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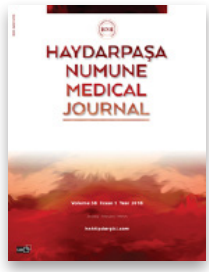

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ORIGINAL ARTICLE

Role of Apparent Diffusion Coefficient Value to Predict Locoregional Invasion and Systemic Metastasis in Cervical Cancer

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Abstract

Introduction: We questioned the relationship between apparent diffusion coefficient (ADC) values and the presence of locoregional invasion and systemic metastases in patients with cervical cancer. We aimed to evaluate the role of ADC values in predicting tumor cellularity and aggressiveness.

Methods: Forty patients with histopathologically proven cervical cancer diagnosis who applied to our center between January 2018 and January 2022 were evaluated retrospectively and included in the study. ADC values were measured from the ADC maps created from the diffusion-weighted images of the patients. In addition, invasion of adjacent organs (bladder-rectum) was evaluated with pelvic magnetic resonance examination (MRI) and distant organ metastases were evaluated, primarily by PET-CT and, if any, other scanning methods (brain MRI, bone scintigraphy) at the time of diagnosis.

Results: The mean ADC value of patients with locoregional invasion was found to be 0.89×10–3 mm^2/s, and the mean ADC value of patients without locoregional invasion was 0.96×10–3 mm^2/s. Although the mean ADC value of the patients with locoregional invasion was lower than the patients who were not detected, this difference between the two groups was not statistically significant (p=0.466). The mean ADC value of patients with systemic metastasis was 0.73×10–3 mm^2/s, and the mean ADC value of patients without systemic metastasis was 0.96×10–3 mm^2/s. The mean ADC value of patients with systemic metastasis was found to be low, close to the statistical significance level (t=1.954, p=0.058). As a result of ROC analysis, the most appropriate cutoff limit for ADC value for systemic organ metastasis was found to be 0.93 (sensitivity=59% and specificity=83%).

Discussion and Conclusion: Systemic metastasis risk and poor prognosis can be predicted by diffusion-weighted imaging and ADC values.

Keywords: Cervix cancer; magnetic resonance imaging; uterine cervix.

Cervical cancer is the second most common malignancy in the female population and is an important cause of cancer-related deaths in developing countries[1]. Magnetic resonance examination (MRI) is the gold standard imaging method in the pre-operative evaluation of cervical cancer. Diffusion-weighted examination (DWI), which was previously used in the diagnosis and follow-up of stroke, has started to be used in cancer imaging with the devel-

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opments in MR technology. Apparent diffusion coefficient (ADC) maps created from DWI imaging, and measured ADC values provide important information in the diagnosis of malignancy[2,3].

Although DWI examination is insufficient in terms of anatomical detail due to its low spatial resolution, it provides invaluable information in the functional evaluation of the tumor. Cervical cancer has lower ADC values than adjacent normal tissue planes[4].

In the studies conducted, the diagnostic value of ADC values in terms of the diagnosis, type, grade, and stage of cervical cancer was questioned, and sufficient evidence could not be reached on this subject.

In our study, we questioned the relationship between ADC values and the presence of locoregional invasion and systemic metastases in patients with cervical cancer. We aimed to evaluate the success of ADC values in predicting tumor cellularity and aggressiveness.

Materials and Methods

Patient Population

Forty patients who applied to our center between January 2018 and January 2022 were suspected of cervical cancer clinically or by transvaginal US and were diagnosed histopathologically, were retrospectively evaluated, and included in the study.

Patients who received previous treatment for cervical cancer (radiotherapy, chemotherapy, and operation history) and patients with a history of pelvic RT for any reason were excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki. Consent was obtained from the patients before contrast-enhanced MRI and our study was approved by the Ethics Committee of our hospital (2022-02/50).

MRI Protocol

MRI was performed with a 1.5-tesla scanner (Signa Explorer, GE), using a pelvic coil, with the patient in the supine position.

Since the routine pelvic MRI examination was performed with contrast, the renal disease history of the patients was evaluated and creatinine levels were measured to prevent contrast-induced nephropathy before the procedure.

The standard sequences included high-resolution sagittal T2-weighted turbo spin-echo (TR/TE=4000/80 ms, turbo factor=14, field of view=240×240 mm, matrix size=400×392, slice thickness=4 mm, intersection gap=0 mm), axial T2-weighted turbo spin-echo (TR/TE=2800/100 ms, turbo factor=12, field of view = 403 × 300 mm, matrix size=787×600, slice thickness=4 mm, intersection gap=0 mm), and T1-weighted turbo-field-echo contrast-enhanced acquisition (TR/TE=2.4/1.2 ms, field of view=350×350 mm, matrix size=212×211, slice thickness=3.0 mm).

DW-MRI was performed using single-shot spin-echo echo-planar imaging, immediately after the axial T2-weighted imaging and before intravenous contrast injection. It was acquired in free breathing with background body signal suppression (pre-saturation inversion recovery fat suppression) using the following parameters: TR/TE=2000/54 ms, field of view=403×300 mm, matrix size=168×124, slice thickness=4 mm, intersection gap=0 mm, parallel imaging with sensitivity encoding factor of 2, receiver bandwidth=1382.5 Hz per pixel. We acquired b values (0, 500, and 1000 s/mm^2) in the axial plane covering 20 slices to include the entire cervical cancer, using motion-probing gradients in three orthogonal axes.

Evaluation of MRI Images

MRI images of the patients were evaluated by two radiologists with more than 10 years of experience. ADC value measurements were made from the ADC maps created from the DWI images of the patients, using similar region of interest (ROI). Measurements were made using ROIs of similar width (5 mm^2), excluding macroscopic necrotic areas, areas adjacent to large vessels, and areas with sensitivity artifacts due to air-water transitions. The mean value was obtained by measuring at least 3 ADC values for each patient. Patients with significant measurement differences between radiologists were re-evaluated and a joint decision was made.

Invasion of adjacent organs (bladder-rectum) was questioned from MRI examinations of the patients. At the time of diagnosis, distant organ metastases were evaluated with PET-CT and other scanning methods (brain MRI and bone scintigraphy), if any.

Statistical Analysis

While evaluating the findings obtained in the study, the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed was analyzed using descriptive, graphical, and statistical methods.

The Shapiro–Wilk test was used to test the normality of the scores obtained from a continuous variable with the statistical method. In addition to descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.) while evaluating the study data, independent sample t-tests were used. The level of relationship between the two variables was evaluated with the Pearson's correlation test. In addition, ROC analysis was used to differentiate the most appropriate ADC score according to the groups. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

Results

Forty patients with histopathologically proven cervical cancer diagnosis were included in the study. The mean age of the patients was 54.93±14.60 years.

The mean ADC value of the patients was 0.93±0.28, and the mean tumor size was 42.68±18.53 mm.

The tumor type in 85% (n=34) of the patients was squamous cell carcinoma and 15% (n=6) were adenocarcinoma.

Systemic metastasis was found in 15% of the patients and locoregional invasion was found in 47.5%. The mean ADC value of the patients with locoregional invasion was 0.89×10–3 mm^2/s, and the mean ADC value of the patients without locoregional invasion was 0.96×10–3 mm^2/s. Although the mean ADC value of the patients with locoregional invasion was lower than the patients who were not detected, this difference between the two groups was not statistically significant (p=0.466).

The mean ADC value of patients with systemic metastasis was 0.73×10–3 mm^2/s, and the mean ADC value of patients without systemic metastasis was 0.96×10–3 mm^2/s. The mean ADC value of patients with systemic metastasis was found to be low, close to the level of statistical significance (t=1 .954, p=0.058) (Table 1).

According to the results of the ROC analysis, the area under the curve was found to be 0.743 (0.534–0.952) for the differentiation of systemic metastases, and accordingly, the ADC diagnostic value was found to be statistically significant ($p\leq0.05$). As a result of ROC analysis, the most appropriate cut-off limit for ADC value for systemic metastasis was found to be 0.93 (sensitivity=59% and specificity=83%).

The relationship between ADC values and parametrial involvement could not be clearly evaluated since the majority of patients who underwent MRI examination for cervical cancer had parametrial involvement.

Pre-treatment MRI of two patients with histopathologically proven diagnoses is presented in Figures 1 and 2.

Table 1. Mean ADC values by adjacent organ invasion and distant organ metastasis

		ADC value		
	n	Mean (SD)	r/t	p
Distant organ metastasis			1.954[a]	0.058
Yes	6	0.73 (0.24)		
No	34	0.96 (0.27)		
Adjacent Organ Invasion			0.737[a]	0.466
Yes	19	0.89 (0.30)		
No	21	0.96 (0.25)		

*=p<0.05, [a](t)=Independent sample t-Test,b(r)=Pearson correlation test, SD: Standard deviation.

Figure 1. (a) T2 weighted, **(b)** contrast-enhanced T1 weighted, **(c)** diffusion weighted, **(d)** ADC mapping images in a 50-year-old patient with a pathological diagnosis of SCC. Mass lesion of the cervix, approximately 5×3 cm in size, with irregular contours, no prominent parametrial extension or adjacent organ invasion, accompanied by diffusion restriction, and low ADC values.

Figure 2. (a) T2 weighted, **(b)** contrast T1 weighted, **(c)** diffusion weighted **(d)** ADC mapping images in an 81-year-old patient with pathologically proven adenocarcinoma: Large heterogeneously enhancing mass lesion starting from the cervix and involving the entire uterus, with parametrial and adnexal extension, accompanied by diffusion restriction.

Discussion

MRI, with high soft-tissue resolution, is the gold standard imaging method in the diagnosis of cervical cancer, determination of the depth of invasion, and regional spread. With these features, it also guides in treatment planning.[5] DWI, which has been used in diagnosis in recent years, provides important information to distinguish cervical cancer from normal cervical tissue and benign lymph nodes from malignant lymph nodes[6].

In studies, the diagnostic success of ADC values in the cervical cancer was evaluated. For example, Naganawa et al.[7] found that mean ADC values were significantly lower in cervical cancer compared to the control group.

McVeigh et al.[8] found lower ADC values in patients diagnosed with cervical cancer in their study, and when they compared it with FIGO staging, they found that it was lower in stages Ib and IIa than in stages IIb, III, and IV[8].

In the literature, ADC values in patients with cervical cancer with and without parametrial invasion were compared, while in some studies, no significant difference was found between the two groups;[9] in some studies, ADC values were found to be significantly lower in patients with parametrial invasion[4].

In the studies performed, DWI and ADC values were evaluated in the differentiation of malignant and benign lymph nodes in patients diagnosed with cervical cancer, and ADC values were found to be significantly lower in malignant lymph nodes[10,11].

All these studies have shown that DWI and ADC values provide important information in staging and prognosis of cervical cancer.

In our study, we evaluated the DWI and ADC values of 40 patients with histopathologically proven cervical cancer diagnosis. We questioned the relationship between the presence of locoregional invasion and systemic metastases at the time of diagnosis and ADC values. The aim of our study was to evaluate the relationship between ADC values and tumor prognosis. We did not find a significant difference between the ADC values of patients with and without locoregional invasion. We found statistically significantly lower ADC values in patients with systemic metastases. According to the results of our ROC analysis, we calculated the most appropriate ADC cutoff value as 0.93×10–3 mm^2/s in predicting systemic metastasis. We concluded that tumors with ADC values below this value may progress more aggressively and cause earlier distant metastases.

Parametrial invasion was present in almost all of the patients since we conducted the study in an oncology branch hospital and the patients included in the study were mostly referred from other centers. Therefore, we could not question the relationship between parametrial invasion and ADC values.

DWI examination is one of the most frequently used imaging methods in the diagnosis and follow-up of cervical cancer in recent years. It helps the radiologist in many issues such as lesion borders and extent, evaluation of malignancy in adjacent lymph nodes, and response to treatment. We believe that if our study is supported by multicenter studies with a large number of patients, the ADC values can also guide treatment options by predicting tumor prognosis.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki. Consent was obtained from the patients before contrast-enhanced MRI and our study was approved by the Ethics Committee of our hospital (2022-02/50).

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Conflict of Interest: None declared.

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