Intravoxel incoherent motion diffusion-weighted imaging evaluated the response to concurrent chemoradiotherapy in patients with cervical cancer

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Abstract
To evaluate the application of multiple b values diffusion-weighted imaging based on biexponential signal decay model to predict the response to concurrent chemoradiotherapy in cervical cancer patients.

This prospective study enrolled 28 patients (mean age: 50.89 ± 10.70 years) with cervical cancer confirmed by biopsy who received concurrent chemoradiotherapy. Pelvic magnetic resonance scans were performed 2 weeks before, 7 days and 21 days after the initiation of therapy, and 1 month after the end of the treatment. Diffusion-weighted imaging with b values of 0, 50, 450, and 850 s/mm² were performed, and tumor volume, means of tumor apparent diffusion coefficient ($\text{ADC}_{\text{mean}}$, $\text{ADC}_{\text{min}}$, $\text{ADC}_{\text{slow}}$, $\text{ADC}_{\text{fast}}$), and $F_{\text{fast}}$ were measured.

Pretreatment $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{slow}}$ of good outcome group were significantly higher than those of poor outcome group ($P < .05$). At the 7th day of the treatment, $F_{\text{fast}}$ and its change rate of good outcome group were significantly higher than those of poor outcome group ($P < .05$). At the 7th day and 21st day of the treatment, $F_{\text{fast}}$ showed a slowly increasing tendency with no significant difference compared with pretreatment value in poor outcome group ($P < .05$). One month post-treatment, only $\text{ADC}_{\text{slow}}$ change rate was significantly higher in good outcome group than that in poor outcome group.

Intravoxel incoherent motion-related ADC values could be utilized to better predict the outcome of cervical cancer chemoradiotherapy.

Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, IVIM = intravoxel incoherent motion, MRI = magnetic resonance imaging, T2WI = T2-weighted imaging.

Keywords: apparent diffusion coefficient, cervical cancer, chemoradiotherapy, diffusion-weighted imaging, intravoxel incoherent motion

1. Introduction
Concurrent chemoradiotherapy is now recognized as the preferred standard for advanced cervical cancer treatment.[1] Early and reliable evaluation of tumor response to the treatment, timely adjustment of treatment plan, and prevention or reduction of drug toxicity are important to improve patient survival.[2]

Conventional assessment of tumor therapy response mostly relies on morphological changes in tumor dimension. However, the changes in gross tumor size frequently lag behind cellular changes that occur earlier in responders. In addition, high signal intensity in stroma on T2-weighted image is nonspecific, and makes it difficult to differentiate between residual tumor and radiation changes, especially in the first 3 months after the completion of chemoradiotherapy.[3]

Diffusion-weighted imaging (DWI) is a unique noninvasive modality that provides image contrast dependent on intravoxel diffusion of water molecules inside the body. Effective therapy-induced apoptosis, necrosis, and increased extracellular space are associated with increased apparent diffusion coefficient (ADC).[4-6] Recently, several clinical studies have shown the potential of DWI in predicting or monitoring responses to concurrent chemoradiotherapy in cervical cancer. However, monoexponential ADC analysis quantitatively characterized only the overall diffusivity of the tissue in most studies. Intravoxel incoherent motion (IVIM) theory predicts a biexponential model of signal attenuation, with the potential to separately reflect the diffusion of water molecules and perfusion effects.[7] Recent study showed that perfusion-related parameter derived from IVIM imaging may predict prognosis in head and neck carcinomas.[8] To the best of our knowledge, no correlation for IVIM parameters during early treatment and prognosis for cervical cancer has been reported.
Therefore, this study aimed to investigate the application of multiple $b$ value diffusion-weighted imaging based on biexponential signal decay model to the evaluation of cervical cancer response to concurrent chemoradiotherapy.

2. Materials and methods

2.1. Patient population

This prospective cohort study was approved by Ethics Committee of Cangzhou Central Hospital. In all, 31 consecutive patients with cervical cancer confirmed by biopsy who scheduled to receive concurrent chemoradiotherapy were included in this prospective study from January, 2015 to January, 2016, and they provided informed consent. The inclusion criteria were as follows: primary cervical cancer, no surgery before and after concurrent chemoradiotherapy, and no contraindication to magnetic resonance imaging (MRI). Exclusion criteria were discontinuation of treatment ($n=1$, due to radiation related intestinal fistula) or withdraw of follow-up MRI scans ($n=2$). In all, 28 subjects (mean age, 47.78 years; age range, 31–69 years) included 1 clinically staged as Fédération Internationale de Gynécologie Obstétrique (FIGO) IB, 26 staged as FIGO IIB, and 1 staged as FIGO IIIB were finally enrolled in our study.

2.2. Treatment

All patients were treated with pelvic external beam radiotherapy (EBRT) combined with intracavitary brachytherapy. EBRT was delivered at a daily dose of 180 cGy, 5 times per week, for a total dose of 5040 cGy (28 times in total). Chemotherapy started at the commencement of radiotherapy (day 1) with concurrent weekly cisplatin administration at 40 mg/m². Intracavitary brachytherapy was delivered once a week with a fractional dose of 600 cGy at point A, for a total dose of 3000 cGy (5 times in total).

2.3. Follow-up

Pelvic MRI was performed within 2 weeks before therapy, 7 days and 21 days after the therapy initiated (during treatment), and 1 month after the treatment completed. Tumor residue was determined by cervical biopsy 1 month after the treatment completed. Follow-up evaluation including clinical evaluation (vaginal speculum, cervical palpation, thinprep cytologic test, or cervical biopsy) with or without imaging examinations was performed after the completion of the therapy. Average follow-up was 12.7 months (range 9–25.5 months). Patients were divided into 2 groups based on the final outcome: good prognosis group (without pathological tumor residue, no recurrence or metastases during follow-up) and poor prognosis group (with pathological tumor residue or development of recurrence/metastases).

2.4. Scanning protocol

The patients were imaged using 3.0 T MR scanner (Discovery 750W, GE Healthcare, Milwaukee, WI) with an 8-channel phased-array body coil. Axial diffusion-weighted images were acquired using a single-shot echo-planar imaging (SS-EPI) sequence with the coverage of entire uterus and cervix. Imaging parameters of DWI with multi-$b$ values (0, 50, 200, 450, and 850 s/mm²) were as follows: repetition time (TR)/echo time (TE), 3500 minimum ms; number of excitations (NEX), 8; matrix, 128 × 128; field-of-view (FOV), 24 cm; slice thickness, 5 mm; slice interval, 0 mm. The routine images included sagittal T2-weighted fast spin-echo (FSE) sequences (TR/TE, 3500/130 ms; slice thickness, 6 mm; slice interval, 0 mm; FOV, 26 cm; matrix, 288 × 224; NEX, 4), axial T2-weighted FSE sequences (TR/TE, 4000/130 ms; slice thickness, 5 mm; FOV, 26 cm; matrix, 320 × 224; NEX, 4), coronal T2-weighted FSE sequences (TR/TE, 4000/130 ms; slice thickness, 6 mm, slice interval, 0 mm; FOV, 30 cm; matrix, 288 × 224; NEX = 4), axial T1-weighted FSE sequences (TR/TE, 45/10 ms; slice thickness, 6 mm; slice interval, 1 mm; FOV, 26 cm; matrix, 288 × 192; NEX = 2).

2.5. ADC measurement

Image postprocessing was performed using the workstation (GE Healthcare, AW4.5) by 1 radiologist with 5 years’ experience in pelvic MRI. Free hand regions of interest (ROIs) ($\geq 50 \text{mm}^2$) were manually drawn around entire lesions excluding hemorrhagic, necrotic, or cystic regions on each consecutive tumor slice of ADC maps with reference to corresponding T2-weighted imaging (T2WI). MADC software of workstation was used for the calculation of IVIM-derived parameters. Biexponential equation $S(b)/S(0) = F_{diff} \exp(-ADC_{fast} b) + (1 - F_{diff}) \exp(-ADC_{slow} b)$ was used for the calculation. Multi-$b$ value DWI images were input into the software, and free hand ROIs ($\geq 50 \text{mm}^2$) were manually placed within the solid components of tumour. The average values of minimum-ADC, mean-ADC, slow-ADC, fast-ADC, and fast-diffusion fraction ($ADC_{min}, ADC_{mean}, ADC_{slow}, ADC_{fast}, \text{and } F_{fast}$, respectively) obtained from all tumor slices were measured. ROIs were placed on the tissue in the original tumor area recognized from the pretreatment images if there was no visible tumor residue after therapy. ADC change rate after treatment was calculated according to the following equation: $(ADC_{post} - ADC_{pre})/ADC_{pre}$.

2.6. Tumor volume measurement

In the baseline MRI examination, during treatment and 1-month follow-up MRI examination, lesions were manually delineated on each consecutive tumor slices of T2-weighted sequence by 1 radiologist with 5 years’ experience in pelvic MRI imaging, then tumor volume was automatically calculated by 3D MIP software on a GE workstation (AW 4.5, GE Healthcare). If tumor was invisible, tumor volume was considered as 0 cm³.

2.7. Statistical analysis

The SPSS for windows 17.0 software was used for statistical analysis. Independent $t$ test was used to compare tumor volume in patients with different outcome. Repeated-measures analysis of variance was used to analyze the changes of ADCs and tumor volume during follow-up. In addition, both intergroup and intragroup comparisons were evaluated by multifactor analysis of variance. $P$ value less than .05 indicated a statistically significant difference.

3. Results

3.1. Treatment outcome

Of the 28 patients, 22 patients presented good prognosis. Other 6 patients presented poor prognosis, 4 had tumor residue at 1-month post-therapy biopsy, 1 developed lumbar vertebral metastasis confirmed by needle biopsy 3 months after the treatment completed, 1 developed peripheral soft tissue of
urethral orifice metastasis detected by MRI examination 6 months after the treatment completed. Among 4 $b$ values (0, 50, 450, and 850 s/mm$^2$) used for DWI, the images showed the most significant differences between normal and cancer tissues at $b$ value of 850 s/mm$^2$, and the representative images of patients with good and poor prognosis outcome were shown in Figs. 1 and 2, respectively.

3.2. Comparison of tumor volume

There was no statistical difference in tumor volume between 2 groups before therapy ($t=0.115, P=.909$). Tumor volume during treatment and tumor-shrinkage rate 1 month after completion of therapy were not significantly different between 2 groups. Only 4 (4/28, 14.3%) patients presented tumor residual
on their 1-month follow-up MRI images, with the average residual tumor volume of $2.774 \pm 0.543\, \text{cm}^3$.

### 3.3. Comparison of $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{mean}}$

The $\text{ADC}_{\text{min}}$ value before treatment was significantly higher in good prognosis group than in poor prognosis group. However, there was no statistical difference in pre-$\text{ADC}_{\text{mean}}$ value between good and poor prognosis group. The changes of $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{mean}}$ after treatment were both not significantly different between 2 groups. During treatment and 1 month after conclusion of therapy, $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{mean}}$ continuously elevated, but there was no statistical difference in ADCs for different outcome group. Change rates of $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{mean}}$
were not significantly different between 2 groups during follow-up (Tables 1–3).

3.4. Comparison of IVIM-derived parameters

Before treatment, ADC\textsubscript{slow} was significantly higher in good prognosis group than in poor prognosis group. ADC\textsubscript{slow} in good prognosis group 21 days after the initiation of therapy was significantly higher than that before treatment. During treatment, ADC\textsubscript{slow} and the change rates in ADC\textsubscript{slow} were not significantly different between 2 groups. The change rates in ADC\textsubscript{slow} of good prognosis group were significantly higher than that of poor group 1 month after the completion of therapy (Tables 1–3).

The ADC\textsubscript{fast} and the change rates in ADC\textsubscript{fast} before and after treatment were not significantly different between 2 groups. There was no significant difference in F\textsubscript{fast} between 2 groups before treatment. F\textsubscript{fast} and the change rates in F\textsubscript{fast} were significantly higher in good prognosis group than in poor prognosis group 7 days after the initiation of therapy. F\textsubscript{fast} in good prognosis group during treatment was significantly higher compared with the baseline F\textsubscript{fast}. There was no statistical difference in F\textsubscript{fast} before and after therapy in poor prognosis group, although an increase trend was observed. Both F\textsubscript{fast} and the change rates in F\textsubscript{fast} showed no statistically differences between 2 groups 1 month after completion of therapy (Tables 1–3).

4. Discussion

Apparent diffusion coefficient was sensitive to the changes in cellular structure after therapy and could provide an early noninvasive indicator of treatment efficacy.\cite{10} With the application of EPI sequence, DWI can be used to assess the response of different body tumors to therapy.\cite{10,11,12} Several previous studies have reported the role of pretreatment ADC in predicting therapeutic efficacy for patients with cervical cancer, but the conclusion has not reached a consensus.\cite{13,14,15,16}

In the current study, pretreatment ADC\textsubscript{mean} of cervical cancer patients with good outcome was significantly higher than that of those with poor outcome. ADC\textsubscript{mean} before therapy did not significantly correlate with tumor response, consistent with previous results.\cite{13,14,15,16} Higano et al.\cite{17} found that ADC\textsubscript{mean} was associated with prognosis of malignant astrocytomas. To our knowledge, there was no published report on ADC\textsubscript{mean}-based predicting treatment outcome of cervical cancer.

Signal decay of DWI is influenced not only by molecular diffusion but also by microcapillary diffusion.\cite{18} IVIM-derived parameters can be obtained with biexponential fitting of multi-b value DWI. Schwarz et al.\cite{19} speculated that biexponential signal decay could reflect water populations in different binding states. ADC\textsubscript{fast} was associated with blood velocity, whereas F\textsubscript{fast} was linked to blood volume in the IVIM model.\cite{20} It was reported that ADC\textsubscript{slow} of water molecules in tissues was about 1 × 10\textsuperscript{-3} mm\textsuperscript{2}/s, whereas ADC\textsubscript{fast} was about 10 × 10\textsuperscript{-3} mm\textsuperscript{2}/s and 70 × 10\textsuperscript{-3} mm\textsuperscript{2}/s in the brain and liver, respectively.\cite{21,22} We speculated that the lowest ADC minimally affected by perfusion contamination, so ADC\textsubscript{min} similar to ADC\textsubscript{slow} were significantly different between good and poor outcome groups before therapy.

In this study, ADC\textsubscript{slow}, ADC\textsubscript{fast}, and F\textsubscript{fast} increased in the process of chemoradiotherapy. F\textsubscript{fast} during treatment in good outcome group were significantly higher compared with pretreatment, whereas F\textsubscript{fast} gradually increased in poor outcome group, which were not significantly higher than that of pretreatment, may be due to insensitivity to chemoradiotherapy because of continuous hypoperfusion during therapy. Yamashita et al.\cite{23} indicated that well-perfused area of cervical cancer was mainly composed of abundant cancer cell fascicles, whereas

| Table 1 | Comparison of ADC values in different outcome groups before and 7 days after therapy. |
|---------|---------------------------------------------------------------------|
| ADCs ($\times 10^{-6}$ mm$^2$/s) | Before therapy | 7 days after therapy | P | Good | Poor | Good | Poor |
| $+$ | $-$ | $+$ | $-$ | | | | |
| ADC\textsubscript{min} | 659.4±79.87 | 556.2±139.4 | .025 | 730.5±93.30 | 671.3±129.5 | .174 |
| ADC\textsubscript{mean} | 977.5±96.42 | 994.5±216.8 | .778 | 1096.3±74.84 | 1148.7±161.5 | .255 |
| ADC\textsubscript{fast} | 13.76±2.501 | 12.32±4.001 | .174 | 14.72±1.930 | 14.40±3.980 | .754 |
| ADC\textsubscript{fast} | 784.3±80.90 | 673.0±68.59 | .005 | 824.0±143.9 | 736.0±49.73 | .074 |
| F\textsubscript{fast} | 0.209±0.057 | 0.223±0.020 | .503 | 0.297±0.064 | 0.241±0.027 | .036 |

The data are expressed as means±standard deviations.

Good=good outcome group, Poor=poor outcome group.

$+$ADCs were significantly different between good and poor outcome groups at the same time point.

$-$ADCs were significantly different before or after treatment compared with the baseline in the same group.

| Table 2 | Comparison of ADC values in different outcome groups 21 days and 1 month after therapy. |
|---------|---------------------------------------------------------------------|
| ADCs ($\times 10^{-6}$ mm$^2$/s) | 21 d after therapy | 1 mo after therapy | P | Good | Poor | Good | Poor |
| $+$ | $-$ | $+$ | $-$ | | | | |
| ADC\textsubscript{min} | 1019.3±148.7 | 849.8±147.8 | .056 | 1022.5±161.57 | 1014.8±179.3 | .870 |
| ADC\textsubscript{mean} | 1391.5±190.4 | 1263.2±150.2 | .065 | 1511.6±71.90 | 1537.9±131.5 | .499 |
| ADC\textsubscript{fast} | 16.77±2.653 | 15.85±5.659 | .449 | 12.63±2.670 | 11.82±2.469 | .488 |
| ADC\textsubscript{fast} | 878.4±143.7 | 778.2±72.92 | .060 | 713.2±140.0 | 799.8±105.8 | .100 |
| F\textsubscript{fast} | 0.325±0.083 | 0.283±0.084 | .202 | 0.302±0.041 | 0.282±0.017 | .318 |

The data are expressed as means±standard deviations.

Good=good outcome group, Poor=poor outcome group.

$+$ADCs were significantly different before or after treatment compared with the baseline in the same group.
poorly perfused area was composed of fibrous tissue with scattered cancer cells. It was reported that hypoperfusion volume of cervical cancer derived from DCE imaging before and during therapy significantly predicted unfavorable disease specific survival. Chandarana et al. found that Flast of renal enhancing masses was significantly higher than that of non-enhancing renal masses, and there was a correlation between Flast and percent enhancement. Heusch et al. revealed a significant correlation between renal allograft perfusion and Flast originated from IVIM imaging. Thus, Flast can provide information on tissue vascularity. Vincens et al. suggested that the evaluation of residual tumor 3 to 8 weeks after chemoradiotherapy with MRI was difficult and the risk of false-positive was high. Our study found that change rate of ADCslow 1 month after therapy was helpful to predict the outcome of cervical cancer treatment. Seierstad et al. monitored ADC changes of colorectal tumor model after irradiation and correlated ADC with necrosis and/or edema after irradiation. Therefore, we speculate that the change rate of necrosis may be reflected by different ADCslow between good and poorly outcome groups.

Several limitations of our study should be mentioned. First, sample size was relatively small, especially for cervical cancer patients with poor outcome. Larger cohort study would be required to further verify our results. Second, the follow-up was short. Third, the evaluation of Flast derived from only 4 b values may be inaccurate. More b values would be recommended in future studies. Fourth, signal intensity of peritumoral edema was significantly different between good and poor outcome group at the same time point.

| Table 3 |
| Change rate of ADCs during and after therapy in different outcome groups. |
| | Good (n=35) | Poor (n=32) | p-value |
| **ADCs** | 7 d after therapy | 21 d after therapy | 1 mo after therapy |
| ΔADCmin | 0.122 ± 0.127 | 0.102 ± 0.120 | .815 | 0.579 ± 0.304 | 0.417 ± 0.232 | .588 | 0.607 ± 0.368 | 0.677 ± 0.247 | .758 |
| ΔADCmean | 0.125 ± 0.055 | 0.179 ± 0.153 | .591 | 0.428 ± 0.169 | 0.392 ± 0.205 | .315 | 0.560 ± 0.187 | 0.608 ± 0.374 | .795 |
| ΔADCfast | 0.102 ± 0.240 | 0.184 ± 0.152 | .436 | 0.262 ± 0.342 | 0.295 ± 0.305 | .514 | 0.049 ± 0.292 | 0.009 ± 0.188 | .751 |
| ΔADCslow | 0.056 ± 0.163 | 0.098 ± 0.064 | .552 | 0.125 ± 0.147 | 0.168 ± 0.170 | .529 | -0.074 ± 0.254 | 0.200 ± 0.297 | .023 |
| ΔFlast | 0.478 ± 0.373 | 0.092 ± 0.177 | .022 | 0.597 ± 0.374 | 0.285 ± 0.409 | .087 | 0.516 ± 0.321 | 0.269 ± 0.113 | .070 |

The data are expressed as means ± standard deviations. Good = good outcome group; poor = poor outcome group.

5. Conclusions

In conclusion, our results suggest that compared with anatomical characteristics, IVIM-related ADC values may be utilized to better predict the outcome of cervical cancer patients after chemoradiotherapy, but a prediction model based on these values should be developed to determine the accuracy of the prediction.

Author contributions

Conceptualization: Fenghai Liu.
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