Value of diffusion-weighted MRI in assessment of surgical margin of cervical cancer after loop electrosurgical excision procedure

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Summary

Purpose of investigation: To investigate the value of magnetic resonance (MR) diffusion-weighted imaging (DWI) and its derived parameter of apparent diffusion coefficient (ADC), in evaluating surgical margin for cervical cancer after loop electrosurgical excision procedure (LEEP). *Materials and Methods:* The authors included 50 cervical cancer patients as the LEEP group and 70 patients with no cervical lesions as the control group. All patients underwent routine pelvic MR and DWI examinations. The LEEP group was separated into two subgroups according to histopathological study results, i.e., negative surgical margin group and positive surgical margin group. The ADC values were calculated and compared between different groups. ROC curve was employed to investigate the discriminatory capability of the ADC values. *Results:* The mean ADC values in the control group, the negative surgical margin, and the positive surgical margin group were $1.393 \pm 0.199 \times 10^{-3}$ mm^2/S, $1.259 \pm 0.157 \times 10^{-3}$ mm^2/S, and $0.961 \pm 0.179 \times 10^{-3}$ mm^2/S, respectively. Significant difference was observed between any two of the three groups ($p < 0.01$). *Conclusion:* The application of DWI with ADC value analysis considerably improved the differentiation of normal cervix tissue from post-treatment inflammation reaction and residual tumor in cervical cancer patients after LEEP therapy.

Key words: Cervical cancer; Magnetic resonance imaging; DWI; ADC; Loop electrosurgical excision procedure.

Introduction

Cervical cancer is the second most common gynecological disease and the third most frequent cause of cancer mortality worldwide [1]. The incidence of young patients with early-stage cervical cancer has been increasing during the past few decades [2]. Many of the young patients wish to preserve fertility and the loop electrosurgical excision procedure (LEEP) may be an appropriate treatment option for them [3-4]. After LEEP, it is vital to judge the status of surgical margin. However, some benign conditions such as necrosis, inflammation, and edema made it difficult to distinguish them from the residual cervical cancer tissue by using the traditional imaging method. Consequently, there is an urgent need for reliable indicators to measure therapeutic response.

Diffusion-weighted imaging (DWI) of magnetic resonance imaging (MRI) measures random water movement in tissue, and its derived parameter of apparent diffusion coefficient (ADC) represents direction-independent water displacement. Studies in recent years have shown that DWI plays an important role in the female pelvic imaging evaluation [5, 6], and DWI with ADC measurement is an attractive diagnostic tool for cervical cancer patients [7-9]. In the light of these considerations, the aim of this study was to assess the value of DWI with ADC values in evaluating the surgical margins of cervical cancer after LEEP.

Materials and Methods

Patients

In this study, 50 patients diagnosed with cervical cancer that underwent LEEP treatment were included in the LEEP group with mean age of 43 and age-range of 27-72 years. Seventy patients with mean age of 47 and age-range of 22-66 years were enrolled in the control group, and their clinical tests and MRI showed no cervical lesions. Among the 50 cervical cancer patients, 14 were pathologically confirmed positive resection margin, while the remaining 36 patients were negative. All the pathological results were reviewed by genito-urinary pathologists blinded to the imaging findings. All the patients signed an informed consent.

MRI protocol

All scans were performed on a 1.5T MR scanner with a pelvic phased-array coil. Before the examination, patients were required to remove any metal objects in their body, such as the contraceptive ring. The three plane location images were first obtained. MRI protocol for pelvic imaging consists of following sequences and corresponding parameters: three planar location images with a repetition time (TR) of 7 ms, echo time (TE) of 2.6 ms, and field of view (FOV) of 400 mm; sagittal fat-suppression: T2WI with a TR of 4490 ms, TE of 83 ms and FOV of 270 mm; axial fat-suppression: T2WI with a TR of 8000 ms, TE of 83 ms, and FOV of 370
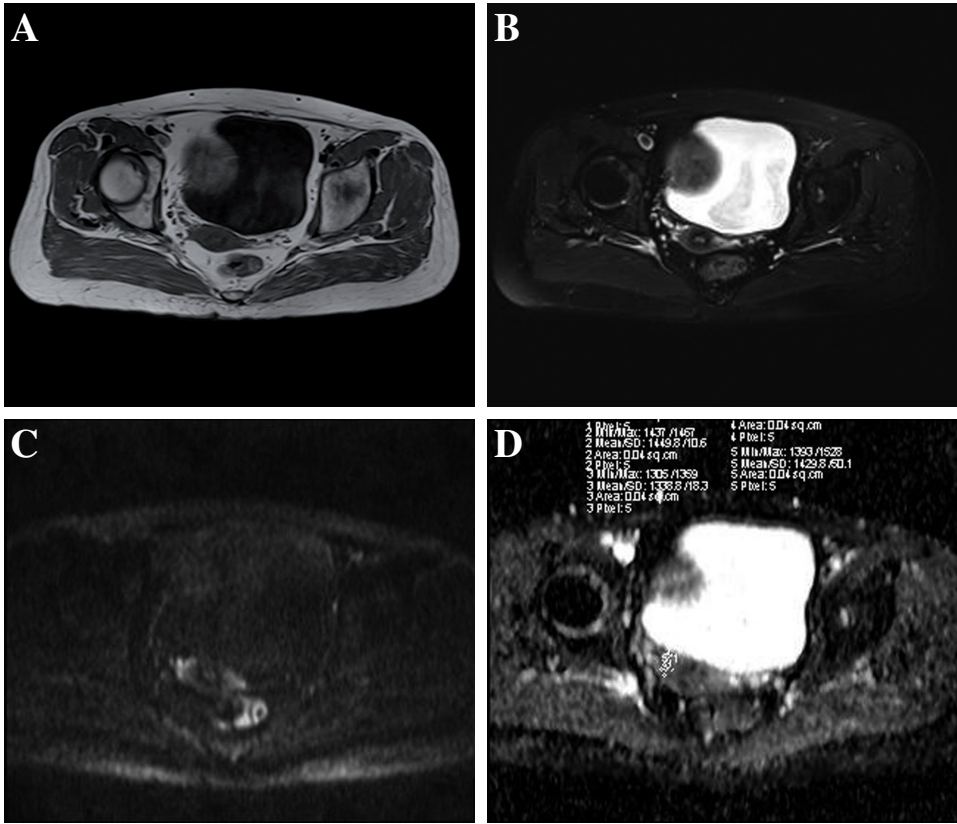
Figure 1. — MRI and ADC features in the normal cervical tissue. A: T1-weighted image shows homogeneous iso-intensity with inconspicuous delamination in cervical tissue. B: Fat-suppression/T2-weighted image shows the cervix from outside to inside: (1) medium intensity of outer zone, (2) obvious hypointensity of binding zone, (3) obvious hyperintensity of internal zone, (4) mucilage in the cervical canals which has similar hyperintensity with the mucosa of internal zone. C: DWI image shows the four structures in the cervix which is similar to the image in T2WI. D: In the ADC map, the ROIs were measured five times in the right side of cervix and the mean value of ADC was 1.378×10^{-3} mm^2/S.
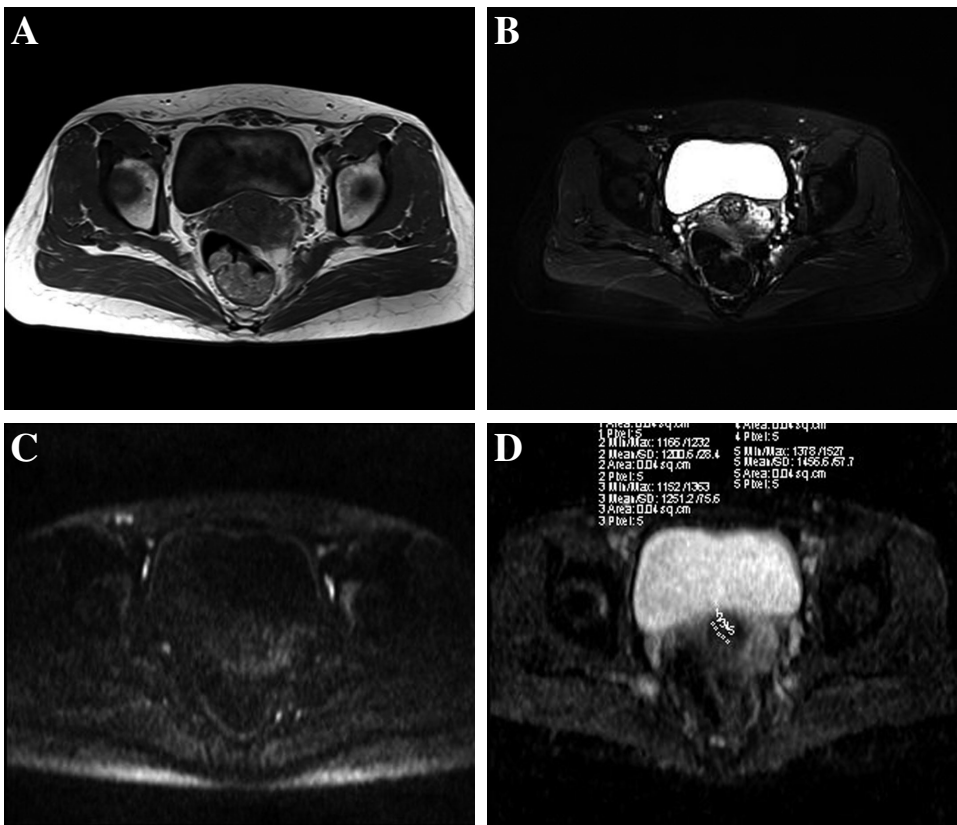

Figure 2. — MRI and ADC features in the patients with negative surgical margin after LEEP. A: T1-weighted image shows homogeneous slightly hypointensity in cervical tissue. B: Fat-suppression/T2-weighted image shows the four structures in cervix; the surgical margin presented a hyperintensity which indicated inflammation and edema. C: DWI image shows the four structures in the cervix; the hydropic margin has a hyperintensity. D: In the ADC map, the ROIs were measured five times along the surgical margin of cervix, the mean value of ADC was 1.225×10^{-3} mm^2/S.
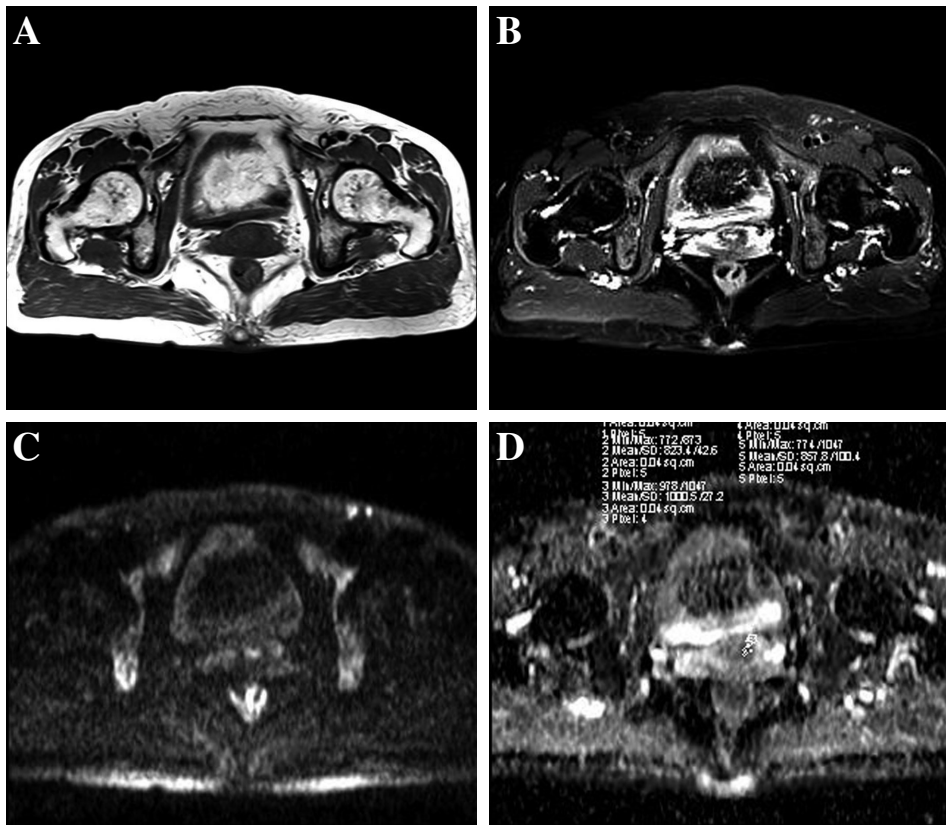
Figure 3. — MRI and ADC features in the patients with positive surgical margin after LEEP. A: T1-weighted image shows homogeneous slightly hypointensity in cervix; the focus is unobvious. B: Fat-suppression/T2-weighted image shows the four structures in cervix; the surgical margin presented a hyperintensity similar to the negative surgical margin patients after LEEP. C: DWI image shows the four structures in the cervix; the hydropic margin has a hyperintensity. D: In the ADC map, the ROIs were measured five times along the surgical margin of cervix, the mean value of ADC was 0.864×10^{-3} mm^2/S.

mm; axial turbo-spin-echo: T1WI with a TR of 627 ms, TE of 10 ms, and FOV of 350 mm; coronal fat-suppression: T2WI with a TR of 3640 ms, TE of 83 ms, and FOV of 400 mm; axial fat–suppression: T1WI with a TR of 4.89 ms, TE of 2.38 ms, and FOV of 380 mm; axial EPI-DWI with a TR of 3600 ms, TE of 83 ms and FOV of 300 mm; axial fat-suppression: T1WI after enhancement with a TR of 4.89 ms, TE of 2.38 ms, and FOV of 400 mm; sagittal fat-suppression: T1WI after enhancement with a TR of 463 ms, TE of 10 ms, and FOV of 270 mm. Contrast medium (gadopentetic acid) was injected at a dose of 0.15 mmol/kg of body weight. DWI was performed with the sequence of EPI-DWI and the b-value was chosen to be 800 s/mm^2. All images were transferred to an image workstation for quantitative analysis. ROI placement was carried out by application of hot spot analysis. The ADCs in ROI were measured five times, and the mean ADCs were calculated. In control group, the ROI was defined at the right side of the normal cervical region. The solid zone around the surgical margin was selected as the ROI in the LEEP group. Special attention was paid to avoid the areas of focal signal intensity changes, susceptibility artifacts, and necrosis.

Statistical analysis

All statistical analyses were performed using SPSS 19.0. One-way ANOVA analysis was used to analyze comparisons and a *p*-value of less than 0.05 was accepted as statistically significant. Mean ADC values in the LEEP group and control group were compared. ROC analysis was employed to investigate the discriminatory capability of the ADC values for distinguishing between the residual malignant tissue and the normal tissue. The ADC values that corresponded to the highest Youden index (Youden index = sensitivity + specificity-1) were chosen as the optimal ADC threshold values. The sensitivity, specificity, and diagnostic accuracy of selected ADC values were calculated.

Table 1. — *ADC value of the LEEP group and the control group ($\times 10^{-3}$ mm^2/S).*

	Positive surgical margin (n=14)	Negative surgical margin (n=36)	Control group (n=70)
Mean ± SD	0.961 ± 0.179	1.259 ± 0.157	1.393 ± 0.199
Minimum	0.648	0.623	0.887
Maximum	-1.352	-1.576	-1.770

Results

The MRI images of different groups are shown in Figures 1, 2, and 3. The mean ADC values of the different groups were as follows: $0.961 \pm 0.179 \times 10^{-3}$ mm^2/S for the positive surgical margin group, $1.259 \pm 0.157 \times 10^{-3}$ mm^2/S for the negative surgical margin group, and $1.393 \pm 0.199 \times 10^{-3}$ mm^2/S for the control group, respectively (Table 1). There were significant differences between any two groups of the ADC values ($p < 0.01$). The ADC values of residual malignant lesion after LEEP were significantly lower than those of the normal cervical tissue and the benign postoperative reaction (Figure 4). To confirm whether the ADC value could have served as a potential diagnostic tool in distinguishing the status of the postoperative lesion, ROC curve was performed (Figure 5). A cut-off value for residual malignant lesions of 1.078×10^{-3} mm^2/S yielded a sensitivity and
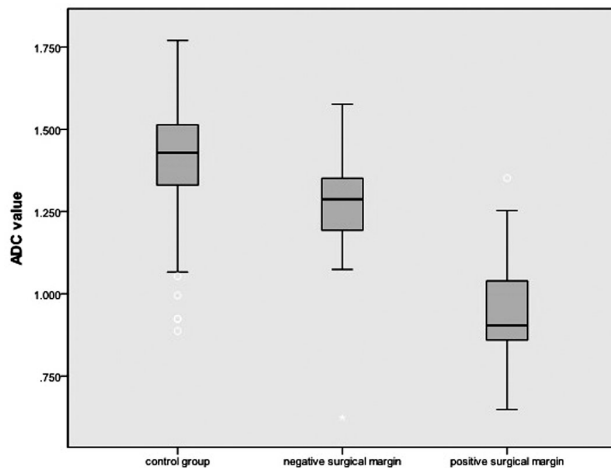
Figure 4. — The box plots compare the value of ADC between LEEP group and control group.

Figure 5. — ROC curve analysis of ADC value for discrimination between the positive surgical margin group and the control group.

specificity of 95.83% and 94.55%, respectively.

Discussion

Currently, LEEP remains the most common method in the treatment of very early stage cervical cancer [10]. The management of cervical cancer patients following LEEP is often dependent on the status of the excision margins [11].

Surveillance has been advocated to detect the residual or recurrent disease at curable stages in patients who successfully underwent LEEP [12]. The use of radiological diagnosis such as MRI is indicated on the basis of clinical suspicion [13]. Nevertheless, post-treatment changes can result in areas of fibrosis, inflammation, and edema that are also difficult to differentiate from residual malignant tissue [14, 15]. Diffusion-weighted MRI is the prevailing technique used to depict uterine malignant tumors with high conspicuity [13]. DWI also provides the ADC value of the tissues, which is considered to be influenced by the nuclear-to-cytoplasm ratio and cellular density [16]. Previous studies have revealed that DWI with ADC measurements is useful in early detection, determination of malignancy, and evaluation of treatment response [7, 9, 13, 15, 17, 18]. To the present authors' knowledge, the use of the ADC value in assessing the margin status of cervical cancer patients after LEEP has not yet been reported.

The normal cervix presented a homogeneous iso-intensity with inconspicuous delamination on T1WI and regular four structures on T2WI (Figure 2). In the present study, the residual malignant tissue had an accordant manifestation as the normal cervix in T1WI and cervical cancer tissue in T2WI, with homogeneous or inhomogeneous hyperintensity. The negative surgical margin after LEEP presented slightly hyperintensity and obvious asymmetrical augmentation in T2WI, which may attribute to the inflammation and edema.
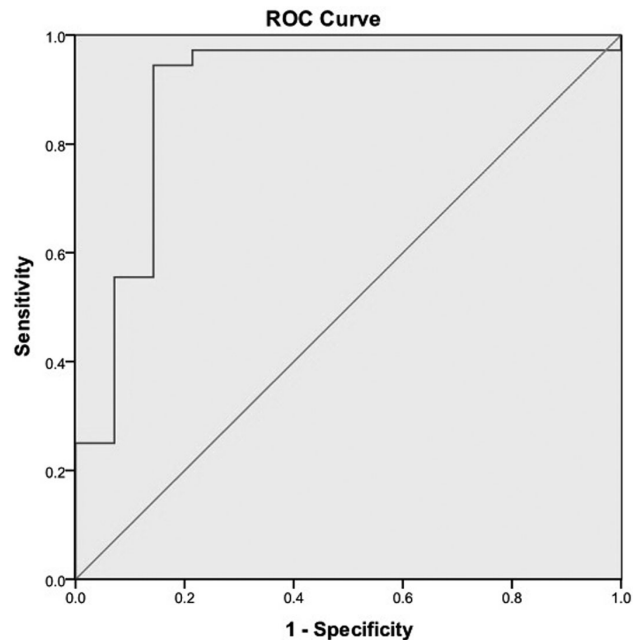
It is difficult to distinguish it from the positive surgical margin. Therefore, the accuracy of conventional MRI in assessing the margin status after LEEP seemed relatively low.

DWI is highly sensitive to cellularity, viscosity, and extracellular free water and it is completely noninvasive and does not involve exposure to ionizing radiation, as compared with other imaging methods. DWI exploits the physical principle that the degree of water diffusion in biological tissues is determined by tissue cellularity and the integrity of cell membranes. The random Brownian motion of water protons through biological tissues is impeded by the tissue architecture, and normal tissues have low cell numbers and larger extracellular spaces, which allows greater mobility of molecular water. On the other hand, tumors at various stages exhibit increasingly complex architecture with densely packed cells, altered membrane permeability, and highly restricted extracellular space, all of which impede water mobility [19]. According to the present study, inflammation and edema reaction in negative surgical margins presented high signal intensity as the residual malignant tissue do in DWI. Nevertheless, the mean ADC value of the positive surgical margin was significantly lower than the negative surgical margin (0.961×10^{-3} mm^2/S $vs.$ 1.259×10^{-3} mm^2/S). This phenomenon can be explained by the inflammation reaction which only increases the extracellular fluid which has less effect on the intracellular water movement. On the contrary, the water movement is restricted by the highly cellular tissues in the residual malignant tissue. Thus, the ADC value is of great use to distinguish the suspicious lesion. Based on

Table 2. — *Fourfold table of the diagnostic test when the ADC value is 1.078×10^{-3} mm²/S.*

		Pathology result after LEEP		Total
		Negative	Positive	
ADC value	Negative	34	2	36
	Positive	2	12	14
	Total	36	14	50

ROC curve analysis, an ADC value of 1.078×10^{-3} mm²/S is an optimal cutoff point. In the present samples, the overall accuracy for diagnosing the residual cervical cancer may have reached up to 92% (Table 2). Moreover, the authors found that the signal intensity of the negative surgical margin was higher than the normal cervical tissue in DWI. There were also significant differences between their ADC values. In the control group of this study, the average ADC value of normal cervical tissue was 1.393×10^{-3} mm²/S, which is in accordance with the range of $1.330\text{-}1.593\times10^{-3}$ mm²/S reported previously [20]. The average ADC values of the normal cervix varied between investigators which might be due to the different b-values used in different experiments. In previous studies, the b-values varied widely among different institutions when studying cervical cancer and this variability raises uncertainty regarding what is considered an ideal b-value combination in cervical ADC calculation. It was previously reported that a b-value higher than 500 S/mm² was necessary for the precise evaluation of ADCs in the female pelvic region [21]. Therefore, the present selected 800 S/mm² as the b-value in this study.

Conclusion

DWI with the ADC values is reliable in judging the property of the surgical margins with a high diagnostic accuracy. It will provide useful information in evaluating the prognosis and will generating appropriate follow-up management planning in patients undergoing LEEP treatment.

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