



Intravoxel incoherent motion diffusion-weighted imaging and dynamic contrast-enhanced MRI for predicting parametrial invasion in cervical cancer

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Abstract

Purpose This study aimed to assess the predictive efficacy of intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in parametrial invasion (PMI) in cervical cancer patients.

Methods A total of 83 cervical cancer patients (32 PMI-positive and 51 PMI-negative) retrospectively underwent pre-treatment IVIM-DWI and DCE-MRI scans. IVIM-DWI parameters included apparent diffusion coefficient (ADC), slow apparent diffusion coefficient (D), fast apparent diffusion coefficient (D*), and perfusion fraction (f). DCE-MRI parameters included volume transfer constant (K^{trans}), flux rate constant (K_{ep}), and fractional extravascular extracellular space volume (V_e). Logistic regression analyses were conducted to identify independent variables associated with PMI. Receiver operating characteristic curves were generated to assess the predictive performance of significant parameters.

Results Multivariable analysis revealed that the MRI parameters D (odds ratio [OR]: 7.05; 95% CI 1.78–27.88; $P=0.005$), D* (OR 6.58; 95% CI 1.49–29.10; $P=0.01$), f (OR 5.12; 95% CI 1.23–21.37; $P=0.03$), K^{trans} (OR 4.60; 95% CI 1.19–17.81; $P=0.03$), and K_{ep} (OR 4.90; 95% CI 1.25–19.18; $P=0.02$) were independent predictors of PMI in cervical cancer patients. The combined parameter incorporating these parameters demonstrated the highest performance in predicting PMI, yielding an area under the curve of 0.906, sensitivity of 84.4%, and specificity of 86.3%.

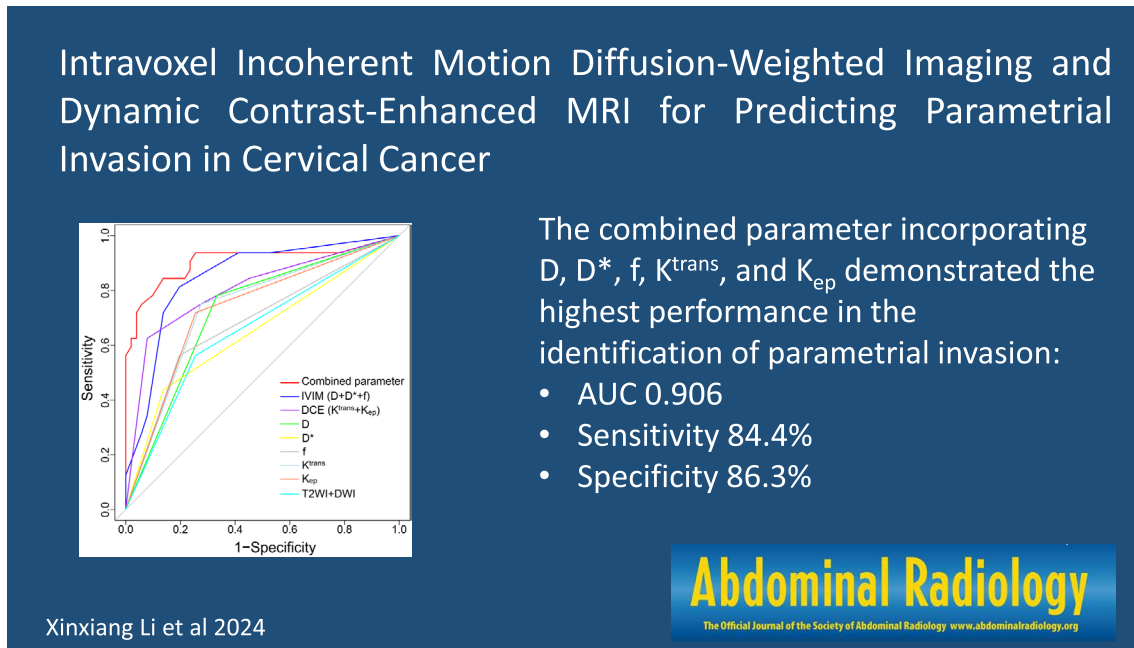
Conclusion The proposed combined parameter exhibited favorable performance in identifying PMI in cervical cancer patients.

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Graphical abstract



Keywords Cervical cancer · Parametrial invasion · Intravoxel incoherent motion · Diffusion weighted imaging · Dynamic contrast-enhanced

Abbreviations

AUC	Area under the curve
DCE	Dynamic contrast-enhanced
DWI	Diffusion-weighted imaging
ICC	Intraclass correlation coefficient
IVIM	Intravoxel incoherent motion
MRI	Magnetic resonance imaging
PMI	Parametrial invasion
OR	Odds ratio
ROC	Receiver operating characteristic
ROI	Region of interest

Introduction

Cervical cancer is a common malignant tumor in the female reproductive system, posing a serious threat to women's health and lives [1]. The treatment of cervical cancer is closely related to its staging, and the chosen treatment modalities vary in clinical practice [2]. Patients without parametrial invasion (PMI) are generally treated with surgery, while those with PMI undergo concurrent chemoradiotherapy [3]. Additionally, PMI in cervical cancer is closely associated with postoperative recurrence, tumor metastasis, and overall survival [4, 5]. Therefore, the accurate

pretreatment assessment of PMI in cervical cancer holds significant importance in clinical practice.

The quantitative imaging techniques of intravoxel incoherent motion diffusion weighted imaging (IVIM-DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can reveal the internal characteristics of tumors at the molecular level [6, 7]. IVIM-DWI can provide the information regarding histological perfusion and tumor angiogenesis on microcirculation without the use of contrast agents [8]. A previous study indicated that the pretreatment f value of IVIM-DWI was associated with treatment response in cervical cancer [9]. Furthermore, our previous study demonstrated that IVIM-DWI combined diffusion tensor imaging can predict the PMI in cervical cancer [10]. Additionally, DCE-MRI allows for the evaluation of vascular permeability, blood flow, and microcirculation within the tumor tissue [11–13]. DCE-MRI could predict the response of concurrent chemoradiotherapy in patients with locally advanced cervical cancer [14]. Similarly, our previous study demonstrated that DCE-MRI combined texture analysis can predict the PMI in cervical cancer [15].

Therefore, the objective of our current study was to assess the predictive value of IVIM-DWI and DCE-MRI for PMI in cervical cancer patients. The quantitative data obtained from the two technologies may increase the preoperative diagnostic accuracy of PMI in cervical cancer patients.

Materials and methods

Patients

Our institutional review board approved this study, and each patient signed an informed consent form (2021-RE-091). Ninety-six patients performed with radical hysterectomy, conforming cervical cancer with parametrial invasion, were admitted to our hospital between October 2017 and October 2019. IVIM-DWI and DCE-MRI examinations were conducted preoperatively for these patients. Exclusion criteria included: (a) patients with a history of treatment for cervical cancer before MRI ($n=5$); (b) insufficient image quality for further analysis ($n=5$); (c) more than two weeks between MRI and surgery ($n=3$). Finally, 83 patients were eligible for our study. The workflow of the patient selection was depicted in Fig. 1.

Imaging acquisition

MRI data were obtained using a 3.0 T Signa HDxT scanner (GE Healthcare, USA). The scanning protocol contained T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, IVIM-DWI, and DCE-MRI, which were performed with an 8-channel phased array body coil. IVIM was acquired using single-shot spin-echo echo planar imaging with 10 b values (0, 10, 20, 50, 100, 200, 400, 800, 1000, and 1200 s/mm²). The scanning parameters of IVIM were as follows: repetition time, 4000 ms; echo time, 85 ms; slice thickness, 4 mm; field of view, 40×22 cm; matrix size, 130×128; and acquisition time, 5 min and 44 s.

DCE-MRI was conducted using a three-dimensional liver acceleration volume acquisition sequence. Before the injection of the contrast medium, three flip angles (5°, 10°, and 15°) were acquired. Patients received gadodiamide (Omniscan, GE Healthcare, USA) at a dosage of 0.1 mmol/kg,

followed by a 20-mL saline flush. The protocol included the following parameters: repetition time of 4.2 ms, echo time of 2.2 ms, flip angle of 15°, slice thickness of 4 mm, field of view measuring 380×340 mm, matrix size of 320×224, time resolution of 7.0 s, a total of 43 phases, and a sampling time of 4 min and 40 s.

Imaging analysis

The IVIM-DWI data were post-processed using the functionality tools of GE Advantage Windows 4.5. The processing of the IVIM-DWI involved applying the bi-exponential model fitting formula, which is expressed as follows [16]: $S_b/S_0 = (1-f) \exp(-b \times D) + f \exp(-b \times D^*)$, where S_b denotes the mean signal intensity with the diffusion gradient b , and S_0 denotes the signal intensity at a b value of 0. Referring to the T2-weighted imaging, the maximum tumor area of IVIM images, demonstrating the most restricted diffusion, was delineated as the region of interest (ROI). ROIs were manually delineated, with the exclusion of necrosis, hemorrhage, cystic degeneration, and artifacts. Subsequently, the IVIM parameters (standard apparent diffusion coefficient [ADC], slow apparent diffusion coefficient [D], fast apparent diffusion coefficient [D*], and perfusion fraction [f]) were automatically generated. to cover as much of the tumor margin as possible.

Omni-Kinetics (O.K.; GE Healthcare, China) software was utilized to process the DCE-MRI data. The process of converting signal intensity into contrast agent concentration involved the use of multi-flip angle T1 mapping. A ROI was manually placed in the iliac artery to assess the arterial input function. The outlined tumor ROI slice was the same as IVIM. A modified Tofts model was used to generate the DCE-MRI parameters (volume transfer constant [K^{trans}], flux rate constant [K_{ep}], and fractional extravascular extracellular space volume [V_e]).

The diagnostic criteria for PMI on T2-weighted imaging were a disrupted cervical stromal ring with tiny nodular or irregular hyperintense signals extending to the parametrium. When using combined T2-weighted imaging and DWI (T2WI+DWI), the criteria were a hyperintense pattern on T2-weighted imaging, low signal intensity on an ADC map, and hyperintensity on DWI. A 5-point grading scale was employed to assess PMI presence: (1) definitely absent; (2) probably absent; (3) indeterminate; (4) probably present; and (5) definitely present. Grades 4 and 5 were considered positive for PMI on MRI, while grades 1 and 2 were deemed negative. Grade 3, indicating inconclusive results, was classified as negative.

IVIM-DWI and DCE-MRI were independently measured by two radiologists (Xinxiang Li, radiologist 1, and Xingui Peng, radiologist 2), with 12 and 20 years of experience in the gynecological system, respectively. IVIM-DWI

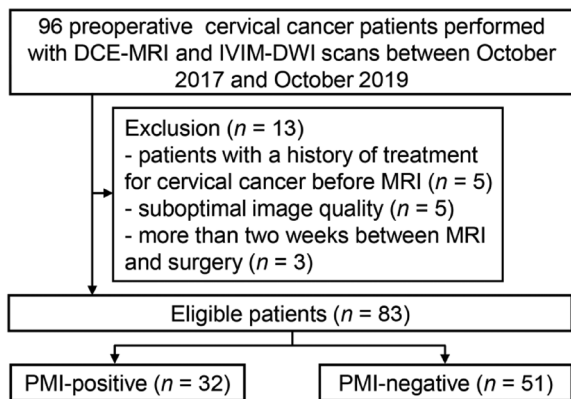


Fig. 1 The flowchart used in selection of the patients

and DCE-MRI measurements were conducted twice within a week by radiologist 1 to determine intraobserver agreement. In order to evaluate interobserver agreement, the first measurement by radiologist 1 was compared with that obtained by radiologist 2. The value of the intraclass correlation coefficient (ICC) is greater than 0.75, indicating good agreement. Moreover, the DCE-MRI maps were integrated with the contrast-enhanced T1-weighted imaging images. The PMI from T2WI and T2WI+DWI were assessed by the same two radiologists. In instances of disagreement between the two radiologists, a collaborative review was conducted to reach a consensus for the final report.

Statistical analysis

Continuous data were presented as median \pm interquartile range. Univariable and multivariable logistic regression analyses were conducted to identify the MRI parameters significantly associated with PMI. Variables with a *P* value of less than 0.05 in the univariable analysis were included in the multivariable analysis, which identified the final variables through a stepwise backward process. Receiver operating characteristic curve analysis was employed to evaluate the predictive ability of IVIM-DWI and DCE-MRI variables in diagnosing PMI. The comparison of the area under the curve (AUC) was conducted using the DeLong test. The determination of cut-off values involved maximizing the Youden's index. In the assessment of data consistency, continuous variables were evaluated using the intraclass correlation coefficient, while categorical variables were assessed

using κ statistics. A *P* value < 0.05 was regarded as statistically significant. Statistical analyses were conducted using SPSS software (version 26.0) and R software (version 4.2.2, <http://www.r-project.org>).

Results

Patient characteristic

The median age of the eligible patients was 50.0 (range: 44.8–58.5) years in the PMI-positive group and 50.0 (range: 46.0–55.0) years in the PMI-negative group. The final diagnosis revealed that 32 out of 83 (38.6%) cervical cancer patients were PMI-positive, while 51 out of 83 (61.4%) were PMI-negative. The clinical 2018 FIGO stage distribution was as follows: IB (*n* = 33), IIA (*n* = 18), IIB (*n* = 17), IIIA (*n* = 8), IIIB (*n* = 5), and IIIC (*n* = 2). The preoperative MRI parameters are listed in Table 1 and Fig. 2.

Interobserver agreement

The intraobserver ICCs for ADC, *D*, *D*^{*}, *f*, *K*^{trans}, *K*_{ep}, and *V*_e measured by radiologist 1 ranged from 0.911 to 0.986. The interobserver ICCs for these parameters between radiologist 1 and radiologist 2 ranged from 0.926 to 0.991. Both intra- and interobserver ICCs indicated excellent agreement for these parameters (see Table 1). Therefore, the data analyzed were those obtained by radiologist 1, who had more experience in software usage. The interobserver consistency for

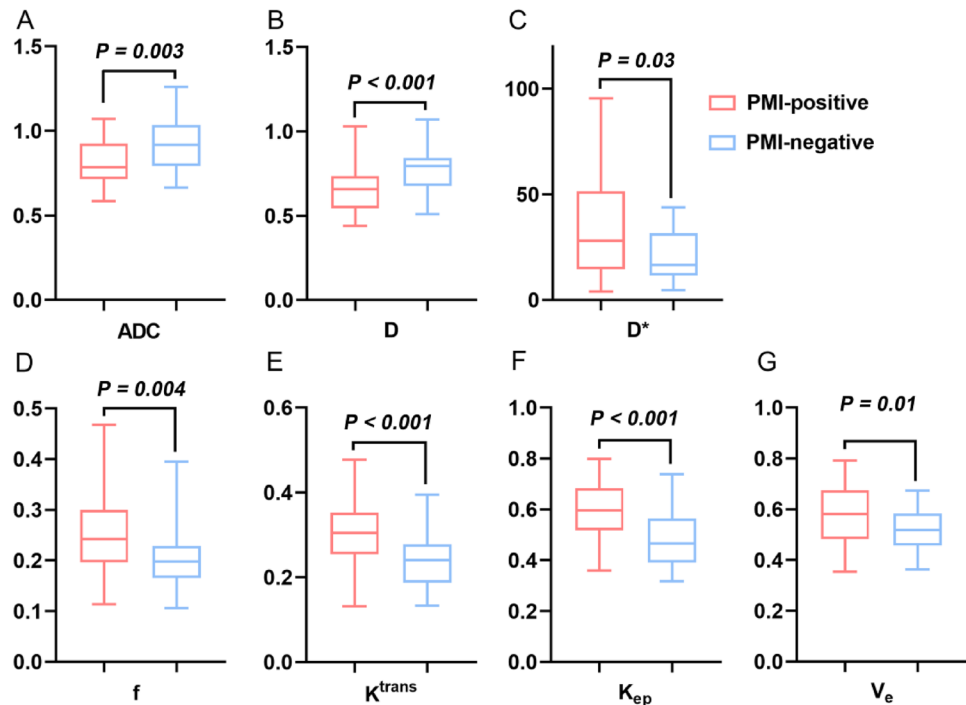
Table 1 T2WI, IVIM-DWI and DCE-MRI parameters and their ICCs

Parameters	PMI-positive (<i>n</i> = 32)	PMI-negative (<i>n</i> = 51)	<i>jP</i> value	ICC [#]	
				Intraobserver (95% CI)	Interobserver (95% CI)
IVIM-DWI					
ADC ($\times 10^{-3}$ mm ² /s)	0.785 (0.714–0.926)	0.917 (0.792–1.036)	0.003	0.899 (0.848, 0.933)	0.849 (0.776, 0.900)
<i>D</i> ($\times 10^{-3}$ mm ² /s)	0.657 (0.546–0.735)	0.794 (0.678–0.842)	< 0.001	0.907 (0.835, 0.945)	0.897 (0.836, 0.935)
<i>D</i> [*] ($\times 10^{-3}$ mm ² /s)	27.95 (14.63–51.43)	16.6 (11.6–31.5)	0.03	0.917 (0.795, 0.958)	0.879 (0.801, 0.924)
<i>f</i>	0.243 (0.197–0.300)	0.198 (0.165–0.229)	0.004	0.877 (0.619, 0.945)	0.833 (0.700, 0.902)
DCE-MRI					
<i>K</i> ^{trans} , min ⁻¹	0.320 (0.255–0.372)	0.241 (0.188–0.278)	< 0.001	0.868 (0.736, 0.927)	0.866 (0.482, 0.946)
<i>K</i> _{ep} , min ⁻¹	0.596 (0.519–0.683)	0.466 (0.390–0.565)	< 0.001	0.965 (0.944, 0.977)	0.961 (0.940, 0.974)
<i>V</i> _e	0.581 (0.484–0.676)	0.518 (0.457–0.584)	0.01	0.956 (0.930, 0.972)	0.951 (0.925, 0.968)
T2WI (+)/(-)	14 (43.8)/18 (56.3)	15 (29.4)/36 (70.6)	0.24		0.841 (0.719, 0.963)
T2WI+DWI (+)/(-)	18 (56.3)/14(43.8)	13 (25.5)/38 (74.5)	0.005		0.870 (0.760, 0.980)

CI, confidence intervals, DCE-MRI dynamic contrast-enhanced magnetic resonance imaging, *V*_e fractional extravascular extracellular space volume, ICC intraclass correlation coefficient, IVIM-DWI intravoxel incoherent motion diffusion weighted imaging, *D*^{*} fast apparent diffusion coefficient, PMI parametrial invasion, *f* perfusion fraction, *D* slow apparent diffusion coefficient, ADC standard apparent diffusion coefficient, *K*_{ep} the flux rate constant, *K*^{trans} the volume transfer constant. (+)/(-) represent parametrial invasion positive/negative identified by MRI

#Categorical variables were analyzed using κ statistics and continuous variables were analyzed using intraclass correlation coefficient

Fig. 2 Boxplots of IVIM-DWI (ADC, D, D*, and f) and DCE-MRI (K^{trans} , K_{ep} , and V_e) between PMI-positive and PMI-negative groups



T2WI and T2WI+DWI in these cases was 0.841 and 0.870, respectively. The κ statistic value also indicated excellent agreement.

IVIM-DWI and DCE-MRI parameters associated with parametrial invasion: uni- and multivariable analyses

Variables with a significance level below 0.05 in the univariable analysis were deemed to be associated with PMI. The MRI parameters statistically related with PMI contained ADC (OR 4.27; 95% CI 1.66–11.00; $P=0.003$), D (OR 7.14; 95% CI 2.57–19.82; $P<0.001$), D* (OR 4.89; 95%

CI 1.70–14.11; $P=0.003$), f (OR 5.27; 95% CI 1.97–14.08; $P=0.001$), K^{trans} (OR 7.93; 95% CI 2.89–21.75; $P<0.001$), K_{ep} (OR 7.47; 95% CI 2.76–20.21; $P<0.001$), and V_e (OR 5.55; 95% CI 1.93–15.97; $P=0.001$) (see Table 2).

Subsequently, a multivariable analysis employing a stepwise backward procedure was conducted to ascertain variables from the univariable analysis that could potentially contribute to distinguishing patients with PMI. Consequently, D (OR 7.05; 95% CI 1.78–27.88; $P=0.005$), D* (OR 6.58; 95% CI 1.49–29.10; $P=0.01$), f (OR 5.12; 95% CI 1.23–21.37; $P=0.03$), K^{trans} (OR 4.60; 95% CI 1.19–17.81; $P=0.03$), and K_{ep} (OR 4.90; 95% CI 1.25–19.18; $P=0.02$)

Table 2 MRI parameters associated with cervical cancer with parametrial invasion: uni- and multivariable analyses

Parameters	Univariable analysis			Multivariable analysis		
	Coefficient	OR (95% CI)	<i>P</i> Value	Coefficient	OR (95% CI)	<i>P</i> Value
Intercept				– 4.21		<0.001
ADC	1.45	4.27 (1.66, 11.00)	0.003	– 0.34	0.71 (0.14, 3.59)	0.68
D	1.97	7.14 (2.57, 19.82)	<0.001	1.95	7.05 (1.78, 27.88)	0.005
D*	1.59	4.89 (1.70, 14.11)	0.003	1.88	6.58 (1.49, 29.10)	0.01
f	1.66	5.27 (1.97, 14.08)	0.001	1.63	5.12 (1.23, 21.37)	0.03
K^{trans}	2.07	7.93 (2.89, 21.75)	<0.001	1.53	4.60 (1.19, 17.81)	0.03
K_{ep}	2.01	7.47 (2.76, 20.21)	<0.001	1.59	4.90 (1.25, 19.18)	0.02
V_e	1.71	5.55 (1.93, 15.97)	0.001	0.67	1.95 (0.42, 9.06)	0.39

CI confidence intervals, V_e fractional extravascular extracellular space volume, ICC intraclass correlation coefficient, D^* fast apparent diffusion coefficient, OR odds ratio, f perfusion fraction, D slow apparent diffusion coefficient, ADC standard apparent diffusion coefficient, K_{ep} the flux rate constant, K^{trans} the volume transfer constant

were identified as independent factors associated with PMI (see Table 2).

Predictive performance of IVIM-DWI and DCE-MRI parameters

According to the Youden’s index, the cutoff values for the parameters of D , D^* , f , K^{trans} , and K_{ep} were determined as $0.740 \times 10^{-3} \text{ mm}^2/\text{s}$, $35.5 \times 10^{-3} \text{ mm}^2/\text{s}$, 0.236, 0.268 min^{-1} ,

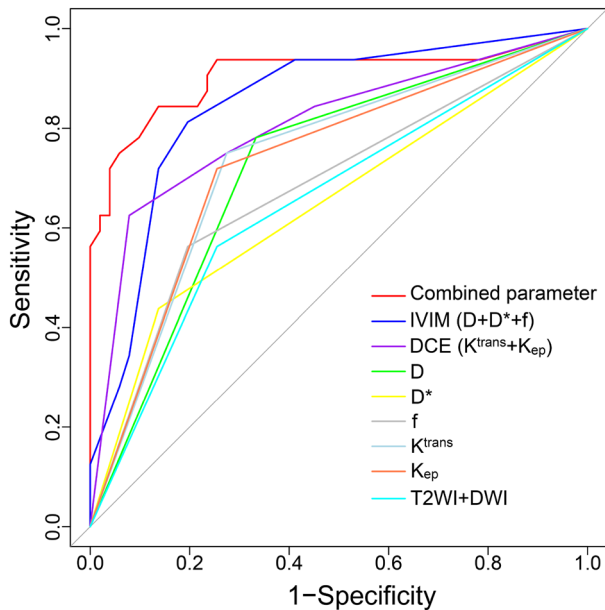


Fig. 3 Receiver operating characteristic curves of D , D^* , f , K^{trans} , K_{ep} , IVIM, DCE, and combined parameter in predicting cervical cancer with parametrial invasion

and 0.561 min^{-1} , respectively. ROC analyses revealed that the AUCs for D , D^* , f , K^{trans} , and K_{ep} were 0.724, 0.650, 0.683, 0.738, and 0.732, respectively. When compared with T2WI + DWI (AUC: 0.654), IVIM and DCE suggested higher predictive ability, with an AUC of 0.849 and 0.806, respectively (Delong test P values of 0.004 and 0.04, respectively). Moreover, comparing with T2WI + DWI, individual parameters (D , D^* , f , K^{trans} , K_{ep}), IVIM ($D + D^* + f$), and DCE ($K^{trans} + K_{ep}$), we found that the combined parameter ($D + D^* + f + K^{trans} + K_{ep}$) achieved the highest AUC of 0.906 (Fig. 3). The Delong test showed that all P values were < 0.05 when comparing the combined parameters with each individual parameter. The combined parameter enabled the identification of PMI with a sensitivity of 84.4% (27 of 32) and a specificity of 86.3% (44 of 51). IVIM identified 81.3% sensitivity (26 of 32) and 80.4% specificity (41 of 51) for PMI, while DCE identified 62.5% sensitivity (20 of 32) and 92.2% specificity (47 of 51) for parametrial invasion. The diagnostic abilities of these independent predictors of PMI are tabulated in Table 3. Representative IVIM-DWI and DCE-MRI images of a patient with cervical cancer are shown in Fig. 4.

Discussion

In our study, the multivariable analysis suggested that D , D^* , f , K^{trans} , and K_{ep} were independent factors associated with parametrial invasion. The combined parameter, which integrated these variables, exhibited the highest predictive performance for parametrial invasion in cervical cancer patients, achieving an AUC of 0.906, sensitivity of 84.4%, and specificity of 86.3%.

Table 3 Performance of the IVIM-DWI and DCE-MRI parameters in predicting cervical cancer with parametrial invasion

Parameters	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P value
Combined parameter		0.906 (0.826,0.986)	84.4	86.3	
IVIM ($D + D^* + f$)		0.849 (0.763, 0.936)	81.3	80.4	0.04 [†]
DCE ($K^{trans} + K_{ep}$)		0.806 (0.707, 0.906)	62.5	92.2	0.02 [†]
D	0.740	0.724 (0.626, 0.822)	78.1	66.7	< 0.001 [§]
D^*	35.5	0.650 (0.551, 0.750)	43.8	86.3	< 0.001 [§]
f	0.236	0.683 (0.580, 0.786)	56.3	80.4	< 0.001 [§]
K^{trans}	0.268	0.738 (0.640, 0.836)	75.0	72.5	< 0.001 [#]
K_{ep}	0.561	0.732 (0.632, 0.831)	71.9	74.5	< 0.001 [#]
T2WI + DWI		0.654 (0.548, 0.760)	56.3	74.5	< 0.001 [§]

AUC area under receiver operating characteristic, CI confidence intervals, DCE dynamic contrast-enhanced, IVIM intravoxel incoherent motion, D^* fast apparent diffusion coefficient, f perfusion fraction, D slow apparent diffusion coefficient, K_{ep} the flux rate constant, K^{trans} the volume transfer constant

#Represent DCE vs. K^{trans} and K_{ep} , respectively

§Represent IVIM vs. D , D^* and f , respectively

†Represent combined parameter vs. IVIM and DCE, respectively

§Represents combined parameter vs. T2WI combined DWI

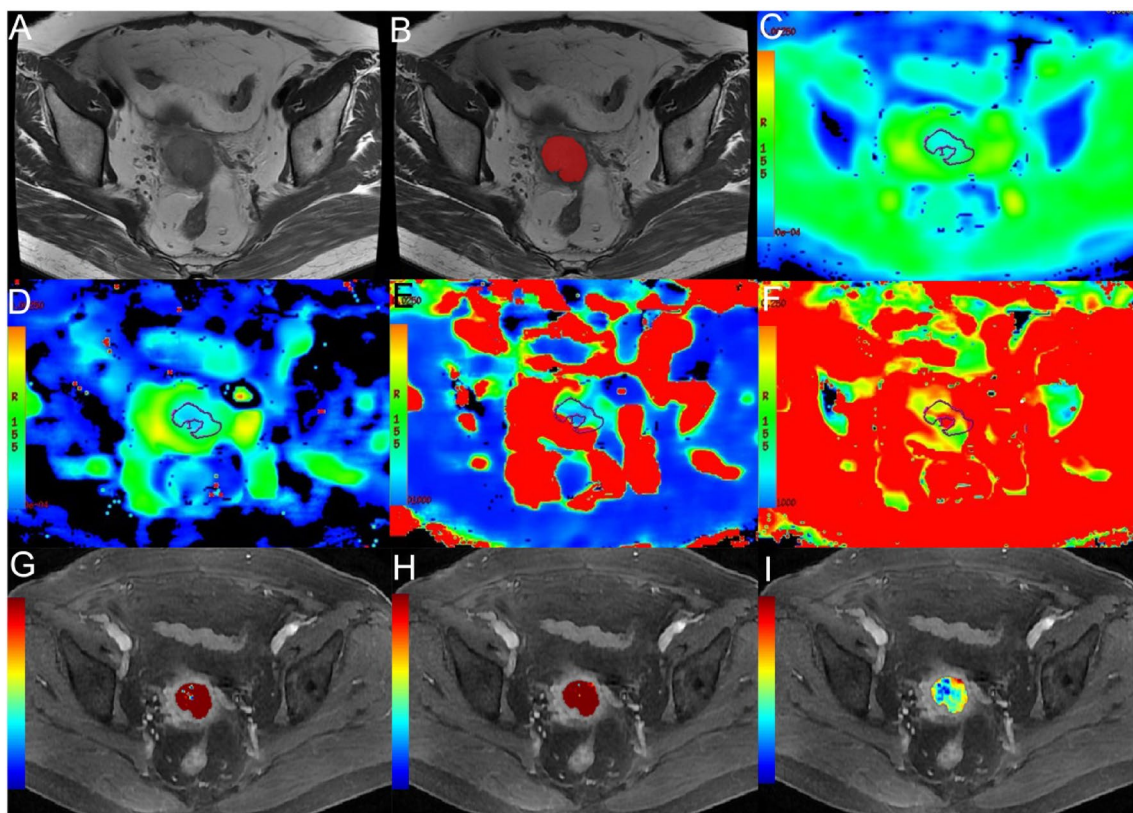


Fig. 4 A 52-year-old woman diagnosed with stage IIB cervical cancer. **A** and **B** T2-weighted images reveal a slightly hyperintense cervical mass. **C–F** ADC, D^* , and f parametric maps are obtained from IVIM-DWI, with corresponding values of $0.958 \times 10^{-3} \text{ mm}^2/\text{s}$,

$0.825 \times 10^{-3} \text{ mm}^2/\text{s}$, $95.4 \times 10^{-3} \text{ mm}^2/\text{s}$, and 0.241, respectively. **G–I** Parametric maps of K^{trans} , K_{ep} , and V_e are derived from DCE-MRI, with corresponding values of 0.425 min^{-1} , 0.582 min^{-1} , and 0.460

Utilizing multiple b -values and based on a bi-exponential model, IVIM-DWI provides insights into tumor water molecule diffusion, tumor angiogenesis, and tissue perfusion through various parameters [17, 18]. In our investigation, we observed a decrease in the D value within the PMI-positive group compared to the PMI-negative group. The D value, which excludes the low b -value perfusion component, portrays the intrinsic characteristics of water molecule diffusion within the tumor [19]. Greater intercellular space in tumor cells correlates with faster water molecule diffusion [19].

Hence, our results suggest that the intercellular space within tumor cells of the PMI-positive group is diminished in contrast to the PMI-negative group. This discrepancy may stem from the more prominent non-directional growth characteristic of tumor cells in the PMI-positive group, indirectly reflecting increased malignancy level in cervical cancer with parametrial invasion. Additionally, our study revealed that both D^* and f values exhibited an elevation within the PMI-positive group when contrasted with the PMI-negative group. This indicates a greater quantity or density of vascular generation in cervical cancer with parametrial invasion compared to those without.

DCE-MRI enables quantitative assessment of tissue microcirculation characteristics, including tumor angiogenesis, permeability, heterogeneity, and spatial distribution [20–22]. In our current study, DCE-MRI parameters K^{trans} and K_{ep} were observed to be higher values in the PMI-positive group in comparison with the PMI-negative group. This suggests greater tumor angiogenesis and vascular density in the parametrial invasion of cervical cancer. Furthermore, it is well-established that cervical cancer with parametrial invasion tends to be at a higher stage than those without parametrial invasion [23], indicating an increased vascular generation with advanced cervical cancer stages. Prior research has associated high K_{ep} values with poor outcomes in cervical cancer patients [24], suggesting an association between K_{ep} values and the malignant behavior of cervical cancer. Consistent with our findings, which link high K_{ep} values to malignant behavior, i.e., parametrial invasion. More importantly, the identification of parametrial invasion in cervical cancer using IVIM and DCE, as well as their combined parameters, was superior to T2WI + DWI in our study, indicating the clinical feasibility of applying IVIM and DCE.

It is important to acknowledge several limitations of the present study. Firstly, IVIM-DWI and DCE-MRI scans were not conducted on every hospitalized cervical cancer patient, which could introduce bias. Secondly, this study is a single-center study with a relatively small sample size. Consequently, in future research, a multi-center study will be conducted to collect a larger sample for further investigation. Thirdly, radiologists manually delineated the regions of interest in the study, potentially introducing subjective factors and variability in both inter- and intraobserver measurements, as well as bias in slice selection.

In conclusion, the combined parameter comprising D , D^* , f , K^{trans} , and K_{ep} demonstrated favorable predictive performance in identifying parametrial invasion in cervical cancer patients. IVIM-DWI and DCE-MRI could offer valuable guidance in treatment decisions and the management of cervical cancer patients.

Author contributions Conception and design: X.X.L., X.G.P.; Administrative support: X.G.P.; Provision of study materials or patients: X.X.L., B.L., X.G.P.; Collection and assembly of data: X.X.L., B.L., Y.C., X.G.P.; Data analysis and interpretation: X.X.L., Y.J., Y.F.Z.; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Declarations

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

Ethical approval The study protocol was approved by the institutional review board (2021-RE-091).

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