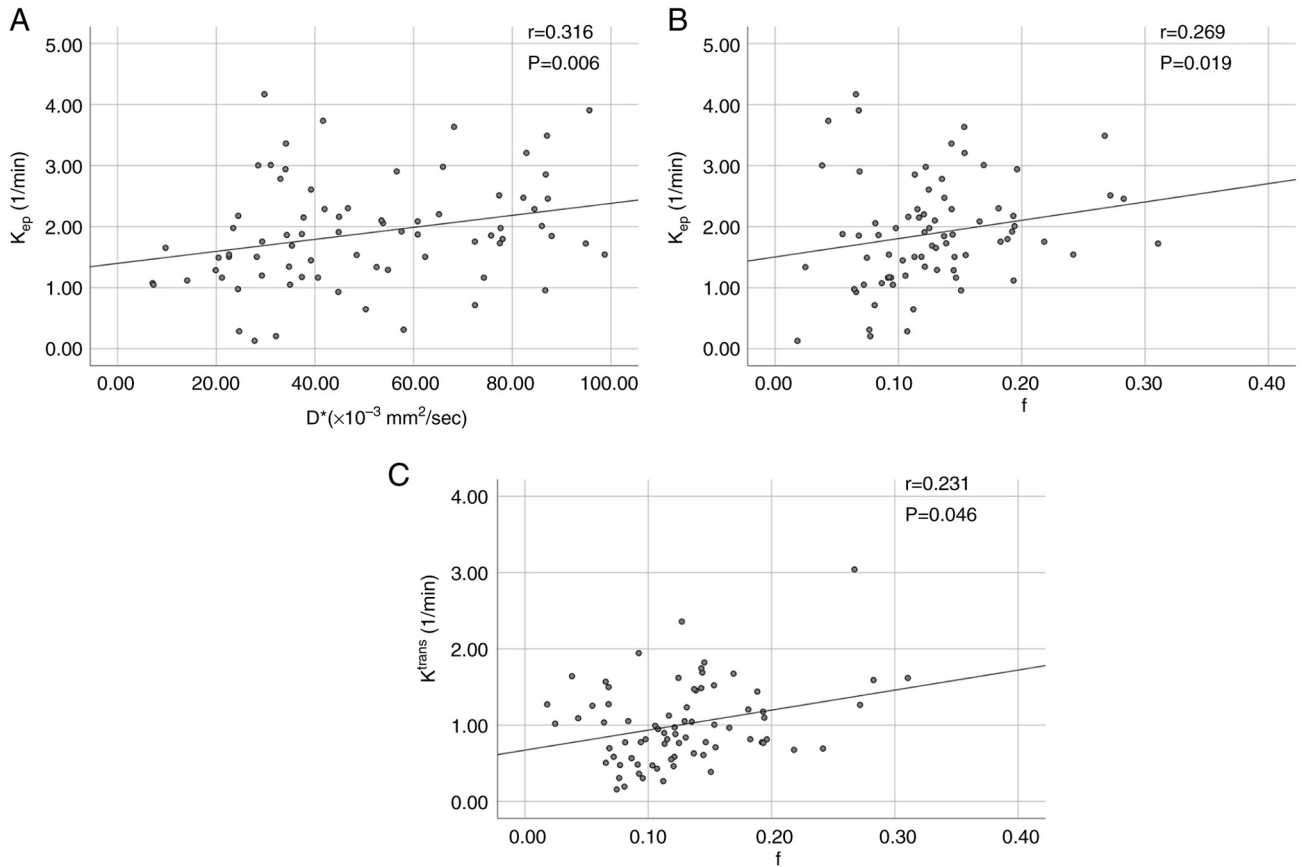


Figure 5. Pearson correlation analysis of dynamic contrast-enhanced MRI and intravoxel incoherent motion parameters. K_{ep} was positively correlated with the (A) D^* ($r=0.316$, $P<0.05$) and (B) f -values ($r=0.269$, $P<0.05$), respectively. (C) K^{trans} was positively correlated with the f -value ($r=0.231$, $P<0.05$). K^{trans} , volume transfer constant; K_{ep} , rate constant; D, true diffusion coefficient; D^* , false diffusion coefficient; f , perfusion fraction.

differences between the other groups were not statistically significant ($P>0.05$).

Correlation between DCE-MRI, IVIM parameters and risk stratification. The K_{ep} ($r=0.307$), f ($r=0.270$) and D^* ($r=0.323$)

Table IV. ICC test for measuring IVIM and DCE parameters by two radiologists.

Parameter	Intraclass correlation	95% Confidence Interval		P
		Lower	Upper	
V_e	0.981	0.971	0.988	<0.001
K_{ep}	0.968	0.950	0.980	<0.001
K^{trans}	0.920	0.877	0.949	<0.001
f	0.917	0.872	0.947	<0.001
D	0.912	0.875	0.948	<0.001
D^*	0.862	0.820	0.924	<0.001

K^{trans} , volume transfer constant; K_{ep} , rate constant; V_e , extravascular extracellular volume fraction; f, perfusion fraction; D, true diffusion coefficient; D^* , false diffusion coefficient; Intraclass Correlation, intraclass correlation coefficient; Lower, lower bound; Upper, upper bound; 95% Confidence Interval, there is a 95% probability that the true values of the overall parameters fall between the upper and lower bounds of the estimated values.

Table V. Comparison of DCE-MRI parameter values in different risk stratification groups.

Group	V_e	K_{ep} , 1/min	K^{trans} , 1/min
Very low-risk	0.59±0.23	1.51±0.89	0.92±0.44
Low-risk	0.59±0.23	1.88±0.87	0.93±0.44
Medium-risk	0.62±0.19	2.17±0.79	1.16±0.63
F	0.189	3.446	1.801
P-value	0.828	0.037	0.173

K^{trans} , volume transfer constant; K_{ep} , rate constant; V_e , extravascular extracellular volume fraction; F value, test result of the ANOVA.

values were all positively correlated with the risk stratification groups and the D^* -value had the highest correlation. No other significant correlation was found, as shown in Table VII. K_{ep} was positively correlated with D^* -value ($r=0.316$; $P=0.006$, <0.05), K_{ep} and f-values were also positively correlated ($r=0.269$; $P=0.019$, <0.05). K^{trans} was positively correlated with the f-value ($r=0.231$; $P=0.046$, <0.05 ; Fig. 5).

Diagnostic efficacy of K_{ep} , D^* and f-values for risk stratification. In the comparison of the very low-risk group with the low-risk group, there were statistically significant differences in the AUCs for D^* , f, $D^* + f$ and $K_{ep} + D^* + f$ -values ($Z=2.042$, 2.100, 2.955 and 2.919; $P<0.05$). $D^* + f$ had the highest diagnostic efficacy (AUC=0.719), with significant discriminatory ability, sensitivity of 100% and specificity of 51.70%. In the comparison of the low-risk group with the medium-risk group, there was a significant statistical difference in the AUC of K_{ep} ($Z=1.340$; $P<0.05$), indicating a significant discriminatory ability (AUC=0.602) with a sensitivity of 72.41% and specificity of 55.56%. In the comparison of the very low-risk

group with the medium-risk groups, there were statistically significant differences in the AUC for K_{ep} , D^* , f, $D^* + f$ and $K_{ep} + D^* + f$ -values ($Z=2.910$, 3.832, 2.733, 5.131 and 7.936; $P<0.05$) and $K_{ep} + D^* + f$ has the highest discriminative ability (AUC=0.887), with a sensitivity of 100% and a specificity of 70.40% (Table VIII; Fig. 6).

Discussion

DCE-MRI is a combination of morphological and hemodynamic imaging technology that reflects tissue perfusion information by analyzing the flow of contrast agents in and out of cells and blood vessels (24). Horvat *et al* (25) showed that DCE-MRI can be used to assess the proliferation and invasion of malignant rectal tumors. DCE-MRI sequences can be used to quantify the microscopic structure of blood vessels and display perfusion and metabolic information of tumor lesions, such as K^{trans} , V_e and K_{ep} , among which K^{trans} and K_{ep} mainly reflect the permeability and blood volume of the blood vessels. V_e refers to the volume fraction of contrast agents within the EES, which is associated with tumor cell proliferation (26).

Based on the pathological results, patients were divided into very low-, low- and medium-risk groups according to the clinical guidelines of the ESMO (2). The difference in K_{ep} -values among the different risk stratification groups was statistically significant, whereas the differences in K^{trans} and V_e -values among the groups were not statistically significant. An increase in tumor malignancy is often accompanied by an increase in the secretion of microvascular endothelial factors, which accelerates the loss of function of intercellular adhesion molecules, resulting in increased vascular permeability and consequent hyperperfusion (27). K_{ep} is an indicator of tissue microvascular density and permeability, and thus increases. A higher K_{ep} -value is associated with a longer time for the blood to return to the vasculature. K_{ep} is only affected by the contrast agent concentration and fractional volume in the extracellular space outside the tumor's blood vessels, and may therefore more accurately reflect the status of tumor capillaries (28). T, N, MRF, EMVI, CRM and metastasis are all indicators of tumor malignancy, which reflect the depth of tumor invasion and malignant state, and are important factors in tumor risk stratification (22). Wang *et al* (29) reported that K^{trans} and K_{ep} could predict risk stratification for early endometrial cancer, which differs from the results of the present study. Sun *et al* (30) demonstrated that the K^{trans} -value does not correlate with the pathological stage of rectal cancer, which is consistent with the results of the present study. The authors considered that K^{trans} refers to the passage rate of the contrast agent from the EES into the blood vessel, which mainly reflects vascular permeability. However, this permeability is affected by the patient's blood pressure, cardiac output, contrast agent injection speed and other factors, resulting in a difference in the value of this parameter. The present study showed no significant differences in the V_e -values between the different risk stratification groups. Ao *et al* (31) showed no statistically significant difference in the V_e -value between the EMVI+ and EMVI- groups of rectal cancer, which was similar to the results of the present study. This may be related to the poor stability of V_e and its susceptibility to pathological edema, microcystic degeneration, complex microenvironment and tumor heterogeneity (32).

Table VI. Comparison of IVIM parameter values of different risk stratification groups.

Group	f (range)	D, $\times 10^{-3}$ mm ² /sec (range)	D*, $\times 10^{-3}$ mm ² /sec (range)
Very low-risk	0.094 (0.07-0.12)	0.73 (0.53-1.55)	34.75 (27.77-41.64)
Low-risk	0.125 (0.09-0.15)	0.83 (0.59-1.14)	53.81 (24.52-77.57)
Medium-risk	0.131 (0.11-0.17)	0.82 (0.67-1.04)	56.59 (34.95-78.05)
H-value	6.344	0.147	8.501
P-value	0.042	0.929	0.014

D, true diffusion coefficient; D*, false diffusion coefficient; f, perfusion fraction; H-value, test result of the Kruskal-Wallis test.

Table VII. Correlation between parameters and risk stratification groups.

Parameter	r value	P-value
K _{ep}	0.307	0.007
K _{trans}	0.130	0.268
V _e	0.057	0.629
f	0.270	0.019
D	0.037	0.753
D*	0.323	0.005

K_{trans}, volume transfer constant; K_{ep}, rate constant; V_e, extravascular extracellular volume fraction; D, true diffusion coefficient; D*, false diffusion coefficient; f, perfusion fraction.

In the past 20 years, MRI has served an increasingly important role in the evaluation of rectal cancer, including TNM staging, EMVI and treatment efficacy (4,33-35). Functional MRI techniques, such as DWI, IVIM and DKI, have served important roles (36). As a form of DWI, IVIM can be used to quantify complex signals, such as cell structure, vascular structure and microenvironment, where the D-value is the true diffusion state of water molecules related to the cell structure. The value of D* is perfusion-related diffusion and f is the perfusion fraction, both of which are related to vascular distribution, length and structure (7). IVIM reflects more of the behavioral characteristics of tumors by analyzing the tumor perfusion and diffusion information (37). IVIM can improve the diagnostic performance of nodal staging of rectal cancer (38). Early changes in the D* and D-values could be used to predict the efficacy of chemoradiotherapy for rectal cancer (39). The D-value of IVIM-DWI is also the most sensitive parameter for the histological classification of rectal cancer (14).

In the present study, the differences in D* and f-values among the different risk-stratification groups of rectal adenocarcinomas were statistically significant and increased with an increase in the risk grade. Both the D* and f-values were correlated with tumor blood vessels, which indicated that the higher the risk stratification, the more abundant the blood perfusion. A previous study has shown that D-values can provide valuable information regarding whether rectal cancer cells have EMVI, whereas f and D*-values do not correlate with EMVI (40), which differs from the results of the present

study. Potentially, the different selection of b-values, the absence of patients with EMVI+ in the present study and the disorder, imperfect function and abnormal leakage of blood vessels in tumor cells complicate tumor tissue perfusion. It has been reported that D* can improve the performance of prostate cancer risk prediction (41). High-risk lesions tend to have a high blood supply, high cell density, longer capillary segment length, faster average blood drug velocity and, therefore, higher D*-values (11). The perfusion fraction f is another parameter that can convey perfusion information, reflecting the density of the blood vessels in tumor cells (42). A higher degree of malignancy of the lesion is associated with a higher f-value. Meng *et al* (43) showed that the f-value in the low-risk group of endometrial cancer was lower compared with that in the non-low-risk group, which is consistent with the results of the present study. Previous studies have shown that IVIM helps evaluate the tumor grade for intracranial and liver tumors and that D-values are negatively correlated with the tumor grade (44,45). In patients with locally advanced cervical cancer, the D-value was significantly higher in those who responded well to neoadjuvant chemotherapy (46). A decrease in the degree of tumor differentiation and increase in malignancy and aggressiveness lead to the active proliferation of cancer cells, an increase in the proportion of the nucleus and plasma and restriction of water molecule movement, ultimately leading to a decrease in the D-value (46). In the present study, there was no correlation between the D-value and rectal adenocarcinoma risk stratification. It may be considered that the density of cells may differ between study participants; therefore, the trend of the D-value may be different. Additionally, malignant tumors are often accompanied by liquefaction necrosis. While cell proliferation restricts the movement of water molecules, liquefaction necrosis relieves the restriction of water molecule movement and the two can interact, leading to instability of the D-value (8,11).

In the present study, the K_{ep}, f and D*-values were positively correlated with the risk stratification of rectal adenocarcinoma. In addition, K_{ep} was positively correlated with the f and D*-values, and K_{trans} was positively correlated with the f-value, indicating that the two methods have a certain correlation in the evaluation of rectal cancer perfusion. A study have shown a significant correlation between the f-value and DCE-MRI parameters in patients with prostate cancer in the transition zone (47). After the Delong test, the differences in the AUC of the D*, f, D* + f and K_{ep} + D* + f were statistically significant when the very low-risk and low-risk groups were compared,

Table VIII. Performance comparison of parameters among different risk stratification groups.

A, Very low- vs. low-risk group

Parameters	Cut-off value	AUC	Sensitivity, %	Specificity, %	Z	P-value
K_{ep} , mm^{-1}	0.272	0.639	78.95	48.28	1.663	0.094
D^* , $\times 10^{-3} \text{ mm}^2/\text{sec}$	0.465	0.662	94.74	51.72	2.042	0.041
f	0.307	0.668	78.95	51.72	2.100	0.036
$D^* + f$	0.517	0.719	100.00	51.70	2.955	0.003
$K_{ep} + D^* + f$	0.517	0.717	100.00	51.72	2.919	0.004

B, Low- vs. medium-risk group

Parameters	Cut-off value	AUC	Sensitivity, %	Specificity, %	Z	P-value
K_{ep} , $1/\text{mm}$	0.279	0.602	72.41	55.56	1.34	0.018
D^* , $\times 10^{-3} \text{ mm}^2/\text{sec}$	0.241	0.563	67.50	87.20	0.831	0.413
f	0.191	0.547	44.38	77.78	0.598	0.550
$D^* + f$	0.556	0.202	27.60	92.60	0.706	0.480
$K_{ep} + D^* + f$	0.327	0.616	58.62	74.07	1.497	0.134

C, Very low- vs. medium-risk group

Parameters	Cut-off value	AUC	Sensitivity, %	Specificity, %	Z	P-value
K_{ep} , $1/\text{mm}$	0.409	0.727	63.16	77.78	2.910	0.003
D^* , $\times 10^{-3} \text{ mm}^2/\text{sec}$	0.540	0.766	94.74	59.26	3.832	0.001
f	0.382	0.712	78.95	59.26	2.733	0.006
$D^* + f$	0.604	0.823	78.90	81.50	5.131	<0.001
$K_{ep} + D^* + f$	0.704	0.887	100.00	70.40	7.936	<0.001

K_{ep} , rate constant; D, true diffusion coefficient; D^* , false diffusion coefficient; f, perfusion fraction; AUC, area under the curve.

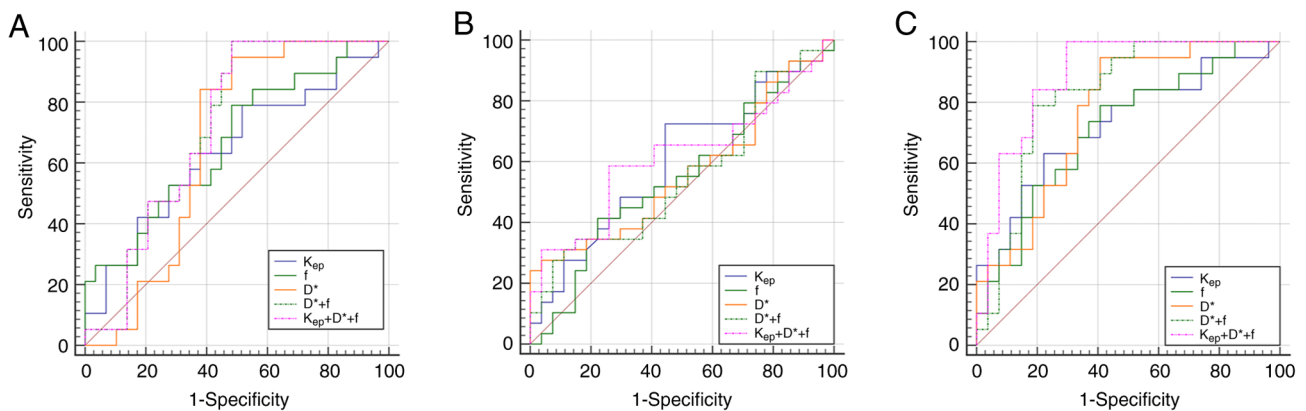


Figure 6. (A) ROC curves for the K_{ep} , D^* , f, $D^* + f$ and $K_{ep} + f + D^*$ values for discrimination between very low- and low-risk groups. (B) ROC curves for K_{ep} , D^* , f, $D^* + f$ and $K_{ep} + f + D^*$ values for discrimination between low- and medium-risk groups. (C) ROC curves for K_{ep} , D^* , f, $D^* + f$ and $K_{ep} + f + D^*$ values for the discrimination between very low- and medium-risk groups. K_{ep} , rate constant; D, true diffusion coefficient; D^* , false diffusion coefficient; f, perfusion fraction; ROC, receiver operating characteristic.

confirming that the AUC of the $f + D^*$ -value was the highest and had the highest discriminatory ability; this indicates that IVIM can be used to distinguish between very low- and low-risk groups of rectal adenocarcinoma, and its diagnostic efficacy

was higher compared with that of DCE-MRI, IVIM combined with DCE-MRI. When the low-risk group was compared with the medium-risk group, a statistically significant difference in the AUC values of the K_{ep} -value was observed, confirming that

K_{ep} has the ability to distinguish between low- and medium-risk groups of rectal adenocarcinoma, with a diagnostic sensitivity of 72.41% and specificity of 55.56%. IVIM had a limited value in distinguishing these two risk groups. The differences in the AUC of K_{ep} , f , D^* , $D^* + f$ and $K_{ep} + D^* + f$ in the very low-risk group compared with the medium-risk group were statistically significant, indicating that the $K_{ep} + D^* + f$ -value has the highest discriminatory ability, further demonstrating that DCE-MRI with IVIM could significantly improve the diagnostic efficiency. The K^{trans} , V_e and f -values were independent predictors of early endometrial cancer in the low- and medium-high-risk groups (29). This is inconsistent with the results of the present study, which may be due to differences in the participants of the present study. In addition, invasive tumors grow rapidly and have insufficient new blood vessels, leading to tissue hypoxia and necrosis, formation of a low-perfusion area and eventual variability in overall tumor perfusion (48). Arian *et al* (20) showed that IVIM with DCE had the highest accuracy in the diagnosis of benign and malignant types of breast cancer. Zhao *et al* (17) showed that risk assessment based on MRI staging is essential for the clinical treatment of advanced rectal cancer. Radiomics features based on IVIM and DCE-MRI can improve the predictive efficiency of high aquaporin-1 expression levels in rectal cancer (49). In the present study, IVIM and DCE-MRI were effective in assessing risk stratification for resectable rectal adenocarcinoma and K_{ep} , f and D^* were potential imaging indicators for the risk stratification of resectable rectal adenocarcinoma.

The number of cases included in the present study was small and the results may be biased, thus requiring further research for verification. In the post-processing of the present study, only the ROI of the largest tumor level was selected, which is highly operable; however, the results may not represent the overall state of the tumor. The present study was conducted by taking multiple measurements of different parts of the maximum cross-sectional area and averaging them to minimize errors. IVIM was based on plane-echo imaging; therefore, the selection of the b-value is important, but currently, it has not been recommended by any guidelines. In the present study, the selection of the b-value was based on several authoritative studies (18-20). The present study lacks follow-up data on the long-term prognosis of patients, and therefore, future work includes the exploration and investigation of the long-term predictive value of DCE-MRI and IVIM parameters for rectal cancer on patient prognosis and survival analysis.

In conclusion, DCE-MRI and IVIM were found to be useful in the non-invasive assessment for risk stratification of resectable rectal adenocarcinoma. K_{ep} , f and D^* -values may be used as imaging indicators for risk stratification of resectable rectal adenocarcinoma, which could potentially improve the diagnostic efficiency when combined.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YXC and JBG designed the study. YXC drafted the manuscript. YXC and YCN performed experiments and analyzed data. RXC performed experiments.. YXC and JBG interpreted the data and edited the manuscript. JBG critically reviewed the manuscript and revised it. YXC and JBG checked and confirmed the authenticity of all the raw data. All authors made a substantial contribution to researching data, discussion of content, and reviewing and editing the manuscript before submission. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Xinxiang Central Hospital Ethics Committee (approval no. 2020-098; Xinxiang, China), with all patients providing written informed consent.

Patient consent for publication

Consent for publication was obtained from patients whose images were contained in the present study.

Competing interests

The authors declare that they have no competing interests.

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