Original Article

# Assessing the Early Response of Advanced Cervical Cancer to Neoadjuvant Chemotherapy Using Intravoxel Incoherent Motion Diffusion-weighted Magnetic Resonance Imaging: A Pilot Study

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## Abstract

**Background:** Diffusion-weighted imaging (DWI) with the intravoxel incoherent motion (IVIM) model has shown promising results for providing both diffusion and perfusion information in cervical cancer; however, its use to predict and monitor the efficacy of neoadjuvant chemotherapy (NACT) in cervical cancer is relatively rare. The study aimed to evaluate the use of DWI with IVIM and monoexponential models to predict and monitor the efficacy of NACT in cervical cancer.

**Methods:** Forty-two patients with primary cervical cancer underwent magnetic resonance exams at 3 time points (pre-NACT, 3 weeks after the first NACT cycle, and 3 weeks after the second NACT cycle). The response to treatment was determined according to the response evaluation criteria in solid tumors 3 weeks after the second NACT treatment, and the subjects were classified as two groups: responders and nonresponders groups. The apparent diffusion coefficient (ADC), true diffusion coefficient (D), perfusion-related pseudo-diffusion coefficient (D*), and perfusion fraction (f ) values were determined. The differences in IVIM-derived variables and ADC between the different groups at the different time points were calculated using an independent samples *t*-test.

**Results:** The D and ADC values were all significantly higher for the responders than for the nonresponders at all 3 time points, but no significant differences were observed in the D* and f values. An analysis of the receiver operating characteristic (ROC) curves indicated that a D value threshold $<0.93 \times 10^{-3}$ mm$^2$/s and an ADC threshold $<1.11 \times 10^{-3}$ mm$^2$/s could differentiate responders from nonresponders at pre-NACT time point, yielding area under the curve (AUC) of which were 0.771 and 0.806, respectively. The ROC indicated that the AUCs of D and ADC at the 3 weeks after the first NACT cycle and 3 weeks after the second NACT cycle were 0.823, 0.763, and 0.787, 0.794, respectively. The AUC values of D and ADC at these 3 time points were not significantly different ($P$ = 0.641, 0.512, and 0.547, respectively).

**Conclusions:** D and ADC values may be useful for predicting and monitoring the efficacy of NACT in cervical cancer. An IVIM model may be equal to monoexponential model in predicting and monitoring the efficacy of NACT in cervical cancer.

**Key words:** Cervical Cancer; Diffusion-weighted Magnetic Resonance Imaging; Intravoxel Incoherent Motion; Neoadjuvant chemotherapy

## Introduction

Uterine cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide.[1] Currently, neoadjuvant chemotherapy (NACT) for advanced cervical cancer is widely utilized in countries such as Japan, Korea, and Italy.[2] The proper stage of cervical cancer at which to use NACT remains debatable,[2,3] and multiple NACT regimens are currently in use. Of these regimens, cisplatin-based chemotherapy is the most common because of its enhanced response rates.[4] The aim of NACT is to either reduce the tumor size or to eliminate latent microlymph node metastases[5] before surgery or

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radiotherapy. However, NACT is only 65.0–87.5% effective against cervical cancer.[6-8] Furthermore, the lack of response to NACT can increase the risk of tumor progression and surgical difficulty, and the response to NACT can itself be considered an independent prognostic factor.[6] When no response to NACT is observed, alternative treatment strategies should be considered, including earlier surgery or radiation therapy. Therefore, it would be useful to identify reliable early predictors of the response to NACT before utilizing the response evaluation criteria in solid tumors (RECIST).

Diffusion-weighted magnetic resonance imaging (DWI) is a proven quantitative biomarker for the therapeutic response to chemoradiotherapy (CRT) and NACT in cervical cancer.[8-10] Studies have demonstrated significantly different apparent diffusion coefficient (ADC) values between responders and nonresponders after therapy; therefore, DWI may be a good tool for evaluating treatment responses. However, ADCs obtained from DWI with a monoexponential model can be influenced not only by molecular diffusion but by microcirculation or blood perfusion; therefore, ADC values that include perfusion effects may limit the reliability of this tool.[11,12]

DWI with the intravoxel incoherent motion (IVIM) model is an extended DWI sequence that can simultaneously obtain microcirculatory and diffusivity information and can distinguish microcirculation or perfusion effects from true tissue diffusion. IVIM magnetic resonance imaging (MRI) acquires multiple *b* values and uses a biexponential curve fit analysis to derive the true diffusion coefficient (D), the perfusion-related pseudo-diffusion coefficient (D*), and the perfusion fraction (f).[11] IVIM imaging has been applied in cancer of the cervix[13] and several other organs[14,15] and has shown useful results in clinical practice. However, feasibility studies on predicting and monitoring the efficacy of NACT in cervical cancer are relatively scarce.

The study aimed to evaluate the potential use of DWI with IVIM and monoexponential models to predict and monitor the response of advanced cervical cancer to NACT administration.

## Methods

### Patients

This study was approved by the Ethics Committee of Tongji Hospital of Huazhong University of Science and Technology. The written consent was obtained from all of the study's participants. The inclusion criteria for the study population included: (1) patients with Stage IIA to IVA cervical cancer based on the International Federation of Gynecology and Obstetrics (FIGO) classification, who were scheduled to undergo NACT before surgery or chemoradiation; (2) patients with normal renal, hepatic, cardiac, pulmonary, and hematologic function; (3) patients who had undergone a complete MRI examination; and (4) the availability of good-quality images.

From March 2013 to September 2014, fifty consecutive patients were enrolled in our prospective study. Eight patients were excluded from the study because their MRI image quality was poor ($n$ = 2) or because they did not undergo a complete MRI examination for personal reasons ($n$ = 6); the remaining 42 patients were included in our study. These 42 consecutive women with cervical cancer (mean age, 50 ± 9 years; 37 cervical squamous cell carcinomas, four cervical adenocarcinomas, and one cervical adenosquamous carcinoma; 28 IIA + IIB, 10 IIIA + IIIB, and 4 IVA) that was histologically confirmed by biopsy were examined using IVIM MRI at 3 time points: pre-NACT, 3 weeks after the first NACT cycle, and 3 weeks after the second NACT cycle.

### Magnetic resonance imaging protocols

All of the scans were performed on a 3.0 T MRI (GE Healthcare 750 Discovery, Milwaukee, Wisconsin, USA) using a 32-Channel Torso Array NeoCoil. Before DWI, sagittal and coronal T2-weighted images (T2-WI) and axial T1-weighted images (T1-WI) were obtained for all patients using a fast spin-echo sequence; axial T2-WI was obtained using a fast recovery fast spin-echo sequence.

The sagittal T2-WI parameters were as follows: repetition time (TR)/echo time (TE), 6181/130 ms; slice thickness/gap, 4 mm/0.4 mm; field of view (FOV), 240 mm; acquisition matrix, 320 × 320; echo train length (ETL), 24; bandwidth, 62.5 kHz; and no fat saturation. The coronal T2-WI parameters were as follows: TR/TE, 68/2600 ms; slice thickness/gap, 4 mm/1 mm; FOV, 300 mm; acquisition matrix, 320 × 256; ETL, 14; bandwidth, 62.5 kHz; and fat saturation. The axial T1-WI parameters were as follows: TR/TE, 360/7.7 ms; slice thickness/gap, 3 mm/1 mm; FOV, 340 mm; acquisition matrix, 256 × 256; ETL, 14; bandwidth, 50 kHz; and fat saturation. The axial T2-WI parameters were as follows: TR/TE, 5004/68 ms; slice thickness/gap, 3 mm/1 mm; FOV, 340 mm; acquisition matrix, 320 × 256; ETL, 16; bandwidth, 62.5 kHz; and no fat saturation.

Subsequently, axial DWI with 9 *b* values (0, 50, 100, 150, 200, 300, 400, 600, and 800 s/mm$^2$) were obtained using a single-shot echo planar imaging sequence and motion-probing gradients in three orthogonalaxes (TR/TE, 4000/59.3–63.1; slice thickness/gap, 3 mm/1 mm; FOV, 340 mm; acquisition matrix, 160 × 192; and receiver bandwidth, 250 kHz). We ensured that the FOV, slice thickness, and intersection gap were identical to those of the axial T2-WI to allow image overlay and co-registration. The images were acquired during free breathing, and the total scan time was 4 min and 36 sec.

### Treatment response analysis

Treatment response was determined according to the final tumor size on MRI 3 weeks after therapy completion. The tumor responses related to pretreatment were classified clinically into four types according to RECIST:[16] Complete response (CR), with no residual tumor on

T2-WI; partial response (PR), with the longest diameter of the tumor <70% of the original size; stable disease, with neither sufficient shrinkage to qualify as PR nor a sufficient increase to qualify as progressive disease (PD); and PD, with at least a 20% increase in the sum of longest diameter of the tumor, with the longest diameter recorded before treatment as the reference. All of the patients were assigned to one of two groups, responders or nonresponders groups. The responders included patients with a CR or a PR, and the nonresponders consisted of patients with an stable disease or PD.

### Image analysis

All the acquired IVIM MRI images were transferred to a workstation (Advance Workstation 4.5, GE Medical System, Milwaukee, WI, USA).

We obtained the ADC value by calculating all 9 *b* values using a monoexponential model, as shown below:[12]

$$S(b)/S(0) = \exp(-b \times \mathrm{ADC}),$$

where $S(b)$ represents the signal intensity (SI) in the presence of diffusion sensitization and $S(0)$ represents the SI in the absence of diffusion sensitization.

In the biexponential IVIM model, the relationship between signal variation and b factors is expressed as follows:[12]

$$S(b)/S(0) = f \times \exp(-b \times D^*) + (1 - f) \times \exp(-b \times D).$$

Where f is the volume fraction of the protons linked to the intravascular component, D is the slow component of diffusion, and D* represents incoherent microcirculation.

In this article, the monoexponential model followed the least-squares fit for linear fitting and the IVIM model followed the Levenberg–Marquardt fit for nonlinear fitting.

The ADC values and IVIM parameters of the patients were measured by drawing a region of interest (ROI) around the largest tumor mass area in the images of axial $b = 0$ s/mm$^2$; if no residual tumor was visible, the ROI was set, as much as possible, to cover the same area used for the first magnetic resonance examination (axial T2-WI). Notably, the ROI should avoid areas of focal SI changes, susceptibility artifacts, and necrosis. Tumor size was defined as the maximum diameter measured using axial, sagittal, or coronal T2-WI on a picture archiving and communication system workstation (AGFA Impax). These processes were performed 3 times every 2 weeks for each patient by a single observer (an abdominal radiologist with 5 years of experience in clinical MRI). The average of these three measurements was used as the average ADC and IVIM parameters and the maximum tumor diameter.

Changes in the ADC and IVIM parameters (%) at each time point were calculated using the following equation:

$$(\mathrm{ADC\ or\ IVIM}_{post} - \mathrm{ADC\ or\ IVIM}_{pre})/\mathrm{ADC\ or\ IVIM}_{pre}.$$

### Neoadjuvant chemotherapy treatment

All patients with cervical cancer were scheduled for two NACT cycles at 3-week intervals, and all of these patients underwent unified NACT treatment. NACT consisted of 2 cycles of intravenous docetaxel (75 mg/m$^2$) and cisplatin (75 mg/m$^2$) at 3-week intervals; cisplatin (75 mg/m$^2$) was administered on day 1, and docetaxel (25 mg/m$^2$) was administered on days 1, 2, and 3. Three weeks after the second NACT cycle, 13 patients underwent surgery for an extensive hysterectomy and double adnexectomy with systematic pelvic lymph adenectomy, and 29 patients underwent concurrent CRT.

### Statistical analysis

The data analysis was performed using SPSS (IBM SPSS for Windows, Version 19.0, Chicago, IL, USA) and MedCalc (Version 13.1, Mariakerke, Belgium). Values are expressed as the mean ± standard deviation (SD). A $P < 0.05$ was considered statistically significant.

The age and tumor size of the responders versus the nonresponders were compared, using an independent samples *t*-test, as were the differences and changes in IVIM-derived variables and ADC values. The disease incidence at various clinical stages between responders and nonresponders was compared using the Chi-square test (4-fold table). In addition, receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of the significant parameters for discriminating responders from nonresponders.

The intraobserver variability for quantitative measures was assessed using Bland–Altman's coefficient of variation, which is defined as the ratio of the absolute difference between two measurements to the mean value of the measurements. In this study, we defined a coefficient of variation of <10% as clinically acceptable.

## Results

### Patient characteristics

Three weeks after the second NACT cycle, 24 patients were identified as responders (CR, 3 cases; PR, 21 cases), and 18 patients were identified as nonresponders (stable disease, 17 cases; PD, 1 case). Figures 1 and 2 provide examples of responding and nonresponding lesions and include the ADC, D, D*, and f values before and after NACT. No significant differences were observed between the two groups in terms of the clinical characteristics [Table 1].

### Apparent diffusion coefficient and intravoxel incoherent motion value analyzes

The intraobserver variation was low, with an error of 5% coefficient of variance, indicating good agreement with the tumor contouring at different time points. The consistency of ADC, D, D*, and f values at the different time points was good. The points within the 95% limit of agreement at 3 time points (pre-NACT, 3 weeks after the first NACT cycle, and 3 weeks after the second NACT cycle) were 40/42 (95%), 42/42 (100%), 40/42 (95%) for ADC; 40/42 (95%), 40/42 (95%), and 40/42 (95%) for D; 41/42 (98%), 40/42 (95%), and 40/42 (95%) for D*; and 41/42 (98%), 40/42 (95%), and 40/42 (95%) for f.

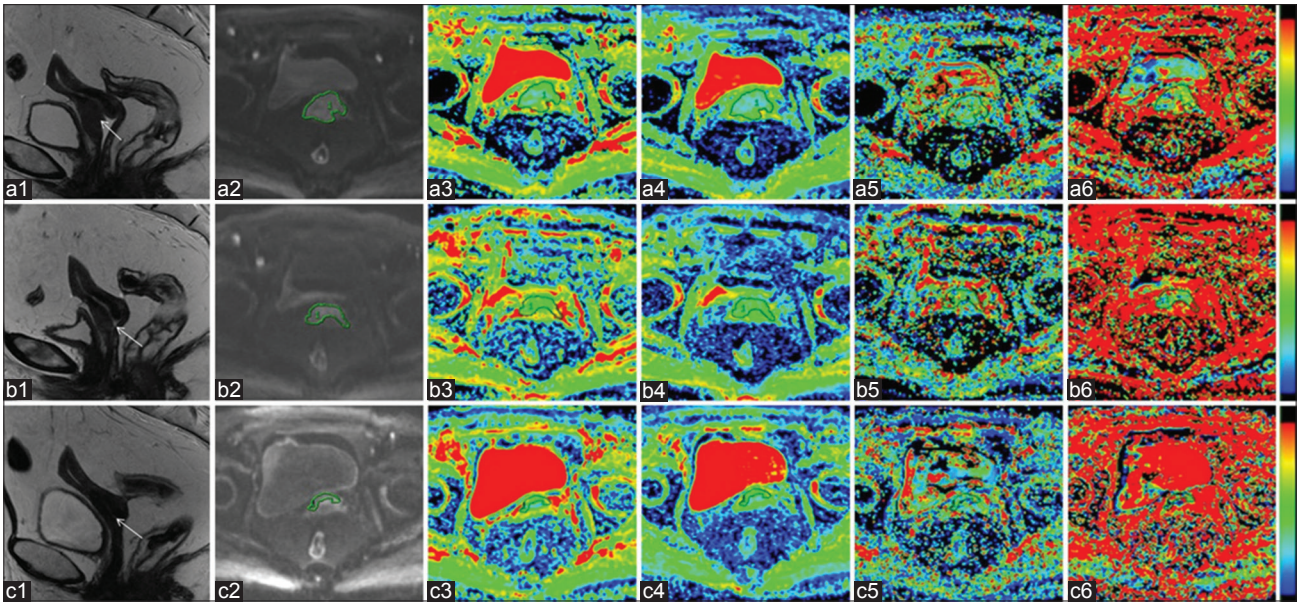


**Figure 1:** A 56-year-old woman with cervical squamous cell carcinoma (white arrow). Complete response after NACT. (a1-a6) Pre-NACT. (b1-b6) 3 weeks after the first NACT cycle. (c1-c6) 3 weeks after the second NACT cycle. (a1-c1) Sagittal T2-weighted images. (a2-c2) axial DWI with $b = 800$ s/mm$^2$. (a3-c3) axial ADC maps. (a4-c4) D. (a5-c5) D*. (a6-c6) f values. Outlines indicate the tumor region. The following values were obtained for the 3 time points: ADC: $1.24 \times 10^{-3}$ mm$^2$/s, $1.40 \times 10^{-3}$ mm$^2$/s, and $1.42 \times 10^{-3}$ mm$^2$/s; D: $0.95 \times 10^{-3}$ mm$^2$/s, $1.13 \times 10^{-3}$ mm$^2$/s, and $1.29 \times 10^{-3}$mm$^2$/s; D*: $1.30 \times 10^{-2}$mm$^2$/s, $1.84 \times 10^{-2}$mm$^2$/s, and $1.23 \times 10^{-2}$mm$^2$/s; and f: 0.161, 0.185, and 0.186, respectively. The ADC and D values of the tumor clearly increased after NACT administration. The changes in the D* and f values were not significant. NACT: Neoadjuvant chemotherapy, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient.

**Table 1: Clinical characteristics of the responder versus nonresponder cervical cancer patients**

| Parameters | Responders ($n$ = 24) | Nonresponders ($n$ = 18) | $t$ or $\chi^2$ | $P$ |
|---|---|---|---|---|
| Tumor diameter (cm), mean ± SD | 5.29 ± 2.05 | 5.24 ± 1.65 | 0.084* | 0.933 |
| Age (years), mean ± SD | 52 ± 7 | 48 ± 10 | 1.491* | 0.147 |
| FIGO stage, $n$ | | | | |
| IIA + IIB | 16 | 12 | 0.000 | 1.000 |
| IIIA + IIIB | 5 | 5 | 0.025 | 0.875 |
| IVA | 3 | 1 | 0.052 | 0.820 |

*Data represents $t$ value. SD: Standard deviation; FIGO: International Federation of Gynecology and Obstetrics.

The tumor ADC, D, D*, and f values for all 42 patients at each time point are summarized in Table 2. The ADC and D values were significantly higher at all-time points in the responders compared with the nonresponders. No significant differences in the D* and f values were observed between the two groups. The changes in the tumor ADC, D, D*, and f values during and after NACT treatment did not significantly differ between the two groups ($P = 0.297$ and 0.509 for ADC, $P = 0.178$ and 0.684 for D, $P = 0.819$ and 0.446 for D*, and $P = 0.703$ and 0.115 for f). The ROC curves of the significant parameters demonstrated good discrimination between the responders and nonresponders using the ADC and D values at the 3 time points [Figure 3].

The area under the curve (AUC) values, sensitivity, specificity, positive predictive value, and negative predictive value of the diffusion parameters (ADC and D values) at optimal cutoff values for differentiating the responders and nonresponders are shown in Table 3. The AUC values of ADC and D were compared at 3 time points, but there were no significant differences ($P$ = 0.641, 0.512, and 0.547, respectively).

## Discussion

Certain parameters are useful for predicting the response of cervical cancer to RT and CRT; these parameters include tumor volume reduction during therapy,[17] ADC,[18] and perfusion-related parameters.[19] To the best of our knowledge, few reports have evaluated the predictive power of DWI for determining the NACT outcome for cervical cancer.[8,9] Based on its molecular diffusion and perfusion properties, IVIM represents a noninvasive method for predicting treatment responses before treatment and for monitoring responses during treatment. We collected a dataset that included 42 cases of cervical cancer and evaluated the predictive value of IVIM parameters in terms of the response to NACT.

In our study, the ADC and D values differed significantly between the responders and nonresponders at the pre-NACT time point. Classically, the low diffusion values of tumors have been attributed to their increased cellular density,[20] and at the pre-NACT time point, there were no significant differences in the age, FIGO stage and tumor size between the two tumor groups. Thus, we concluded that the cervical cancers of responders may have reduced cellular density compared with those of the nonresponders, which

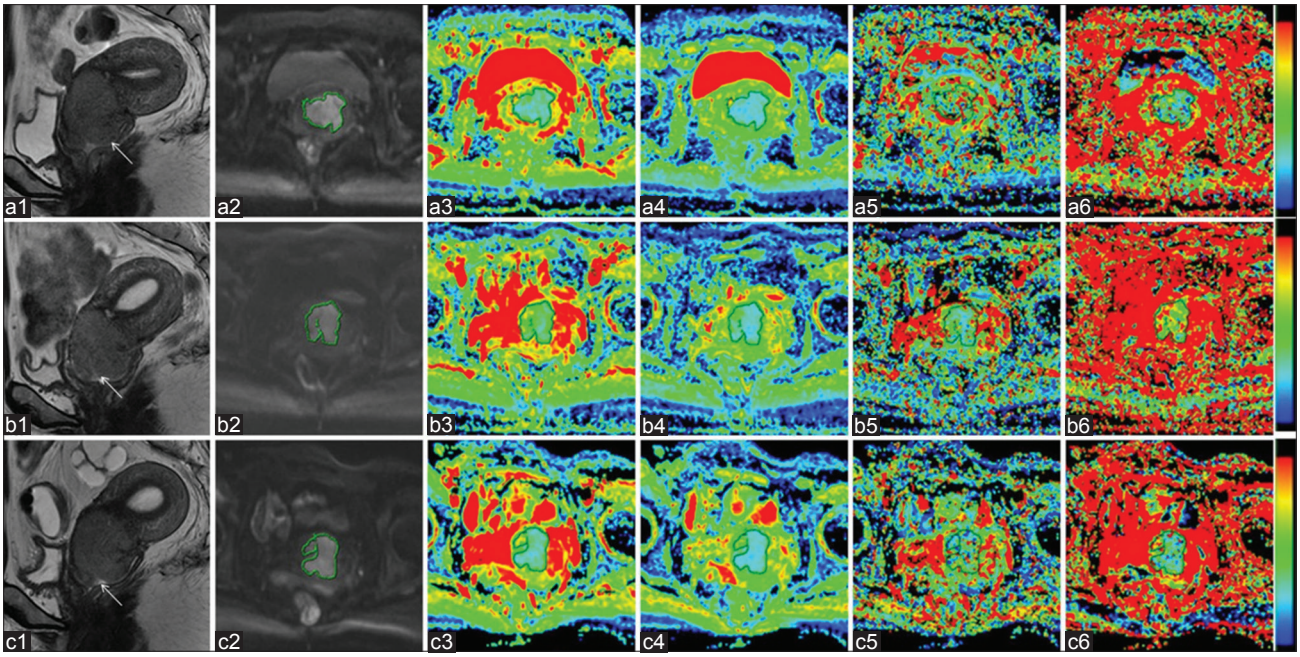


**Figure 2:** A 37-year-old woman with cervical squamous cell carcinoma (white arrow). Stable disease after NACT. (a1-a6) Pre-NACT. (b1-b6) 3 weeks after the first NACT. (c1-c6) 3 weeks after the second NACT. (a1-c1) Sagittal T2-weighted images. (a2-c2) axial DWI with $b = 800$ s/mm$^2$. (a3-c3) axial ADC maps. (a4-c4) D. (a5-c5) D*.(a6-c6) f values. Outlines indicate the tumor area. The following values were obtained for the 3 time points: ADC: $0.98 \times 10^{-3}$ mm$^2$/s, $1.21 \times 10^{-3}$ mm$^2$/s, and $0.97 \times 10^{-3}$ mm$^2$/s; D: $0.78 \times 10^{-3}$ mm$^2$/s, $0.84 \times 10^{-3}$ mm$^2$/s, and $0.79 \times 10^{-3}$ mm$^2$/s; D*: $1.63 \times 10^{-2}$ mm$^2$/s, $1.35 \times 10^{-2}$ mm$^2$/s, and $1.15 \times 10^{-2}$ mm$^2$/s; and f: 0.135, 0.185, and 0.144, respectively. The ADC and D values of the tumor increased slightly after NACT administration. NACT: Neoadjuvant chemotherapy, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient.

**Table 2: ADC and IVIM values for the responders and nonresponders at each MRI examination (mean ± SD)**

| Time point | Responders ($n$ = 24) | Nonresponders ($n$ = 18) | $t$ | $P$ |
|---|---|---|---|---|
| ADC ($\times 10^{-3}$ mm$^2$/s) | | | | |
| ADC0 | 1.200 ± 0.099 | 1.097 ± 0.085 | 3.540 | 0.001 |
| ADC1 | 1.350 ± 0.206 | 1.179 ± 0.114 | 3.176 | 0.003 |
| ADC2 | 1.344 ± 0.160 | 1.200 ± 0.107 | 3.336 | 0.002 |
| D ($\times 10^{-3}$ mm$^2$/s) | | | | |
| D0 | 0.916 ± 0.068 | 0.843 ± 0.070 | 3.414 | 0.001 |
| D1 | 1.023 ± 0.176 | 0.873 ± 0.086 | 3.323 | 0.002 |
| D2 | 1.031 ± 0.168 | 0.918 ± 0.084 | 2.618 | 0.012 |
| D* ($\times 10^{-3}$ mm$^2$/s) | | | | |
| D*0 | 17.904 ± 5.212 | 15.950 ± 3.348 | 1.389 | 0.173 |
| D*1 | 18.013 ± 5.445 | 16.152 ± 4.512 | 1.177 | 0.246 |
| D*2 | 19.858 ± 9.305 | 18.889 ± 7.469 | 0.363 | 0.719 |
| f | | | | |
| f 0 | 0.159 ± 0.041 | 0.166 ± 0.051 | 0.510 | 0.613 |
| f 1 | 0.188 ± 0.040 | 0.184 ± 0.046 | 0.294 | 0.770 |
| f 2 | 0.205 ± 0.085 | 0.172 ± 0.020 | 1.833 | 0.116 |

SD: Standard deviation; ADC: Apparent diffusion coefficient; D: The true diffusion coefficient; D*: Perfusion-related pseudo-diffusion coefficient; f: Perfusion fraction; 0 denotes the ADC and IVIM values at the pre-NACT time point; 1: The ADC and IVIM values at 3 weeks after the first NACT cycle; 2: The ADC and IVIM values at 3 weeks after the second NACT cycle; IVIM: Intravoxel incoherent motion; MRI: Magnetic resonance imaging.

may have resulted in the higher ADC and D values in responders. Moreover, the ADC values were higher than the D values, suggesting that a monoexponential model would overestimate water diffusivity within tumors as a result of "contamination" from the perfusion element in the ADC calculation.[13] These may suggest that the ADC and D values may be good early predictors of NACT responses before the utilization of RECIST. Cervical cancers with higher pretherapy ADC or D values were more likely to respond to NACT. The pre-NACT D and ADC values could indicate whether NACT should be administered when the chemotherapy regimen is docetaxel plus cisplatin. These results offer an opportunity to modify initial treatment regimens and thereby improve clinical outcomes.

In this study, we also included mid-therapy (3 weeks after the first NACT cycle) and posttherapy (3 weeks after the second NACT cycle) time points to assess the overall value of IVIM for monitoring treatment responses to NACT in cervical cancer. The ADC and D values remained significantly higher for the responders than for the nonresponders at both of these later time points. However, the changes in the tumor ADC and D values during and after treatment were not significantly different between the two groups. These observed trends in ADC and D may be attributed to the higher ADC and D values at the pre-NACT time point, or they may be related to tumor cell degeneration and necrosis resulting from chemotherapy in the responders. Therefore, the significant differences in the ADC and D values between

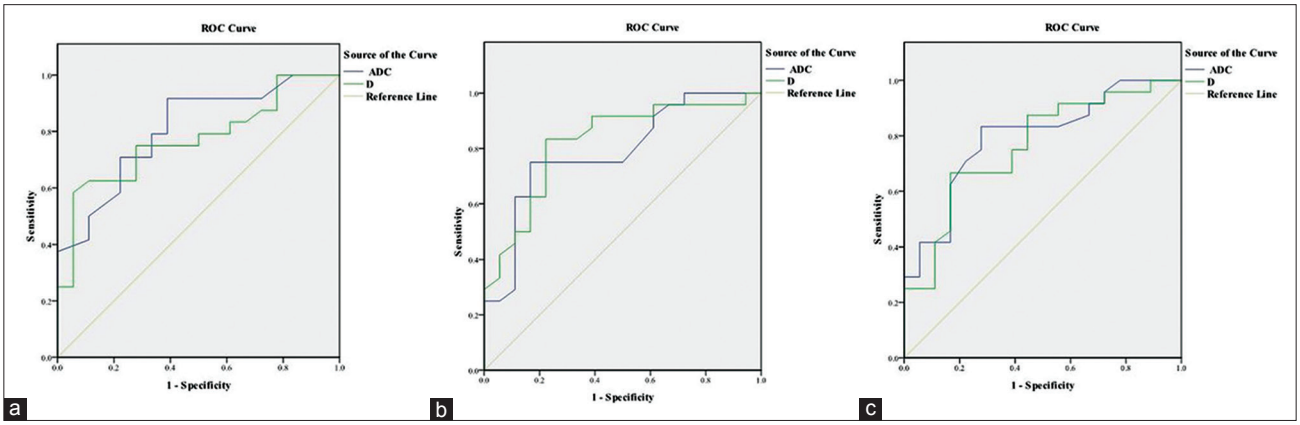


**Figure 3:** (a) ROC curves of the D and ADC values for differentiating responders from nonresponders at the pre-NACT time point. (b) ROC curves of the D and ADC values for differentiating responders from nonresponders 3 weeks after the first NACT cycle. (c) ROC curves of the D and ADC values for differentiating responders from nonresponders at 3 weeks after the second NACT cycle. NACT: Neoadjuvant chemotherapy, ADC: Apparent diffusion coefficient, ROC: Receiver operating characteristic.

**Table 3: Sensitivity, specificity, PPV, and NPV of diffusion parameters at optimal cutoff values for differentiating responders from nonresponders**

| Diffusion parameter | AUC | Optimal cutoff value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| ADC0 ($mm^2/s$) | 0.806 | $1.11\times10^{-3}$ | 91.7 | 61.1 | 93.3 | 63.0 |
| ADC1 ($mm^2/s$) | 0.787 | $1.265\times10^{-3}$ | 75.0 | 83.3 | 85.7 | 71.4 |
| ADC2 ($mm^2/s$) | 0.794 | $1.255\times10^{-3}$ | 83.3 | 72.2 | 80.0 | 76.5 |
| D0 ($mm^2/s$) | 0.771 | $0.925\times10^{-3}$ | 58.3 | 94.4 | 66.7 | 77.8 |
| D1 ($mm^2/s$) | 0.823 | $0.897\times10^{-3}$ | 83.3 | 72.2 | 83.3 | 77.8 |
| D2 ($mm^2/s$) | 0.763 | $0.966\times10^{-3}$ | 66.7 | 83.3 | 88.9 | 66.7 |

AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; ADC: Apparent diffusion coefficient; D: The true diffusion coefficient; 0: The ADC and IVIM values at the pre-NACT time point; 1: The ADC and IVIM values at 3 weeks after the first NACT cycle; 2: The ADC and IVIM values at 3 weeks after the second NACT cycle; IVIM: Intravoxel incoherent motion; NACT: Neoadjuvant chemotherapy.

the responders and nonresponders indicate that these values could be used to monitor treatment responses in cervical cancer both mid-treatment and after therapy. The changes in tumor ADC and D values during and after treatment were not significantly different between the two groups. The unfavorable results may be related to the timing of follow-up, the small number cases or other factors. A follow-up study regarding the changes in tumors is needed.

The present study did not show significant differences in perfusion-related IVIM parameters (D* and f ) between the nonresponder and responder groups. One reason for this finding may be that the choice of *b* values and the method used to calculate f and D* could influence their measurement accuracies. Cohen *et al.*[21] recommended including at least two low *b* values (<50 s/mm$^2$) when performing liver IVIM. Of note, no low *b* values (<50 s/mm$^2$) other than 0 s/mm$^2$were used in our study. Another reason for the lack of significant differences in D* may be the large standard deviations in the D* data, the data's instability and its dependence on signal-to-noise ratio levels.[22,23] The f value did not significantly differ between the two groups. In addition, the f value changes in the responders during and after treatment were higher than those of the nonresponders, but the difference was not significant. These results may indicate that greater therapy-induced changes in the f value may signify a better treatment response. Although the f value is likely dependent on various factors and complex interactions within the tumor microcirculatory network, including the abundance and permeability of capillaries, exchange surface areas, interstitial volume and interstitial fluid pressure,[13] the relationship between the response to chemoradiation, and f values requires further investigation.

The AUC values of ADC and D were compared at the 3 time points, but there are no significant differences in any of them. This suggests that the two types of models for using diffusion characteristic parameters to predict and monitor the response of cervical cancer to NACT differed very little. Therefore, we believe that the monoexponential model is adequate for clinical use and would reduce both scanning time and patients' pain.

This study has several limitations. First, the sample size was relatively small, the study included patients with different stages of cervical cancer, and our study was preliminary exploratory research. Second, NACT was somewhat effective in all of the patients; only one patient experienced disease progression during the NACT course. If more patients had shown PD, these results might have been more clinically useful. Third, we did not separate the patients by pathological type, and the proportion of patients with nonsquamous cell carcinoma was small. Finally, we chose the highest *b* value of

800 s/mm$^2$, which may have been too conservative. However, according to the literature, measurements at higher *b* values have been shown to be relatively stable and reproducible.[24] Thus, it is theoretically possible to use fewer high *b* value samplings (e.g., 2–3, >200 s/mm$^2$) and acquire more data at lower *b* values (e.g., 4 or more) to concentrate the acquisition time on the more challenging perfusion-sensitive range.[23]

In conclusion, this study shows that ADC and D values may be useful for predicting and monitoring the efficacy of NACT in cervical cancer and that their AUCs had no significant difference. Therefore, the monoexponential DWI model is adequate for predicting and monitoring the efficacy of NACT in cervical cancer.


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## Conflicts of interest

There are no conflicts of interest.

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