Clinical Research

Tumor apparent diffusion coefficient value and ratio in magnetic resonance imaging on cervical cancer

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ABSTRACT

BACKGROUND Diffusion-weighted magnetic resonance imaging (DW-MRI) is a noninvasive, non-contrast sequence for cancer detection. Research involving DW-MRI in cervical cancer has revealed lower apparent diffusion coefficient (ADC) values. This study aimed to evaluate the difference in tumor ADC values and ADC ratios (tumor-to-urine and tumor-to-muscle) with respect to tumor staging (early *versus* late) and histological subtype (squamous cell carcinoma *versus* adenocarcinoma).

METHODS This retrospective study included 56 patients with cervical cancer, divided into early- and late-stage groups. DW-MRI was performed in all patients, and the tumor ADC value, ADC ratio between the tumor and urine (ADC ratio$_{t-u}$), and ADC ratio between the tumor and gluteal muscle (ADC ratio$_{t-m}$) were measured. Statistical methods were employed to assess the difference in the tumor ADC value, ADC ratio$_{t-u}$, and ADC ratio$_{t-m}$ with respect to cervical cancer stages and histopathological findings.

RESULTS The median tumor ADC value was lower in the early-stage group than in the late-stage cervical cancer (0.75×10^{-3} mm^2/s *versus* 0.8×10^{-3} mm^2/s, $p = 0.022$). However, no differences were observed in ADC ratio$_{t-u}$ and ADC ratio$_{t-m}$ concerning the tumor staging, nor in ADC value, ADC ratio$_{t-u}$, and ADC ratio$_{t-m}$ concerning histopathological findings ($p = 0.560$, 0.920, and 0.397, respectively), with no significant differences in the ADC ratio$_{t-u}$ ($p = 0.153$) and ADC ratio$_{t-m}$ ($p = 0.260$). In receiver operating characteristic analysis, the tumor ADC value was 75.0% sensitive and 50.0% specific in predicting late-stage cervical cancer with a cut-off value of 0.750×10^{-3} mm^2/s.

CONCLUSIONS The median tumor ADC value in early-stage patients was significantly lower than in the late-stage patients, suggesting that tumor ADC value has valuable potential for characterizing cervical cancer staging.

KEYWORDS cervical cancer, diffusion magnetic resonance imaging, magnetic resonance imaging

Cervical cancer is the second most prevalent cancer among women in Indonesia and the fourth most common cancer worldwide. As of 2020, Indonesia reported 36,633 new cases and 63,661 prevalent cases, with a mortality rate of 18,000 cases per year.[1,2] The diagnosis and staging of cervical cancer were based on The International Federation of Gynecology and Obstetrics (FIGO) 2018 guidelines, utilizing clinical assessment, radiological examination, and anatomical histopathology. Magnetic resonance imaging (MRI) is the preferred radiological modality, with a diagnostic accuracy of 75–96%.[3–7]

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a noninvasive, non-contrast technique for identifying cancers in oncological imaging. This method reveals cellularity by analyzing the diffusion behavior. Tumor cells display a unique microenvironment characterized by a compact interstitial structure, increased cellular density, and build-up of solid stress. Diffusion-weighted imaging (DWI) can highlight these tumor features and is recognized as a biomarker for cancer imaging. Studies utilizing DW-MRI for cervical cancer have indicated that the apparent diffusion coefficient (ADC) values are significantly lower in tumor tissues than in normal tissues. In contrast to non-tumor tissues, increased cellularity in tumor tissues hinders water movement between cells, leading to retained signal intensity on DWI and lower ADC values. ADC calculations rely on the differences in the diffusion of water molecules within biological tissues.[8–11] Previous studies have reviewed the different diagnostic accuracies of tumor ADC values and ADC ratios in various cancers, such as renal and prostate cancers.[12–15] This study aimed to evaluate the differences between tumor ADC values and ADC ratios (tumor-to-urine and tumor-to-muscle) at different stages of cervical cancer.

METHODS

Patients and method

This retrospective study included 56 patients diagnosed with cervical cancer based on histopathological findings. The patients were referred to the Department of Radiology for MRI between November 2020 and November 2023, after this study was approved by our Institutional Review Board. We collected their data from electronic medical records and classified them as having stage I–IV cervical cancer, according to FIGO 2018. These patients were divided into early- and late-stage cervical cancer groups. The early-stage group (n = 20) consisted of patients with cervical cancer without parametrial invasion or those classified as FIGO stages IB–IIA, whereas the late-stage group (n = 36) included patients with parametrial invasion or those classified as FIGO stages IIB–IV.

MRI protocol

Conventional MRI

MRI scans were conducted using 1.5 Tesla Magnetom Avanto MRI Machine (Siemens Healthineers, Germany) and 1.5 Tesla Optima MRI Machine (General Electric, USA). Conventional MRI sequences included T2-weighted imaging (T2WI) of sagittal and axial oblique images. The imaging parameters for T2-weighted fast spin-echo were as follows: repetition time (TR) of 6,188 ms; echo time (TE) of 117 ms; bandwidth of 20.83 kHz; echo train length of 28 kHz; slice thickness of 3 mm; gap of 1 mm; field of view (FOV) of 24 cm; matrix size of 256 × 256; two excitations and acquisition duration of 2 min. After tumor detection using standard T2WI, axial DWI was performed with b-values of 0 and 1,000 s/mm. The image parameters included a TR of 6,274 ms, TE of 72 ms, FOV of 24 cm, bandwidth of 25 kHz, slice thickness of 3 mm, no gap (0 mm), six excitations, a matrix of 128 × 128, and an acquisition time of 4 min.

DW-MRI

Before administering intravenous contrast and after axial T2WI, DW-MRI was performed using single-shot spin-echo echo-planar imaging. This acquisition occurred during free-breathing, with background signals from the body minimized through pre-saturation inversion recovery fat suppression. The parameters employed were a TR/TE of 5,238/64 ms, FOV of 240 × 240 mm, matrix size of 128 × 128, slice thickness of 4 mm, and an intersection gap of 0 mm. We employed parallel imaging by applying a sensitivity encoding factor of two and a receiver bandwidth of 62.5 Hz per pixel. B-values of 0 and 1,000 s/mm^2 were gathered in both the axial and sagittal planes, covering 20 slices to encompass the entire cervical cancer. This was accomplished by using motion-probing gradients along three orthogonal axes. To ensure proper image overlay and co-registration, we ensured uniformity in the FOV, slice thickness, and intersection spacing using anatomical axial T2WI.

Imaging analysis

All images were evaluated by a radiologist with 5 years of experience in gynecological imaging using the Picture Archiving and Communication System (PACS) (INFINITT Healthcare, South Korea), blinded to the patient's clinical data and pathology reports. The tumor was identified on T2WI as a soft tissue lesion, characterized by a high signal intensity on DWI, high signal intensity on T2WI, and low signal intensity on the ADC map. We evaluated the tumor dimensions, parametrial invasion, and invasion of other pelvic organs using T2WI. The radiologist independently examined

the images and assessed the greatest transverse tumor dimensions in the axial oblique orientation, in addition to the maximum anteroposterior and craniocaudal tumor diameters aligned with the long axis of the cervical lumen in the sagittal view (Figure 1).

ADC values were calculated in axial ADC maps from axial DWI, corresponding to the organ morphology on axial T2WI. ADC values were measured using the largest region of interest (ROI) within the tumor, urinary bladder, and gluteal muscles (Figure 2). The ROI technique used a freehand ROI tool on PACS, defined on three slices containing the tumor, urinary bladder, and gluteal muscle along the organ's borders to include a minimum of 70% of the tumor or organ area in the measurement (Figure 2). The mean tumor or organ ADC value was calculated as the average of the three measured ADC.

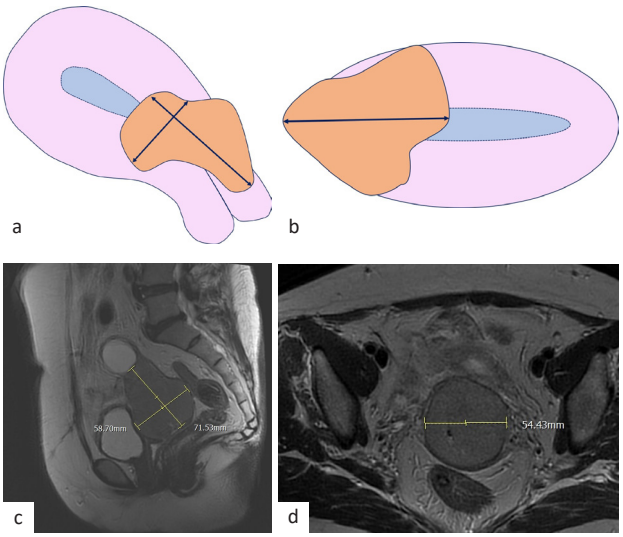

Figure 1. Example of measurement in 35-year-old female with cervical cancer. Measurement scheme of cervical tumor in sagittal (a) and axial (b) plane; correlate with measurement of cervical tumor on T2WI MRI sequence in sagittal (c) and axial (d) plane. MRI=magnetic resonance imaging; T2WI=T2-weighted imaging

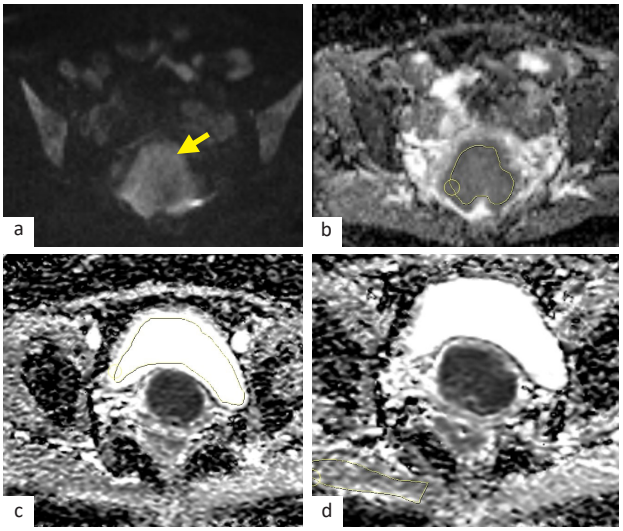

Figure 2. Diffusion MRI sequences on an axial plane in cervical cancer. (a) DWI with b-value = 1,000 s/mm² showed hyperintensity lesion within the tumor (yellow arrow); (b–d) ROI in the tumor, urinary bladder, and gluteal muscle. DWI=diffusion-weighted imaging; MRI=magnetic resonance imaging; ROI=region of interest

In the present study, we used two ADC ratios. The first measurement was the ratio between the tumor and urine ADC (ADC ratio$_{t-u}$), and the second was the ratio between the tumor and gluteal muscle ADC (ADC ratio$_{t-m}$).

Data analysis

Data analysis was conducted using the SPSS software version 29.0 (IBM Corp., USA). Data distributions are presented as frequencies and percentages. Data normality was tested using the Kolmogorov–Smirnov test. Data exhibiting an abnormal distribution are shown as the median and interquartile range (IQR). The non-parametric two-sample Mann–Whitney *U* test was used to analyze the differences in ADC value, ADC ratio$_{t-u}$, and ADC ratio$_{t-m}$ based on tumor stage (early *versus* late) and histological subtype (squamous cell carcinoma [SCC] *versus* adenocarcinoma). Receiver operating characteristic (ROC) curves were developed to identify appropriate thresholds for distinguishing between the groups. The diagnostic effectiveness of the ADC values was assessed based on the cut-off value, sensitivity, and specificity.

RESULTS

Participant characteristics

This study included 56 patients with confirmed cervical cancer. The mean age of participants was 46.7 (9.8) years, ranging from 25 to 73 years. This study found that the most common tumors were SCC, followed by adenocarcinoma. Based on staging, the majority were in the late stage (minimal stage IIB, according to FIGO 2018) (Table 1).

The mean tumor diameter was 41.8 mm (range, 12–100 mm) (Table 1). The average ADC value for the tumor was 1 × 10^{-3} mm²/s. The mean ADC ratio$_{t-b}$ was recorded at 1.25 × 10^{-3} mm²/s, and the mean ADC ratio$_{t-m}$ was 0.25 × 10^{-3} mm²/s.

Table 1. Participant characteristics

Characteristic	n (%) (N = 56)
Age (years), mean (SD)	46.7 (9.8)
25–49	30 (54)
50–73	26 (46)
Histological subtype	
SCC	44 (79)
Adenocarcinoma	10 (18)
Adenosquamous	1 (2)
Neuroendocrine	1 (2)
Staging	
Early	20 (36)
Late	36 (64)
Tumor diameter, mean (SD)	41.8 (18.8)

SCC=squamous cell carcinoma; SD=standard deviation

Tumor ADC value, ADC ratio, and histopathology

The median tumor ADC value in both the SCC and adenocarcinoma groups was 0.8 × 10^{-3} mm^2/s. The median ADC $ratio_{t-u}$ was also identical between the groups (0.3 × 10^{-3} mm^2/s). The median ADC $ratio_{t-m}$ in SCC was 0.7 × 10^{-3} mm^2/s, which was higher than the adenocarcinoma group (0.6 × 10^{-3} mm^2/s). The Mann–Whitney *U* test showed no significant difference in the ADC values ($p = 0.560$), ADC $ratio_{t-u}$, ($p = 0.920$), and ADC $ratio_{t-m}$ ($p = 0.397$) between SCC and adenocarcinoma (Table 2).

Tumor ADC value, ADC ratio, and staging

Among the 56 patients, the median tumor ADC value was 0.75 × 10^{-3} mm^2/s in early-stage cervical cancer and 0.80 × 10^{-3} mm^2/s in late-stage. There was a significant difference in the ADC values between the early- and late-stage groups ($p = 0.022$). The median ADC $ratio_{t-u}$ in the early- and late-stage groups were the same (0.3 × 10^{-3} mm^2/s). The median ADC $ratio_{t-m}$ in early-stage cervical cancer was 0.6 × 10^{-3} mm^2/s and 0.75 × 10^{-3} mm^2/s in the late-stage of cervical cancer. The Mann–Whitney *U* test showed no significant difference in ADC $ratio_{t-u}$ ($p = 0.153$) and ADC $ratio_{t-m}$ ($p = 0.260$) between the early- and late-stage groups (Table 2).

Our study revealed an area under the curve value of 0.681, indicating a predictive effectiveness of approximately 68.1% (Figure 3). Upon assessing the various coordinates produced by the ROC analysis, the tumor ADC value demonstrated a sensitivity of 75.0% and a specificity of 50.0% in predicting late-stage cervical cancer. The cut-off value for tumor ADC in identifying late-stage cervical cancer was 0.750 × 10^{-3} mm^2/s.

DISCUSSION

This study found no significant differences in tumor ADC values, ADC $ratio_{t-u,}$ and ADC $ratio_{t-m}$ in relation to cervical cancer histopathology. The median ADC $ratio_{t-m}$ in SCC was higher than in adenocarcinoma, but the ADC values for the tumor and the ADC $ratio_{t-u}$ in both groups were identical. This is contrary to earlier research by Hasan et al,[16] who indicated significantly lower average tumor ADC values in the SCC group (0.91 × 10^{-3} mm^2/s) compared to the adenocarcinoma group (0.88 × 10^{-3} mm^2/s) ($p<0.050$). Similarly, Lin et al[17] revealed that the median, mean, and 25th percentile ADC values were notably higher in adenocarcinoma than in SCC ($p<0.050$). SCC is typically densely packed and clustered, whereas adenocarcinoma has larger intercellular spaces with glandular formations that allow greater water diffusion, resulting in a higher ADC value.[17] The discrepancy in sample sizes between the groups in this study might have caused the difference in results, as the SCC samples were much larger than the adenocarcinoma group. Nuranna et al[3] reported that the most prevalent histopathological type of cervical

Table 2. ADC value and ADC ratios in relation with tumor histological subtype and tumor staging

Parameter	Tumor histological subtype		*p*	Tumor staging		*p*
	SCC, median (IQR) (n = 44)	Adenocarcinoma, median (IQR) (n = 10)		Early, median (IQR) (n = 20)	Late, median (IQR) (n = 36)	
ADC value	0.8 (0.7–0.9)	0.8 (0.7–0.8)	0.560	0.75 (0.65–0.80)	0.80 (0.75–0.90)	**0.022**
ADC $ratio_{t-u}$	0.3 (0.2–0.3)	0.3 (0.2–0.3)	0.920	0.30 (0.20–0.30)	0.30 (0.20–0.30)	0.153
ADC $ratio_{t-m}$	0.7 (0.5–0.9)	0.6 (0.5–0.8)	0.397	0.60 (0.50–0.80)	0.75 (0.50–0.90)	0.260

ADC=apparent diffusion coefficient; ADC $ratio_{t-m}$=ADC ratio between the tumor and gluteal muscle; ADC $ratio_{t-u}$=ADC ratio between the tumor and urine; IQR=interquartile range; SCC=squamous cell carcinoma

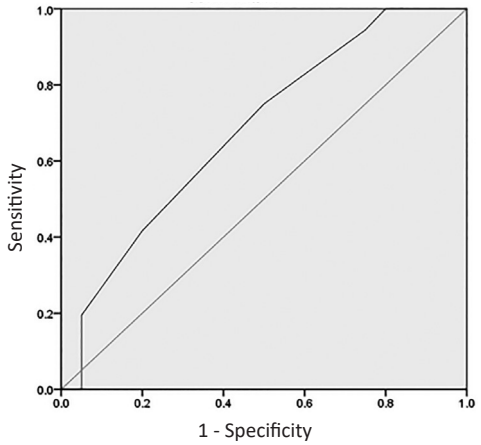

Figure 3. ROC curve of ADC value based on tumor stage. ADC=apparent diffusion coefficient; ROC=receiver operating characteristic

cancer among Indonesians was SCC, comprising 71.6% of all cases. Similar findings have been reported in other developing countries with geographic and population characteristics similar to those in Indonesia. Wang et al[18] showed that SCC is the most common histopathological type of cervical cancer (70%), followed by adenocarcinoma (20%). Similarly, Rana et al[19] reported that the most common histopathological type was SCC (80.1%), followed by adenocarcinoma (13.2%).

This study found no statistically significant differences between ADC ratio$_{t-u}$ and ADC ratio$_{t-m}$ in early- and late-stage cervical cancer. Five samples in this study had abnormal urinalysis results, including pyuria, bacteriuria, hematuria, and proteinuria, which may correlate with the results. In contrast, patients with early-stage cervical cancer showed significantly lower median tumor ADC values than those with late-stage cervical cancer. Specifically, the median tumor ADC value for early-stage cervical cancer was 0.75 × 10^{-3} mm^2/s (IQR 0.65–0.80 × 10^{-3} mm^2/s), while late-stage cervical cancer measured 0.80 × 10^{-3} mm^2/s (IQR 0.75–0.90 × 10^{-3} mm^2/s). Dashottar et al[8] measured tumor ADC values using a large ROI that covered a minimum of 60% of the tumor area. They found that the mean tumor ADC value in cervical cancer without parametrial invasion was 0.902 × 10^{-3} mm^2/s compared to 0.762 × 10^{-3} mm^2/s in cervical cancer with parametrial invasion. The differences between the mean tumor ADC in the early and late stages were significant (p = 0.001). Hasan et al[16] utilized a small ROI within the tumor area and revealed that the average tumor ADC value in early-stage cervical cancer was 0.83 (0.05) × 10^{-3} mm^2/s, which was notably lower than in the late-stage disease (0.98 [0.06] × 10^{-3} mm^2/s) (p<0.050). Our findings also indicated significant differences in the median tumor ADC values between early- and late-stage disease. In this study, most patients were diagnosed at a late stage, while the remaining patients were diagnosed at an early stage. Nuranna et al[3] reported that most participants (69.4%) with cervical cancer in Indonesia were in the late-stage of the disease (IIB and higher). These comparable results may be due to the similar characteristics of the study population at the same research institution. Furthermore, in India, Dashottar et al[8] found that most cervical cancers are diagnosed at a late stage (62.8%).

The limitations of this study include the small sample size and narrow sample distribution. Within these limitations, the results indicate that tumor ADC values are valuable for cervical cancer staging. Further research with a larger sample size and a broader distribution is required to validate these findings, particularly in relation to tumor histopathology. In conclusion, this study indicates a significant difference in median tumor ADC values between early- and late-stage cervical cancer, with a cut-off value of 0.750 × 10^{-3} mm^2/s. The tumor ADC value has the potential to be used as a biomarker for distinguishing early- and late-stage cervical cancer and provides more information for the treatment, management, and prognosis of patients with cervical cancer.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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