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Can Maximum, Mean or Minimum ADC Values of the Cervix-Parametrium Boundary Estimate Parametrial Invasion for Cervical Carcinoma?

Mine Sorkun[1*], Hande Özen Atalay[2], Afak Durur Karakaya[2]

[1]Department of Radiology, Gediz State Hospital, Kütahya, Türkiye
[2]Department of Radiology, Koç University Hospital, Koç University, İstanbul, Türkiye

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****Corresponding Author***
Mine Sorkun
Department of Radiology
Gediz State Hospital
Kütahya, Türkiye
Phone: +90 5056449714
E-mail: minealacagoz@gmail.com

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Authors' ORCIDs
Mine Sorkun
https://orcid.org/0000-0002-9474-2640
Hande Özen Atalay
http://orcid.org/0000-0003-3524-9597
Afak Durur Karakaya
http://orcid.org/0000-0003-3604-6791

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Abstract: Diffusion weighted imaging (DWI), which is quantified by apparent diffusion coefficient (ADC), can predict tissue microstructure. It has become an essential part of the gynecological magnetic resonance imaging (MRI) protocol. In our study it was aimed to evaluate the value of the maximum, mean, and minimum ADC values of the cervix-parametrium boundary to estimate parametrial invasion for cervix carcinoma. Totally 50 patients with cervical carcinoma, 18 of which had no parametrial invasion (48±11-year-old) and 32 had parametrial invasion (58±12-year-old) according to conventional T2 weighted imaging were enrolled. Maximum, mean, and minimum ADC values of cervix-parametrium boundary of primary tumors were statistically compared between the groups without and with parametrial invasion. The diagnostic performances of the maximum, mean and minimum ADC values were evaluated by ROC analysis in terms of estimating parametrial invasion. The mean maximum, mean and minimum ADC values were lower for the patients with parametrial invasion. However, only the minimum ADC values had statistically significant differences between the groups. ROC analysis showed an AUC value of 0.726 for minimum ADC in estimating parametrial invasion. A minimum ADC cut-off value of $0.553x10^{-3}$ mm^2/s had a sensitivity of 63%, specificity of 73%, negative predictive value of 52% and positive predictive value of 80% and accuracy of 66%. ADC values can be applied for the determination of parametrial invasion of cervical carcinoma. Lower minimum ADC values obtained from cervix-parametrium boundary of primary cervical carcinoma may help parametrial invasion. Especially positive predictive value of the cervix-parametrium boundary ADC is remarkable. ©2024 NTMS.

Keywords: Apparent Diffusion Coefficient; Cervix Carcinoma; Diffusion-Weighted Imaging; Magnetic Resonance Imaging; Parametrial Invasion.

1. Introduction

The staging of cervical carcinoma is determined by the revised International Federation of Gynecology and Obstetrics system (FIGO) [1]. This system incorporates multiple parameters, such as tumor size, degree of local invasion, and the existence of metastasis, in order to determine the stage of the disease [1, 2]. The involvement of the parametrium is a significant factor in determining the extent of the local spread, staging, prognosis, and treatment strategies of cervical carcinoma [3]. Parametrial invasion (PMI) is a term used

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to describe the infiltration of malignant cells into the parametrial tissues. The presence of a significant amount of lymphatic and vascular structures in the parametrium may explain the frequent association of PMI with carcinoma metastasis, recurrence, and decreased survival rate [4, 5].

Treatment options of cervical carcinoma include radical hysterectomy, primary or adjuvant chemotherapy, and radiotherapy. Cervical carcinoma patients with PMI were advised to be treated with primary chemoradiotherapy or undergo radical surgery involving the excision of the parametrium and adjuvant treatment [6]. Performing parametrectomy is not recommended in patients diagnosed with early-stage cervical carcinoma due to the increased risk of morbidity and mortality associated with complications [7]. Therefore, an accurate assessment of PMI is crucial to determine appropriate treatment. This emphasizes the significance of utilizing non-invasive techniques such as magnetic resonance imaging (MRI) to assess PMI.

T2-weighted imaging (T2-WI) has played a pivotal role in assessing cervical carcinoma stages due to its exceptional soft-tissue contrast, providing detailed anatomical information [8]. A preserved hypointense stromal rim on T2-WI is a specific finding indicating the absence of parametrial invasion, whereas focal or diffuse full-thickness disruption of the low T2 signal intensity of the cervical stromal ring is highly sensitive to parametrial invasion [9]. However, challenges emerge when dealing with larger tumors that disturb the stromal ring, or the hypointense ring is interrupted by non-tumorous tissue, such as edema. In such circumstances, it becomes hard to accurately identify parametrial invasion based solely on T2-WI, as it may be susceptible to creating false-positive findings [10]. Diffusion-weighted magnetic resonance imaging (DWI) has become a significant companion to conventional imaging techniques, providing functional information about tumor characteristics. DWI shows higher signal intensity and lower apparent diffusion coefficient (ADC) values in tumors compared to nearby normal tissue. This provides important insights on cellular density and the microstructure of the tissue [11, 12].

This study aims to investigate potential applications of DWI in evaluating PMI in cervical carcinoma. While previous studies have explored DWI in tumor detection, prognosis, and therapeutic response prediction, our research focuses on evaluating ADC values (minimum, mean, or maximum) at the cervix-parametrium boundary to determine the presence of PMI. We propose that integrating DWI into the diagnostic framework could significantly improve MRI accuracy in predicting PMI, offering valuable insights for clinical decision-making, particularly in avoiding unnecessary parametrectomy for low-risk patients in early-stage cervical carcinoma.

2. Material and Methods

The institutional review board obtained approval for this retrospective study and waived the need for informed consent.

2.1. Patient Cohort

We retrospectively reviewed our medical records and MRI scans between January 2017 and December 2021. A total of 102 patients diagnosed with cervical carcinoma were reviewed.

Exclusion criteria were as follows: (a) patients who received any chemoradiotherapy before MRI; (b) DWI sequence was not included in the MRI; (c) the presence of inadequate imaging, due to artifacts or distortion. Of the 102 patients, 6 were excluded due to insufficient MRI scans, and 46 were excluded due to a previous history of chemotherapy or radiotherapy for cervical carcinoma. Consequently, the study cohort consisted of 50 patients who had not received prior chemotherapy or radiotherapy and who had pelvic MRI scans including T2-WI and DWI. According to the T2-WI, 18 patients without parametrial invasion and 32 patients with parametrial invasion were included in the retrospective study (Fig 1).

2.2. Pelvic MRI Protocol

MR examinations were performed using a 3.0-Tesla MR scanner, equipped with a phased-array coil. In order to decrease the movement of the bowel, a dose of 20 mg of butyl scopolamine was administered before the examination. The vagina is filled with ultrasound gel if the patient can tolerate. The MRI protocol included T2-WI and DWI. Axial, sagittal, and coronal planes were obtained with a T2-weighted turbo spin-echo sequence. The axial and coronal images were oriented perpendicularly and parallel to the cervical axis, respectively. The imaging settings of T2-WI were TR/TE, 4,560–5,300/100 ms; intersection gap, 0.4 mm; matrix, 800 x 690. The DWI gradients were applied in axial and sagittal directions. The parameters for diffusion sequence were as follows: repetition time ms/echo time ms, 6800/98; FOV, 250x250 mm^2; matrix, 192x130; section thickness, 3.0 mm. Diffusion was measured with b values of 0 and 800 s/mm^2, and ADC maps were automatically created by the software.

2.3. Image Analysis and Measurement

All images were evaluated by one radiologist (ADK) with 21 years of experience in pelvic MRI. To reduce bias, the radiologist was blind to the clinical findings and histological results for each patient. The DWI and T2-WI were evaluated together on a Picture Archiving and Communication System (PACS) workstation, using the anatomical features of T2-WI. The automatic cursor placement function of the PACS workstation was utilized to facilitate the synchronization of corresponding locations on T2-WI and DWI.

The diagnostic criterion for cervical carcinoma on T2-

WI alone was a focal cervical lesion of high signal intensity compared with normal uterine myometrium. PMI on T2-WI was considered present if the cervical stromal ring was disrupted with nodular or irregular tumor signal intensity extending to the parametrium.

To determine the ADC values of the cervical tumor with or without PMI, a circular or ellipsoid region of interest (ROI) was manually placed on the ADC map (Fig 2). ROI was delineated on the ADC map to cover the largest possible extent of the primary tumor closest to the parametrial border. This was done on the slice that displayed the greatest visible size of the tumor, as determined by the anatomical features observed on T2-WI. ROIs were chosen to specifically exclude any cystic or necrotic changes within the tumors. In cases showing parametrial invasion on T2-WI, measurement was made from the point closest to the parametrium at the invasive border. The ADC values were measured twice, and the average of the two measurements was calculated to minimize error. Maximum (ADC-max), mean (ADC-mean) and minimum (ADC-min) values were recorded.

2.4. Statistical Analysis

The statistical calculations were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). The patients were classified into two groups based on the presence of PMI, as evaluated by T2-WI. Distribution was determined by the Kolmogorov-Smirnov test. Maximum, mean, and minimum ADC values of the tumors were compared by independent samples t-test between the patients without and with PMI. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance, cut-off points for the prediction of PMI, and their sensitivity and specificity values. The significance level was set as 0.05.

3. Results

Of the 102 patients reviewed, 52 were excluded due to insufficient MRI scans and previous history of chemotherapy or radiotherapy for cervical carcinoma. Ultimately, a cohort of 50 cases diagnosed with cervical carcinoma, who had not received any previous chemotherapy or radiotherapy treatments and had completed pelvic MRI scans that contained T2WI and DWI, were included in the study. The retrospective study included 18 patients (48±11-year-old) without parametrial invasion and 32 patients (58±12-year-old) with parametrial invasion, as determined by the T2-WI. The patients with PMI had ADC-max of 1.16±0.22, ADC-mean of 0.72±0.19, and ADC-min of 0.48±0.13. Whereas the patients without PMI had ADC-max of 1.24±0.21, ADC-mean of 0.83±0.18, and ADC-min of 0.62±0.11. The patients with parametrial invasion showed lower maximum, mean, and minimum ADC values, with corresponding p-values of 0.709, 0.059, and 0.019, respectively (Table 1, Fig 3). Only the minimum ADC values were significantly different between the groups (p=0.019).

Table 1: Comparison of ADC values between the patients with and without parametrial invasion.

Variables *(10^{-3} mm²/s)*	**Parametrial invasion (+) (n=32)**	**Parametrial invasion (-) (n=18)**	***p* value**
ADC-max	1.16 ± 0.22	1.24 ± 0.21	0.709
ADC-mean	0.72 ± 0.19	0.83 ± 0.18	0.059
ADC-min	0.48 ± 0.13	0.62 ± 0.11	0.019

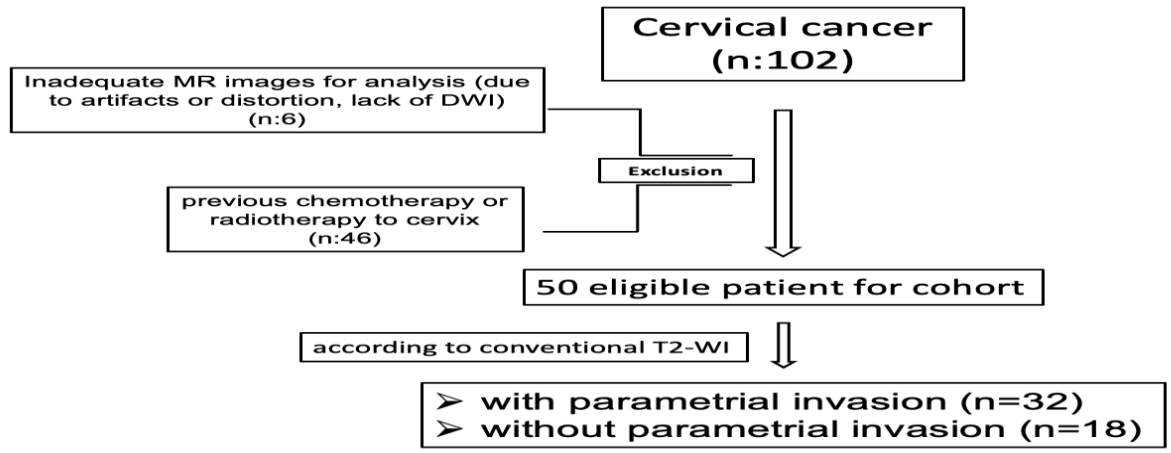

Figure 1: Flowchart of the study.

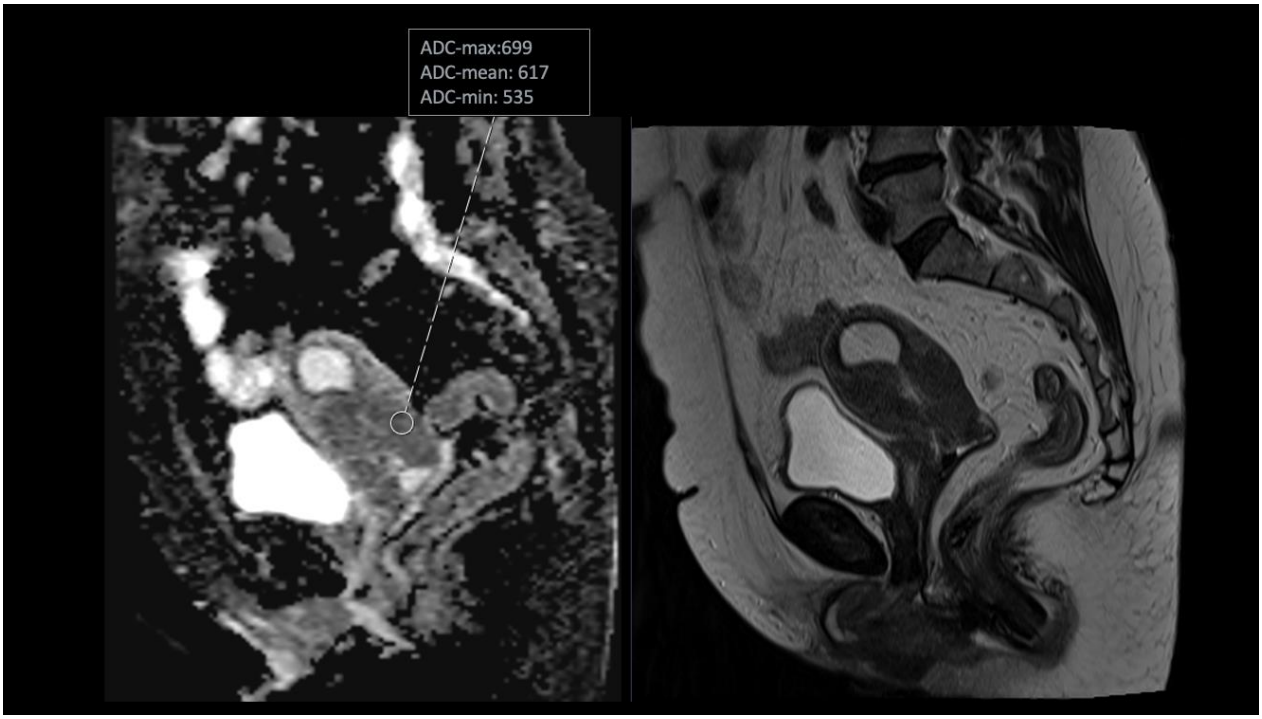

Figure 2: Placing ROI on ADC map and corresponding images on T2-WI.

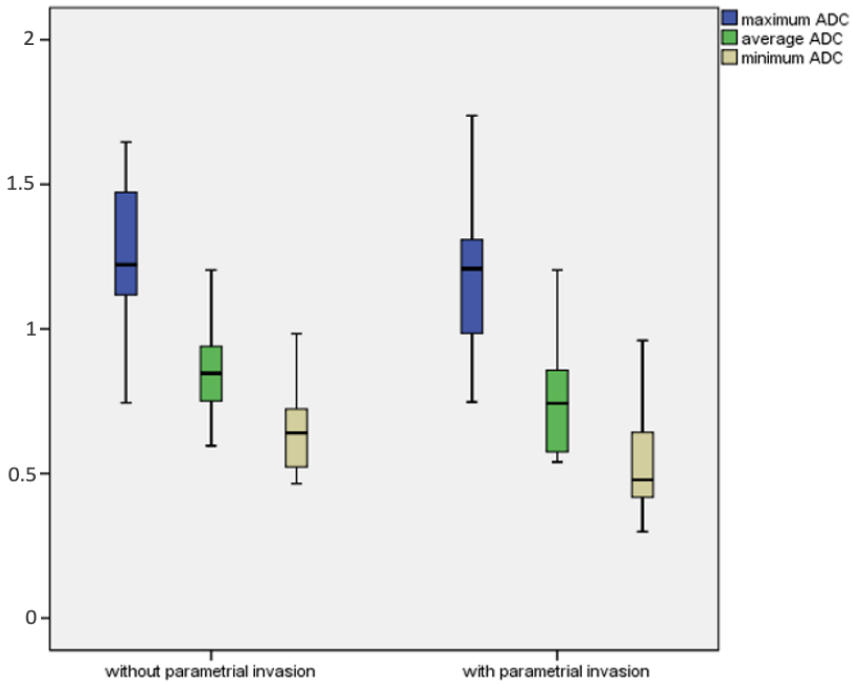

Figure 3: Comparison of the maximum, mean, and minimum ADC values between the patients with and without parametrial invasion.

The ROC analysis was applied to determine the optimal threshold of ADC-min values for determining PMI. Based on the ADC-min cut-off value of $0.553x10^{-3}$ mm^2/s, the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were calculated as follows: 63%, 73%, 52%, 80%, and 66% respectively. With this cut-off level, the area under the curve (AUC) value for estimating PMI with ADC-min was 0.726 (Fig 4).

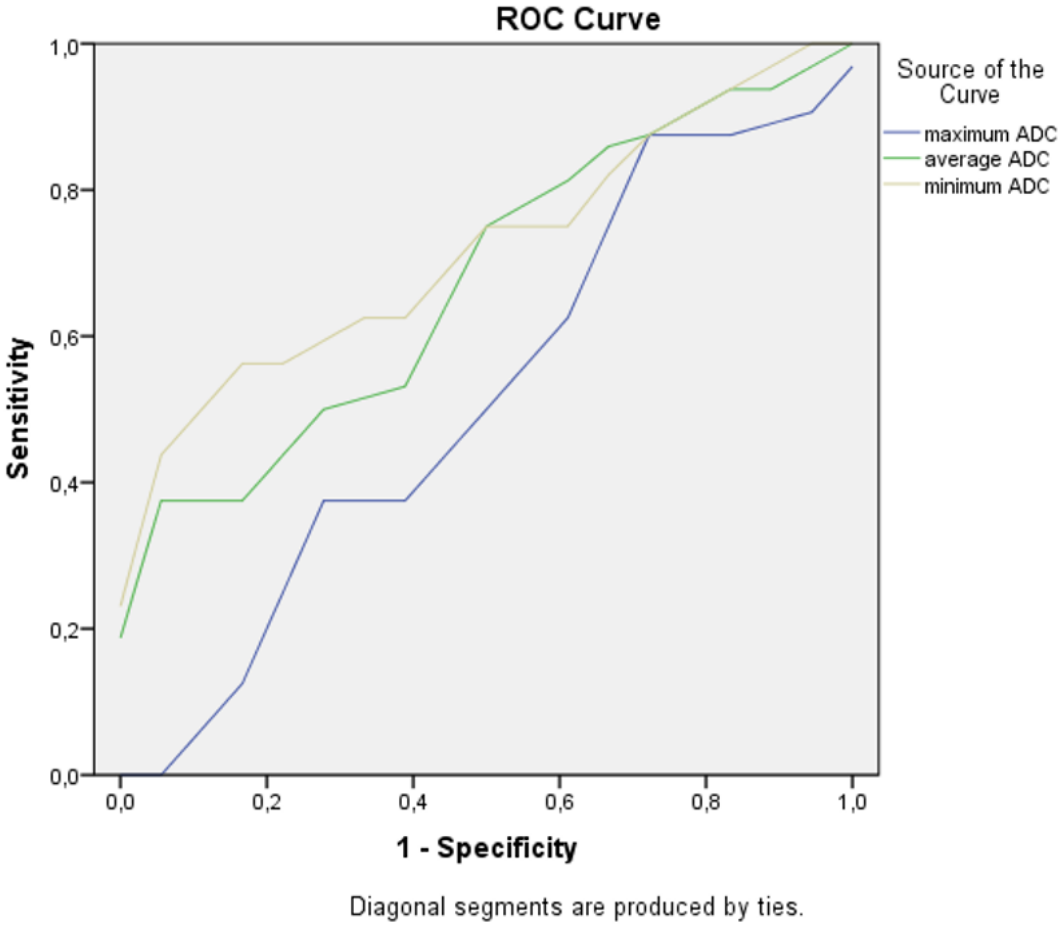

Figure 4: ROC analysis of maximum, mean, and minimum ADC values for the parametrial invasion.

4. Discussion

In our study, we aimed to compare the maximum, mean, and minimum ADC values obtained from the tumor-parametrium border in patients with cervical carcinoma to differentiate between patients with and without PMI. The present study demonstrated minimum ADC values obtained from the parametrium boundary of primary cervical carcinoma can potentially serve as an indicator of PMI. The especially positive predictive value of the ADC level obtained from the cervix-parametrium boundary is remarkable. The results indicate that the minimum ADC value could offer valuable additional information for evaluating the PMI, which may assist in determining appropriate treatment for patients diagnosed with early-stage cervical carcinoma.

It is crucial to make an accurate evaluation of parametrial invasion in order to determine which patients require chemoradiation therapy. If parametrial invasion is detected following surgery, it is recommended to have further chemoradiation to improve local control and survival [6]. However, this treatment approach is linked to increased morbidity and higher costs. The current study found an improvement in both negative and positive predictive values in assessing PMI with the utilization of minimal ADC values in imaging.

T2-WI is an MRI sequence that is utilized to rule out parametrial invasion in cervical carcinoma. The presence of a preserved cervical stromal rim with low signal intensity on T2-WI is a consistent MRI finding suggesting an intact parametrium [8, 9]. T2-WI has been shown to have a 97% accuracy rate for parametrial invasion [13]. Nevertheless, when a tumor extends through the entire thickness of the cervical stroma, it becomes challenging to assess whether parametrial invasion is present or not. In this case, the accuracy of T2-WI is restricted to 80% [14]. Also the presence of peritumoral edema or inflammation, which exhibits comparable high signal intensity to cervical carcinoma, frequently limits the accurate identification of the tumor boundary.

DWI is a technique used to observe to the three-dimensional microscopic movement of water molecules in both intra- and extracellular compartments. DWI visualizes the variability in water mobility due to changes in tissue cellularity, membrane integrity, and viscosity [15]. The presence of restricted diffusion can differentiate inflammation from malignancy. Several studies have documented the

efficacy of ADC in assessing the severity of cervical carcinoma or the prognosis of patients following treatment. Kuang et al. showed a significant statistical difference in the apparent diffusion coefficient (ADC) between well-/moderately differentiated tumors and poorly differentiated tumors [16]. Downey et al also found that the median ADC of cervical carcinoma was decreased in poorly differentiated tumors [17]. These results indicate that the ADC values of cervical malignancies may be associated with their aggressiveness, including PMI. Qu et al. reported a higher sensitivity specificity PPV accuracy and AUC values of the combination of T2-WI and ADC values in detecting parametrial invasion than T2-WI alone [18]. In this study, the minimum ADC values of cervical carcinoma in patients with PMI were significantly lower compared to those in patients without PMI. Our findings support prior studies.

In this study, the importance of ADC value in determining the PMI which has not been studied in the literature has been investigated. In our study, in patients with parametrial invasion, the ADC values obtained from the tumor-parametrium border were lower than those without invasion. In the field of invasion, tumoral infiltration leads to an increase in cellularity, resulting in a high ratio of nucleus to cytoplasm, the presence of intracellular organelles and macromolecules, and restricted diffusion of extracellular matrix. Patients with parametrial invasion demonstrated lower maximum, mean, and minimum ADC values obtained from the cervix-parametrium border. However, only the minimum ADC values exhibited a significant difference among the groups ($p<0.05$). This may indicate that the minimum ADC value is more strongly associated with the tumor stage.

5. Conclusion

In conclusion, cervical carcinoma patients with parametrial invasion have lower ADC values than patients without parametrial invasion. Especially minimum ADC values at the boundary of the parametrium in primary cervical carcinoma might potentially serve as a significant predictor of parametrial invasion in addition to T2-WI. The positive predictive value of the ADC levels derived from the cervix-parametrium boundary is particularly remarkable. These results suggest that minimum ADC values can provide valuable additional information for the assessment of PMI, which could be helpful in determining the most appropriate treatment strategies for patients diagnosed with early-stage cervical carcinoma.

Limitations of the Study

The most important limitations of this study were retrospective methodology and relatively small sample size. The sample size was limited due to the exclusion of patients with confirmed PMI who had undergone previous or concurrent therapies. These treatments are known to affect the MRI characteristics and histopathologic outcomes by causing tumor cell death. There is a need for further research on more patients with prospective design and pathological confirmation.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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Author Contributions

Conception: MS, HÖA, ADK. Design: MS, HÖA, ADK. Supervision: ADK. Materials: MS. Data Collection and/or Processing: MS, HÖA. Analysis and Interpretation: HÖA, ADK. Literature Review: HÖA. Writing: MS, ADK. Critical Review: ADK.

Ethical Approval

The ethical guidelines were strictly adhered to and laid out in the Declaration of Helsinki by the World Medical Association. The study was sanctioned by the Koç University's ethics committee.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

All the patients who agreed to participate in the study signed the informed consent form.

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