Research Article

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The Value of Diffusion-Weighted Magnetic Resonance Imaging in Predicting the Efficacy of Radiation and Chemotherapy in Cervical Cancer

Abstract: Background: To analyze the application value of apparent diffusion coefficient (ADC) and exponent apparent diffusion coefficient (EADC) in evaluating the efficacy of radiation and chemotherapy in cervical cancer using pre- and posttreatment diffusion-weighted magnetic resonance imaging (DW-MRI) scans. Methods: 52 patients with cervical cancer were administered radiation and chemotherapy. Both MRI and DW-MRI were obtained at different stages. The ADC and EADC values, as well as the maximum tumor diameter, were measured and analyzed. Results: We found that the ADC value increased after treatment, and the EADC value decreased. Changes in the calculated ADC occurred earlier than the morphologic changes of the tumors. A negative correlation was detected between reduced rates in the maximum tumor diameter two months after treatment and pretreatment ADC value (r = −0.658, P < 0.05). An ROC curve and nonlinear regression analysis showed that the formula, $y = (1525500.122x^2 − 4689.962x + 3.482) \times 100\%$, can be used to calculate the percentage of complete remission after treatment according to the pretreatment ADC value. Conclusion: Our data suggest that pretreatment ADC and EADC values are predictive of the efficacy of radiation and chemotherapy. Both ADC and EADC values during treatment were instrumental in early monitoring and dynamic observation.

Keywords: Cervical Cancer; Diffusion-Weighted Imaging (DWI); Radiation; Chemotherapy

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1 Introduction

Cervical cancer is one of the most common malignancies of the genital tract in women. With the implementation of cervical screening programs, such as the Pap test, and HPV DNA test, the incidence of cervical cancer in developed countries has decreased; however, it remains the third most common cancer in developing countries [1]. Persistent, recurrent, and metastatic cervical cancers have a poor prognosis, so cervical cancer is still a major cause of morbidity and mortality for women [2]. Multiple therapeutic modalities have been used to treat cervical cancers, including surgery, concurrent chemoradiation, targeted therapy, cell-based therapy, combined siRNA, chemotherapy, and immunotherapy [3]. In general, early-stage cervical cancer is mainly treated with surgery; however, concomitant radiochemotherapy is typically the first choice for intermediate-stage and terminal cervical cancers [4, 5].

In fact, radioresistance and drug resistance are major obstacles for patients with cervical cancer. By enhancing sensitivity, it is hoped that lower doses of radiation and drugs, will increase the survival rate and improve the quality of life [4]. A means of forecasting and monitoring the radio- and chemosensitivity for cervical cancers has become an intense area of clinical research. Studies have shown that radiosensitivity of cervical cancer is related to the apoptosis of cervical cancer cells, and mainly depends on the balance between pro- and antiapoptotic proteins. The expression of Bcl2, Bax, and p53 in cancer cells is related to the sensitivity to radiation therapy [4, 6–8]. Tumor hypoxia is also associated with radioresistance, suggesting that monitoring and manipulating the level of tumor hypoxia would be helpful for the treatment of cervical cancer and prediction of the prognosis [9–11]. Temperature also influenced the treatment effect of cancers. Interestingly, hypothermia enhanced human tumor cell radiosensitivity [12].

Studies have shown that the diffusion properties of water vary in areas of necrosis, high cellularity, inflammation, and fibrosis. Based on this mechanism, quantitative analysis of water diffusion in diseased tissues would be helpful to diagnose and predict the prognosis of diseases. Diffusion-weighted imaging (DWI) is an MRI technique widely used to quantify the movement of water molecules at a cellular level [13, 14]. Recent studies have shown that DWI could be used for the detection cancers, staging and follow-up after treatment [15, 16]. DWI can also be used to differentiate true progression and pseudoprogression of tumors after chemoradiotherapy [17, 18]. In this study, we explored the predictive value of DWI on the efficacy of radiation and chemotherapy in patients with cervical cancer.

2 Materials and Methods

2.1 Study patients

Patients with cervical cancer (n = 52) were administered concomitant radiochemotherapy in the Affiliated Hospital of Qingdao University from January 2012 to November 2014. Cervical cancers included squamous carcinoma (n = 48) and adenocarcinoma (n = 4). The average patient age was 53.3 ± 2.4 years (range, 37-75 years). The average maximum diameter was 47.2 ± 3.8 mm (range, 23-89 mm). Patients who underwent treatment prior to admission were excluded from this study.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

2.2 Radiotherapy planning and chemotherapy regimen.

All patients received concurrent chemoradiotherapy. The chemotherapy regimen was a TP (Taxol+ Cisplatin) scheme based on platinum. In detail, Cisplatin (50-70mg/m2) and Taxol aclitaxel (135-175mg/m2) were administered through intravenous drip for one to two courses. The treatment course was 4 weeks. The radiation regimen (5 times per week and 2 Gy per dosing) lasted for two weeks and the total dosage was 20 Gy.

2.3 MRI and DWI

Imaging patients was performed using a GE Signa 3.0T MR. Scanning and DWI examinations were performed at different stages, including pretreatment, 15 days after treatment, and at 1 and 2 months following treatment. Patients fasted 8–12 h before the examination. Scanning areas included the superior border of the ilium to the lower margin of the pubic bone. Imaging parameters were as follows: axial T1W TR, 300–600 ms; TE, 2–20 ms; T2W TR, 2000–8000 ms; TE, 80–150 ms; coronal T2W TR, 2000–8000 ms; TE, 80–150 ms; axial DWI TR, 2000–8000 ms; TE, 80–150 ms; depth, 6 mm; interlayer spacing, 2 mm; matrix, 230 × 256; FOV, 40 × 40; NEX, 4 times; and b value, 0.800 s/mm^2.

2.4 Imaging post-processing and measurement

The original data were uploaded to an AW 4.3 workstation and Functool software was used for further analysis. According to T2WI and DWI imaging, signal homogeneity for the ADC was selected as the region of interest (ROI), and the ADC and EADC values were measured. Based on the response evaluation criteria in solid tumors (RECIST), cases were divided into complete remission (CR), partial remission (PR), and stable disease (SD) [19].

2.5 Statistical analyses

Two independent sample *t*-test, random analysis of variance, and a Pearson correlation analysis between the 2 variables were used to analyze the data using SPSS 19.0. A *p* value of <0.05 was regarded as significant.

3 Results

3.1 Prediction of ADC for treatment efficacy in cervical cancer

Two months after treatment, MR scans showed that tumors had completely disappeared in 9 patients (CR group); partial remission was observed in 42 patients (PR group, at least a 30% decrease in the maximum tumor diameter). Less than a 30% decrease was observed in 1 patient (SD group). We did not analyze the SD group due to the small number of samples. The ADC and EADC values for the different time periods (pretreatment, 15
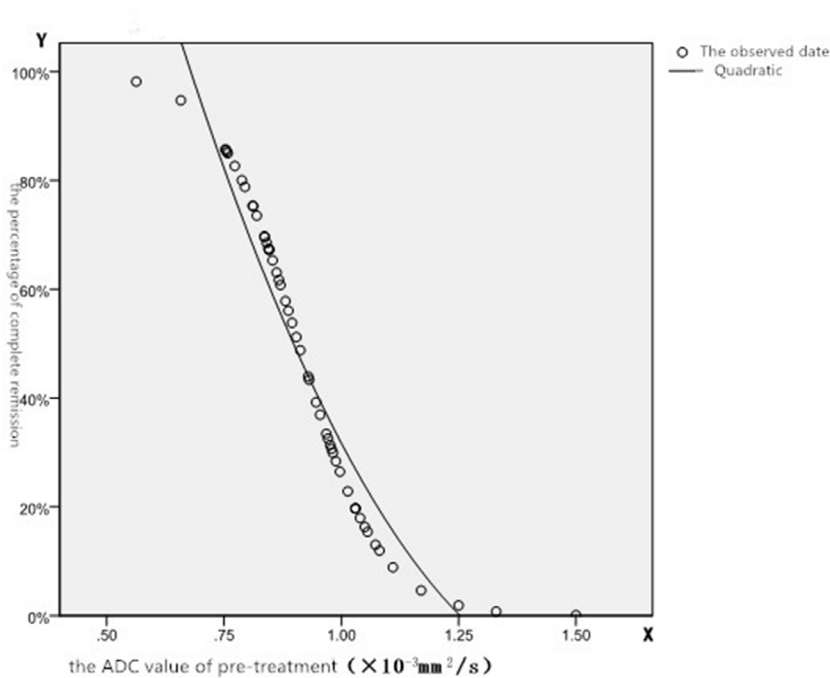
Figure 1. Relationship between the probability of CR and pretreatment ADC value
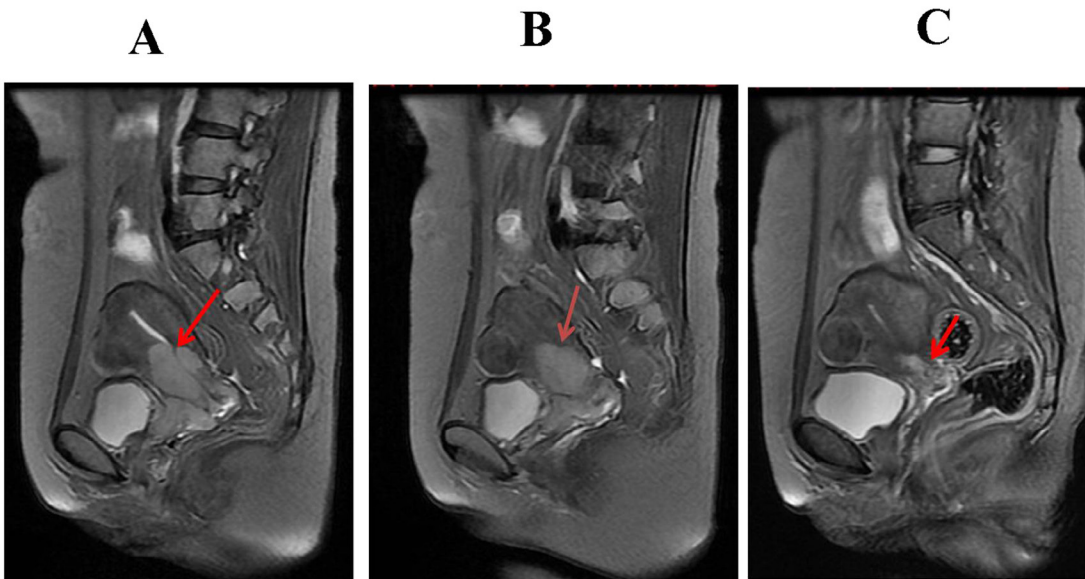

Figure 2. Representative image of cervical squamous cell carcinoma, 45-year-old female; A, B, and C are T2WI images of the patient in a sagittal position before treatment, 15 days after treatment, and 2 months after treatment, respectively. The tumor was noticeably reduced.

days after treatment, 1 month after treatment, and 2 months after treatment) are shown in Table 1. There were significant differences observed in the ADC and EADC values between the CR and PR groups before treatment ($p < 0.05$). However, no differences in ADC and EADC values were seen between CR and PR groups during and post-treatment scan. In both groups, the ADC value increased after treatment, but the EADC value decreased. The maximum ADC value in the CR group before treatment

was 0.895×10^{-3} mm^2/s. The minimum EADC value in the CR group before treatment was 0.489. The minimum ADC value in the PR group before treatment was 0.754×10^{-3} mm^2/s. The maximum EADC value in the PR group before treatment was 0.547.

An ROC curve analysis for the ADC is shown in Table 2. The value of the state variable was selected from the PR group. After ROC curve analysis, the maximum point for Youden's index (YI) was analyzed using the ROC curve

and was designated as the diagnosis point. The ADC value at this point was 0.891×10^{-3} mm^2/s, and the YI was 0.794. If the ADC value was less than, or equal to the diagnosis point, it implied that the tumor would completely disappear after treatment. If the ADC value was greater than the diagnosis point, it implied that a CR would be difficult to achieve for a patient with this tumor.

The significance of the ADC value in the CR and PR groups was assessed in a discriminant analysis, curve estimation, and nonlinear regression analysis to determine the probability that the ADC value can help predict the CR of tumors. The formula, $y = (1525500.122x^2 - 4689.962x + 3.482) \times 100\%$, can be used to calculate the percentage of CR after treatment according to the pretreatment ADC value. X represents the pretreatment ADC value (mm^2/s). Y represents the percentage of CR. The standard error was 0.079, and the probability of PR was equal to $1 - Y$.

3.2 Correlation between tumor diameter and the ADC and EADC values

The average value of the maximum tumor diameter at different stages is shown in Table 3. There was no apparent difference between 15 days after treatment and pretreatment. However, after 1 month and 2 months, the maximum tumor diameter had decreased. The ADC value increased after treatment and the EADC value decreased. The difference in the ADC and EADC values was identified 15 days after treatment and morphological changes occurred after the ADC and EADC values had changed. The average ADC value for the 52 patients before treatment was $(0.944 \pm 0.046) \times 10^{-3}$ mm^2/s. After 2 months, the decreased ratio of the maximum tumor diameter was $85.69 \pm 2.38\%$. A negative correlation was observed between the decreased maximum tumor diameter 2 months after treatment and pretreatment ADC value ($r = -0.658$, $P < 0.05$). The increase in ADC values was $40.24 \pm 3.24\%$ and $44.03 \pm 2.51\%$ at 15 days and 1 month after treatment, respectively. The ADC values were positively correlated with the reduction ratio of the maximum tumor diameter after 2 months ($r = 0.783$, $p = 0.000$; $r = 0.676$, $p = 0.001$, respectively).

4 Discussion

Radiological imaging techniques are widely used to evaluate the posttreatment tumor response; however, this evaluation is dependent on the reduction in tumor size after treatment [20].

Interestingly, the increased use of targeted therapies in advanced cancer, which typically induces necrosis

Table 1. ADC value and EADC value in different stages of treatment

Stages	CR Group		PR Group	
	ADC value (×10^{-3}mm^2/s)	EADC value	ADC value (×10^{-3}mm^2/s)	EADC value
Pretreatment	0.764±0.073	0.546±0.033	0.986±0.049	0.457±0.018
15 days after treatment,	1.703±0.044**	0.258±0.009*	1.577±0.047**	0.289±0.012**
One month after treatment	1.730±0.024**	0.251±0.005*	1.674±0.025**	0.261±0.005**
Two month after treatment	1.799±0.035**	0.237±0.007*	1.752±0.009**	0.246±0.002**

VS before treatment* p<0.05, ** p<0.01

Table 2. ROC curve analysis of ADC

Parameter	AUC	Standard error	P value	95% confidence intervals	Threshold (×10-3mm^2/s)	Sensitivity (%)	Specificity (%)
ADC	0.902	0.046	0.000	0.812~0.991	0.891	84.4	95.0

Table 3. ADC value, EADC value and the maximum tumor diameter

Stages	ADC value (×10^{-3}mm^2/s)	EADC value	Maximum tumor diameter (mm)
Pretreatment	0.944±0.046	0.474±0.017	47.21±3.83
15 days after treatment,	1.601±0.040**	0.283±0.010**	46.86±3.77
One month after treatment	1.685±0.097**	0.259±0.004**	21.57±1.50**
Two month after treatment	1.761±0.047**	0.244±0.002**	6.48±1.09**

** VS before treatment p<0.01

and cavitation, does not consistently reduce tumor size. Thus, traditional anatomical methods are not efficient to evaluate treatment efficacy [21]. DWI is a newly developed MRI technique that provides functional information regarding the behavior of water molecules in tissues [22]. Studies have shown that DWI holds promise in cancer diagnosis and outcome prediction [23–25]. In cervical cancer, DWI improved the prediction of disease progression after concurrent chemoradiotherapy (CCRT), along with T2WI [26]. As a promising tool for functional imaging, studies of cell and animal models also showed that DWI has the potential to help predict the effect of different treatments on tumors [27–30].

In this study, we found that the ADC value in cervical cancer was increased 15 days after treatment and that the EADC value was decreased. However, the maximum tumor diameter had no apparent changes, indicating that the ADC and EADC values changed before the tumor volume changed. After 15 days, there was a negative correlation between the decreased maximum tumor diameter and ADC value, suggesting that the ADC value is also an indicator of tumor diameter. In our study, the results also showed there were significant differences in the ADC and EADC values between the CR and PR groups before treatment. In fact, CR and PR groups were grouped according to the extent of tumor shrinkage, but not histopathology. There were no differences of ADC and EADC values between CR and PR groups during and posttreatment scan. This inconsistency may be related to the histopathology.

The theoretical basis of DWI in distinguishing between normal and tumor tissues lies within the difference between water diffusion in the different tissues [28]. The density of cells is also related to DWI signals and ADC values [31]. Naganawa et al. showed that the average ADC value for cervical lesions and normal cervical tissues was $1.09 \pm 0.20 \times 10^{-3}$ and $1.79 \pm 0.24 \times 10^{-3}$ mm^2/s, respectively [32]. Malignant cells proliferate robustly, and the water content inside and outside cells is increased. Protein adsorption of water is enhanced, and the volume of cells is consequently increased, and the effective movement of water in tumors is limited. Thus, the DWI signal increases, and the ADC value decreases [33]. After effective treatment, cells die or undergo apoptosis. As the integrity of the cell membrane disappears, extracellular space is increased and the density of cells decreases. The DWI signal decreased, and the ADC value increased [34]. Killing of malignant cells and protection of normal cells is the purpose of treatment. Certainly, functional changes precede morphologic changes [35], and early assessment is feasible with DWI before changes are apparent in the

tumor size. Since the ADC value of tumors is linked to their growth rates and remission after treatment, it can be used to predict the sensitivity of tumors to treatment [36]. Following treatment, the ADC value of the cervical tumors returns to norma^l [32]. DWI can be easily assessed and is more rapid. Combined with other methods, the ADC value certainly has a significant clinical value for the early monitoring of cervical cancers [37, 38].

In this study, we also analyzed the maximum point of YI using an ROC curve that was defined as the diagnosis point. The ADC value at this point was 0.891×10^{-3} mm^2/s and the YI was 0.794. If the ADC value was less than or equal to the diagnosis point, it implied that the tumor would completely disappear after treatment. If the ADC value was greater than the diagnosis point, it implied that CR would be difficult to achieve. To further analyze the probability that the ADC value could predict the ability of a tumor to achieve a CR, the significant ADC value in the CR and PR groups was assessed using a discriminant analysis, curve estimation and nonlinear regression. The derived formula, $y = (1525500.122x^2 - 4689.962x + 3.482) \times 100\%$, could be used to calculate the likelihood of CR after treatment according to the pretreatment ADC value. A standard error of 0.079 was calculated. According to the formula, the probability of CR could be determined. It holds great value in predicting the sensitivity of cervical cancers to radiation and chemotherapy. In fact, Meng J et al reported that pre- and mid-treatment whole-lesion ADC histogram and texture analysis hold great potential in predicting tumor recurrence of advanced cervical cancer treated with concurrent chemo-radiotherapy [39]. Certainly, our results and other studies suggest ADC value and EADC values are useful for the prediction of cervical cancer treatment efficacy and recurrence .

Although there were limitations in this study, including the small number of samples, and subjectivity in measuring the diameter of tumors, our data warrant further study using a larger number of samples and optimized measuring criteria to explore a new grouping standard. Indeed, our data provide strong evidence for the quantitative prognostic value of ADC and EADC during cervical cancer treatment.

5 Conclusion

In this study, we observed that changes in ADC values preceded changes that occurred in tumors after treatment. We also found that pretreatment ADC and EADC values could be used to predict the efficacy of radiation and chemotherapy. The results from our study

further underscore the instrumental use of ADC and EADC values during treatment during early monitoring and dynamic observation.

Conflict of interest: Authors state no conflict of interest.

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