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ORIGINAL ARTICLE

Intravoxel incoherent motion magnetic resonance imaging for diagnosis of cervical cancer and evaluation of response of uterine cervical cancer to radiochemotherapy: A pilot study*

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Abstract

Objective The aim of this study was to investigate the ability of intravoxel incoherent motion (IVIM) diffusion-weighted magnetic resonance imaging (MRI) to diagnose cervical cancer and to evaluate the response of uterine cervical cancer to radiochemotherapy (CRT).

Methods This prospective study was approved by the institutional review board, and informed consent was obtained from all patients. A total of 23 patients with primary cervical cancer who were undergoing CRT and 16 age-matched healthy subjects were prospectively recruited for IVIM (b = 0–800 s/mm^2) and standard pelvic MRI. Bi-exponential analysis was performed to derive f (perfusion fraction), D* (pseudo-diffusion coefficient), and D (true molecular diffusion coefficient) in cervical cancer (n = 23) and the normal cervix (n = 16). The apparent diffusion coefficient (standard ADC) was calculated. The independent-samples t-test and paired-samples t-test were used for comparisons.

Results Pre-treatment cervical cancer had the lowest standard ADC (1.15 ± 0.13 × 10^{-3} mm^2/s) and D (0.89 ± 0.10 × 10^{-3} mm^2/s) values, and these were significantly different from the normal cervix and post-treatment cervical cancer (P = 0.00). The f (16.67 ± 5.85%) was lowest in pre-treatment cervical cancer and was significantly different from the normal cervix and post-treatment cervical cancer (p = 0.012 and 0.00, respectively). No difference was observed in D*.

Conclusion IVIM is potentially promising for differentiating between the normal cervix and cervical cancer because pre-treated cervical cancer has low perfusion and diffusion IVIM characteristics. Further, the standard ADC, D, and f of cervical cancer showed a tendency to normalize after CRT; thus, IVIM may be useful for monitoring the response to CRT in cervical cancer.

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Key words: diffusion-weighted imaging; magnetic resonance imaging (MRI); investigate the ability of intravoxel incoherent motion (IVIM); cervical cancer; radiochemotherapy

Uterine cervical cancer remains one of the most common malignancies in women [1]. Thus far, concomitant chemoradiotherapy is considered the standard treatment of bulky and locally advanced cancer of the cervix [2]. Diagnosing cervical cancer and observing the effect of radiochemotherapy (CRT) are very important.

With superior soft-tissue resolution, magnetic resonance imaging (MRI) has become an indispensable tool in the management of cervical cancers, and it is widely used for diagnosis, treatment planning, and response monitoring [3–5]. Presently, there is growing interest in using MR techniques such as dynamic contrast-enhanced (DCE) and diffusion-weighted imaging (DWI) to improve diagnosis [6–7] and to predict and monitor the response to CRT

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[8–9] or neoadjuvant chemotherapy (NACT) [10–11].

Intravoxel incoherent motion (IVIM) imaging is an extension of DW-MRI that can reveal both diffusion and microcirculation within human tissues. IVIM MRI acquires multiple b-values and uses a bi-exponential curve fit analysis to derive the true diffusion coefficient (D), perfusion-related pseudo-diffusion coefficient (D*), and perfusion fraction (f) values [12]. Clinical applications are emerging for the use of these IVIM-derived parameters to resolve diagnostic dilemmas [13–15] and to differentiate tumor histological types [16]. Thus far, only one study about the use of IVIM MRI for the diagnosis of cervical cancer has been published [17]. Further, to the best of our knowledge, no article has reported the use of IVIM to predict and monitor the response of cervical cancer to CRT or NACT.

The purpose of this study was to evaluate prospectively the monitoring power of the IVIM MRI parameters and standard apparent diffusion coefficient (ADC) values obtained at pre-treatment and after therapy for determining the response of cervical cancer to CRT. Furthermore, we retrospectively assessed whether the differences in IVIM and standard ADC values between normal cervical and cervical cancer could be useful as a quantitative diagnostic method for cervical cancer.

Materials and methods

Patients

This prospective study was approved by our institutional review board, and informed consent was obtained from all patients. Patients who were scheduled to undergo CRT were eligible for this study. The inclusion criteria for the patients participating in this prospective study were the same as the criteria for primary patients undergoing CRT in our hospital: cervical cancers that were clinically staged as the International Federation of Gynecology and Obstetrics classification IIB to IVB. The exclusion criteria were: (a) previous surgery for cervical cancer or radiation therapy for a tumor in another organ (n = 0), (b) contraindication to MR imaging examination (n = 0), or (c) discontinued MR imaging examinations during therapy (n = 51).

A total of 74 consecutive patients who met the study criteria were recruited from our clinics between March 2013 and January 2015 at the Department of Radiology, Tongji Medical Hospital, Huazhong University of Science and Technology; however, 51 patients subsequently withdrew or were excluded because of discontinued MR imaging examinations during therapy.

A total of 23 consecutive women (mean age, 53 years; SD, 8 years; range, 39–62 years) with cervical squamous cell carcinoma (SCC) histologically confirmed with biopsy results were examined by using IVIM MRI at 2 time points: before starting treatment and after 1 month of therapy completion.

During the same period, a control group of 16 age-matched, healthy volunteer female subjects (median age, 48 years; range, 26–64 years; pre-menopausal/post-menopausal, 5:11) with no known gynecological symptoms, gynecological disease, or previous history of carcinoma underwent only 1 pelvic MR IVIM examination.

MRI acquisition

All scans were performed on a 3.0-T MRI scanner (GE Healthcare 750 Discovery, USA) by using a 32-Ch Torso Array (NeoCoil). Before DW-MRI, sagittal and coronal T2-weighted images (T2WI) and axial T1-weighted images were obtained in all patients by using a fast spin-echo sequence [sagittal T2-weighted: repetition time (TR)/echo time (TE), 6181/130 ms; field of view (FOV), 240 mm; acquisition matrix, 320 × 320; slice thickness, 4 mm; interslice gap, 0.4 mm; echo train length (ETL), 24; no fat saturation; bandwidth, 62.5 kHz; coronal T2-weighted: TR/TE, 68/2600 ms; FOV, 300 mm; acquisition matrix, 320 × 256; slice thickness, 4 mm; interslice gap, 1 mm; ETL, 14; fat saturation; bandwidth, 62.5 kHz; axial T1-weighted: TR/TE, 360/7.7 ms; FOV, 340 mm; acquisition matrix, 256 × 256; slice thickness, 3 mm; interslice gap, 1 mm; ETL, 14; fat saturation; bandwidth, 50 kHz]. Axial T2WIs were obtained in all patients by using a fast recovery fast spin-echo sequence (TR/TE, 5004/68 ms; FOV, 340 mm; acquisition matrix, 320 × 256; slice thickness, 3 mm; interslice gap, 1 mm; ETL, 16; no fat saturation; bandwidth, 62.5 kHz). Axial DW-MR images with 9 b-values (0, 50, 100, 150, 200, 300, 400, 600, and 800 s/mm^2) were obtained by using a DW-MR echo-planar sequence (TR/TE, 4000/minimum; FOV, 340 mm; acquisition matrix, 160 × 192; section thickness, 3 mm; interslice gap, 1 mm; receiver bandwidth, 250 kHz).

Image analysis

All acquired IVIM MRI images were transferred to a workstation (ADW4.5, GE Medical System, USA). In the IVIM model, the relationship between signal variation and b factors is expressed as [18]:

$$Sb/S0 = (1-f)\exp(-bD) + \{f\exp[-b(D^* + D)]\},$$

where f was the volume fraction of the protons linked to the intravascular component, D is the slow component of diffusion, and D* represents incoherent microcirculation. In cervical cancer patients, the ADC with all 9 b values and IVIM parameters were measured by drawing a region of interest (ROI) around the largest mass area of the tumor in the images. If no residual tumor was present, the ROI was traced as much as possible in the same area used in the first MR examination.

In healthy subjects, the ROI was set in an area of normal cervical tissue with exclusion of the cervical stroma,

which normally has a low signal on T2WI. It was generally thought that the cervical stroma should be included in the ROI for the ADC measurement, even in subjects with a normal cervix, because cervical cancers invaded and involved the cervical stroma. However, erroneous values might be obtained when the ADC was calculated in tissues with short T2 values [19–20]. Therefore, the cervical stroma was excluded from the measurement in normal cervical tissue. A single observer (Y.C.W., with 5 years of experience in clinical MRI) obtained measurements 3 times at 2-week intervals for each patient, and the average of these 3 measurements was taken as the average ADC and IVIM parameters. Response to treatment was determined by comparing the first MRI and follow-up MRI. A complete response (CR) was concluded if no residual tumor was observed on T2WI; a partial response (PR) was concluded if the longest diameter of the tumor was less than 70% of the original size; stable disease was concluded in the absence of sufficient shrinkage to qualify for PR or sufficient increase to qualify for progressive disease (PD); and PD was concluded in the presence of at least a 20% increase and a 5-mm absolute increase in the sum of the longest diameter of the tumor, using the longest diameter recorded before treatment as the reference [21].

Therapeutic regimen

All patients were treated with a combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICR) after NACT [NACT consisted of 2 cycles of intravenous docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) at 3-week intervals]. EBRT was delivered to the whole pelvis with a total dose of 45–54 Gy and was accompanied by concurrent chemotherapy (3 × 6 cycles of weekly cisplatin with 30 mg/m^2), and ICR was initiated after an EBRT dose of 30–49 Gy. ICR was delivered in 5 × 7 fractions with a fractional dose of 6 Gy at point A. The overall CRT time for each patient was 8-night weeks.

Statistical analysis

All data analyses were performed by using SPSS software (IBM SPSS for Windows, version 19.0; SPSS, USA). The independent-samples t-test was used to compare the standard ADC, D, D*, and f values between the pretreatment cervical cancer and control groups. The differences between pre-treatment and post-treatment standard ADC, D, D*, and f values and pretreatment and post-treatment tumor diameters were calculated by using the paired-samples *t*-test. A P-value < 0.05 was considered to indicate a statistically significant difference.

Results

Tumor diameter measurement and response to therapy results are listed in Table 1. The follow-up MR of cervical cancer revealed a CR in 4 patients and a PR in 19 patients

Table 1 Summary of the cervical cancer patients

No.	Age (years)	Tumor diameter of pre-treatment (mm)	Tumor diameter of after treatment (mm)	Clinical stage	Response determined by the second MRI scan
1	40	94	30	SCCIIIB	PR
2	42	79	28	SCCIVb	PR
3	58	26	9	SCCIIb	PR
4	56	39	0	SCCIIb	CR
5	55	58	7	SCCIIIB	PR
6	62	39	0	SCCIIb	CR
7	40	63	35	SCCIIIB	PR
8	60	47	0	SCCIIIB	CR
9	52	63	13	SCCIVB	PR
10	42	44	26	SCCIIIa	PR
11	50	72	16	SCCIIb	PR
12	53	52	24	SCCIIIb	PR
13	39	44	23	SCCIIIB	PR
14	53	35	15	SCCIIb	PR
15	55	20	8	SCCIIb	PR
16	61	37	8	SCCIIb	PR
17	61	30	8	SCCIIb	PR
18	52	77	25	SCCIVB	PR
19	58	39	0	SCCIIb	CR
20	61	113	27	SCCIVB	PR
21	46	25	16	SCCIIB	PR
22	60	32	16	SCCIIb	PR
23	61	40	20	SCCIIIB	PR
Mean	53	50.8	15.4		

SCC: squamous cell carcinoma

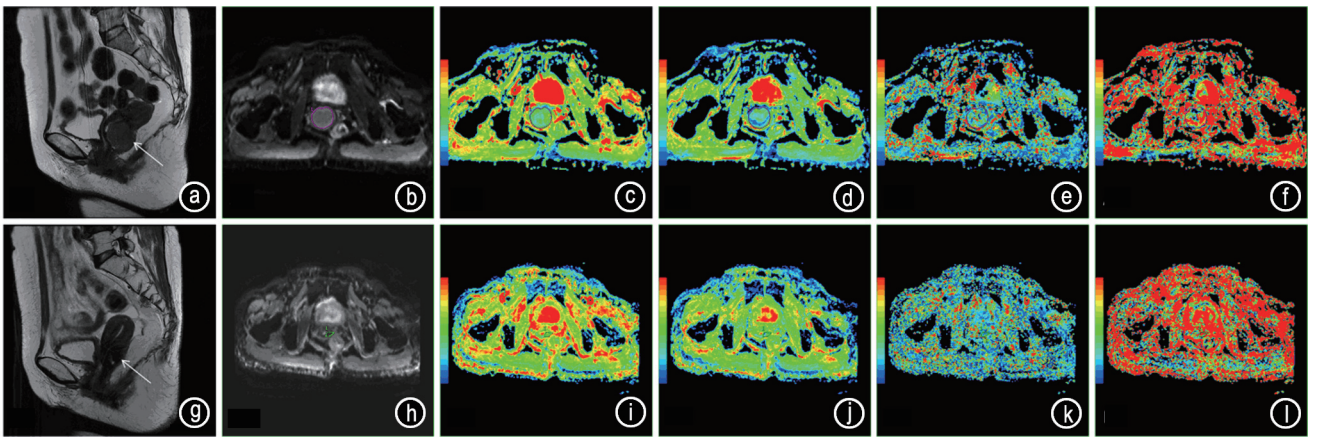

Fig. 1 Images obtained from a 56-year-old woman with cervical SCC (arrow). A CR was observed 1 month after therapy completion. (a–f) (pre-treatment) corresponding to the sag T2WI, axial DW-MRI with b = 0 s/mm^2, and the axial standard ADC, D, D*, and f maps, respectively. (e–l) (post-treatment). The outlines indicated the tumor region

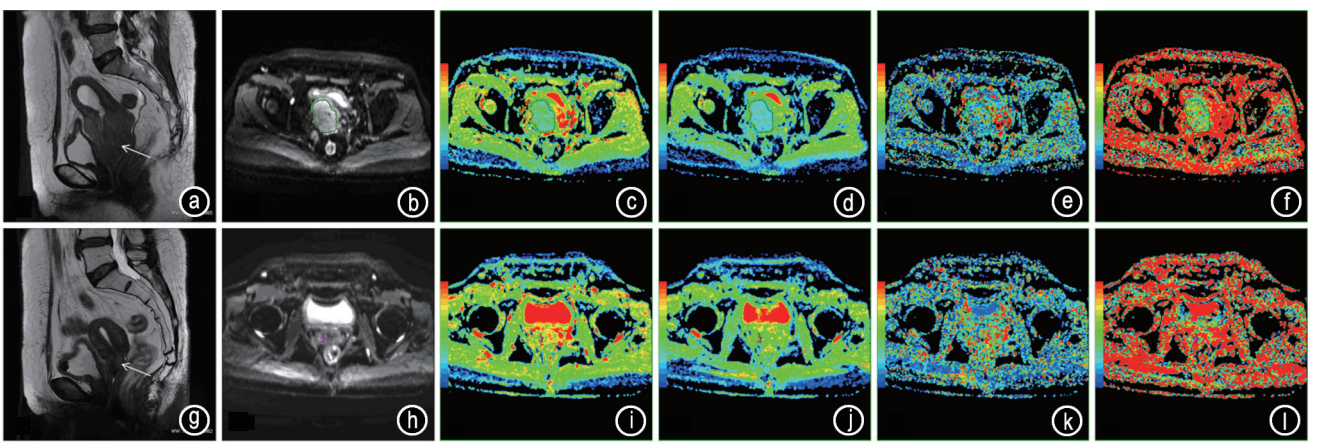

Fig. 2 Images obtained from a 50-year-old woman with cervical SCC (arrow). A PR was observed 1 month after therapy completion.(a–f) (pre-treatment) corresponding to sag T2WI, axial DW-MRI with b = 0 s/mm^2, and axial standard ADC, D, D*, and f maps, respectively. (e–l) (post-treatment). The outlines indicated the tumor region

(Fig. 1 and 2).

Comparison between the normal cervix and pre-treatment cervical cancer

The mean standard ADC and D values of pre-treatment cervical cancer were 1.15 ± 0.13 ± 10^{-3} mm^2/s and 0.89 ± 0.10 ± 10^{-3} mm^2/s, respectively, and those of normal cervical tissue were 1.91 ± 0.37 ± 10^{-3} mm^2/s and 1.42 ± 0.18 (both P = 0.00; Fig. 3 and 4). The f value was significantly different between the normal cervix and pre-treatment cervical cancer (P = 0.012), but the D* showed no significant difference (P = 0.995; Fig. 5).

Comparison between pre-treatment cervical cancer and post-treatment cervical cancer

The mean standard ADC and D values of post-treatment cervical cancer were 1.65 ± 0.19 × 10^{-3} mm^2/s and 1.26 ± 0.19 × 10^{-3} mm^2/s, respectively. The standard ADC and D values were different between pre-treatment cervical cancer and post-treatment cervical cancer (both P = 0.00; Fig. 3 and 4).

The f value of pre-treatment cervical cancer was significantly lower than that of post-treatment cervical cancer (P = 0.000; Fig. 5). No difference was observed in the D* in the pre-treatment and post-treatment cervical cancer groups (P = 0.541; Table 2)

Comparison between the normal cervix and post-treatment cervical cancer

The mean standard ADC and D values of post-treatment cervical cancer were significantly lower than those of the normal cervical tissue (P = 0.016 and 0.015, respectively; Fig. 3, 4). No difference was observed in the D* and f in the post-treatment cervical cancer and normal cervix groups (P = 0.645 and 0.707, respectively; Table 2).

Table 2 IVIM-derived parameters and standard ADC for the normal cervix and cervical cancer groups

	Normal cervix (n = 16)	Pre-treatment cervical ncer (n = 23)	Post-treatment cervical ancer (n = 23)
Standard ADC (× 10^{-3} mm^2/s)	1.91 ± 0.37	1.15 ± 0.13	1.65 ± 0.19
D (× 10^{-3} mm^2/s)	1.42 ± 0.18	0.89 ± 0.10	1.26 ± 0.19
D*(× 10^{-3} mm^2/s)	15.61 ± 6.28	15.62 ± 3.78	16.84 ± 9.18
f (%)	25.51 ± 11.80	16.67 ± 5.85	24.43 ± 5.83

The data were expressed as the mean ± SD

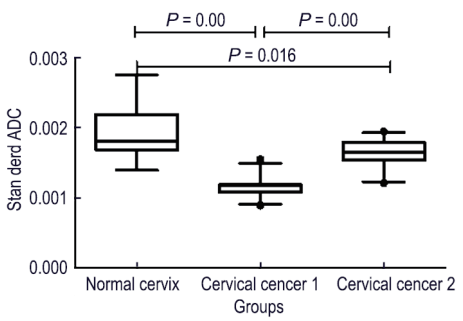

Fig. 3 The standard ADCs of various female pelvic tissues. The standard ADC of cervical cancer 1 (representing pre-treatment cervical cancer) was the lowest and was significantly different from the normal cervix and cervical cancer 2 (representing post-treatment cervical cancer)

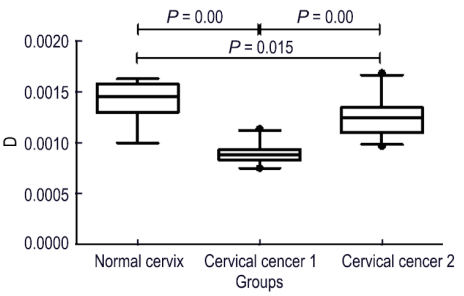

Fig. 4 The pure molecular diffusion values of various female pelvic tissues. The pure molecular diffusion of cervical cancer 1 (representing pre-treatment cervical cancer) was significantly different from the normal cervix and cervical cancer 2 (representing post-treatment cervical cancer).

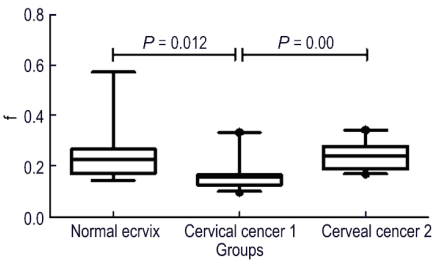

Fig. 5 The perfusion fractions of various female pelvic tissues. The perfusion fractions were significantly different between cervical cancer 1 (representing pre-treatment cervical cancer) and the normal cervix, and between cervical cancer 1 and cervical cancer 2 (representing post-treatment cervical cancer).

Discussion

The diffusion and perfusion parameters obtained from the IVIM model could efficiently differentiate cervical cancer from the normal cervix with high sensitivity and specificity. The standard ADC and D values in malignant lesions or high-grade tumors were significantly lower than those in benign lesions and normal tissues or low-grade tumors, consistent with the results reported in other studies [22–23]. Further, our standard ADC and D values in cervical cancer were significantly lower than those in the normal cervix (both $P = 0.00$), which is consistent with the dense cellularity within cervical cancer that results in restricted water diffusion [24–26]. This result is also consistent with the only report on such an IVIM model application in cervical cancer in the literature [17].

The f value of cervical cancer was lower than that in the normal cervical tissue ($P = 0.012$), which is concordant with a previous study showing that the f value in cervical cancer was markedly reduced when compared with healthy cervical tissue and normal outer myometrium [17]. This result may be explained by the findings of previous studies, which showed that tumors and their blood supplies grow outward, with reduced microvessel density in the central or tumor core when compared with the adjacent normal tissue on histology [27–28]. In our study, the D* value was not significantly different between cervical cancer and normal cervical tissue, and our D* value was similar to that of the cervical cancer cohort reported by Lee *et al* [17]. Koh *et al* [29] reported poor reproducibility of the perfusion-sensitive low ADC range (0–100 s/mm^2). Another reason for the large perfusion-related diffusion coefficient variations may be biexponential data fitting errors. In general, biexponential fitting is considered difficult to perform reliably [30], and further improvements in mathematic modeling of DWI signal decay behavior might provide improved curve fits and a better understanding of the physiologic basis of DWI.

Therefore, on the basis of our results, we propose that standard ADC, D, and f values might be good quantitative indicators for differentiating cervical cancer from normal cervical tissues.

In our study, the pre-treatment standard ADC, D, and f values of cervical cancer patients were significantly lower than those of post-treatment cervical cancer patients (both $P = 0.00$). Moreover, the standard ADC, D, and f

values of post-treatment cervical cancer were lower than those of the normal cervical tissue (P = 0.016, 0.015, and 0.707, respectively). Further, we demonstrated the feasibility of applying the IVIM model for monitoring the response of cervical cancer. To our knowledge, this is the first report on such an application in cervical cancer. Several articles that evaluated the use of ADC to monitor the radiotherapy and chemotherapy response of cervical cancer showed that the post-treatment ADC values were significantly higher than those of the pre-treatment ADC [31–33]; our standard ADC and D values were similar to the ADC results in these studies. The standard ADC, D, and ADC values all reflect the diffusion of water molecules, but the principle of formation is slightly different. The standard ADC values were calculated from the fitness data with b = 0 and b ≥ a set point according to a single exponential model. Traditional ADC values are affected by the diffusion of water molecules, capillary perfusion processes, and the b values applied. In contrast, standard ADC values are more objective and precise, as they show less perfusion contamination and fewer regional ADC variations. Although D also reflects the diffusion of water molecules, it is not as reliable as ADC, which represents the true diffusion coefficient. F is a quantitative index that reflects tumor tissue perfusion, and the f of cervical cancer showed a tendency to normalize after CRT, suggesting that f can be used to monitor the treatment response. However, f is likely to be dependent on various factors and their complex interactions within the tumor microcirculation, like the abundance of the capillary network, the permeability of the capillaries, the exchange surface areas, the interstitial volume, and the interstitial fluid pressure. Although it has not been fully elucidated, f remains a potentially important parameter, and further research should be performed regarding its role for predicting and assessing the CRT response in cervical cancer. Lastly, the D* value was not significantly different between pre-treatment cervical cancer and post-treatment cervical cancer.

Thus, the expected clinical significance of the standard ADC, D, and f measurements in cervical cancer would be their usefulness for monitoring the response to CRT. Further study in a larger numbers of patients is needed to establish the accuracy of these measurements for monitoring the effect of therapy for uterine cervical cancer.

This study had several limitations. First, the sample size was relatively small. Second, the evaluation of the response to CRT in cervical cancer was not divided into responders and non-responders, and further dividing the patients into responders and non-responders may have yielded results that are more clinically useful. Finally, we chose the highest b-value (800 s/mm^2) for our study, which may have been too conservative. However, according to the literature, the overall discriminatory capacity for differentiating responders from non-responders was greater for high b-value combinations (0, 1000 s/mm^2) than for low b-value combinations (0, 600 s/mm^2) [33].

In conclusion, this preliminary study showed that the IVIM model potentially has the ability to differentiate between the normal cervix and cervical cancer. The standard ADC, D, and f values of cervical cancer showed a tendency to normalize after CRT. Further study is necessary to determine the accuracy of the IVIM model for monitoring the treatment response.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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