

Differentiating Between Low- and High-grade Glioma Tumors Measuring Apparent Diffusion Coefficient Values in Various Regions of the Brain

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ABSTRACT

Objectives: Our study aimed to apply the apparent diffusion coefficient (ADC) values to quantify the differences between low- and high-grade glioma tumors. **Methods:** We conducted a multicenter, retrospective study between September to December 2019. Magnetic resonance imaging (MRI) diffusion-weighted images (DWIs), and the pathologic findings of 56 patients with glioma tumors (low grade = 28 and high grade = 28) were assessed to measure the ADC values in the tumor center, tumor edema, boundary area between tumor with normal tissue, and inside the healthy hemisphere. These values were compared between the two groups, and cut-off values were calculated using the receiver operating characteristic curve. **Results:** We saw significant differences between the mean ADC values measured in the tumor center and edema between high- and low-grade tumors ($p < 0.005$). The ADC values in the boundary area between tumors with normal tissue and inside healthy hemisphere did not significantly differ in the groups. The ADC values at tumor center and edema were higher than $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 100% and specificity = 96.0%) and $1.15 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 75.0% and specificity = 64.0%), respectively, could be classified as low-grade tumors. **Conclusions:** The ADC values from the MRI DWIs in the tumor center and edema could be used as an appropriate method for investigating the differences between low- and high-grade glioma tumors. The ADC values in the boundary area and healthy tissues had no diagnostic values in grading the glioma tumors.

Glioma tumors are the most common tumors of the central nervous system causing 40–50% of brain tumors and 2–3% of all cancers globally.¹ Despite modern techniques developed for brain tumor treatments, high-grade gliomas are still considered hard responding to treatments.² Early diagnosis of malignant glioma helps successful treatment;³ therefore, developing methods to detect malignant tumors is essential. It has been demonstrated that Magnetic resonance imaging (MRI) is a valuable diagnostic tool in oncology due to the high spatial resolution and contrast of soft tissues.^{4–6} Although common MRI sequences have many advantages in the diagnosis and evaluation of brain tumors, these

sequences are not effective tools for differentiation of the tumor types or grades.⁴

Diffusion-weighted imaging (DWI) relies on the diffusion of water molecules to create contrast between normal and abnormal tissues; it has a proven ability to differentiate between benign and malignant tumors in various sites.^{4,7,8} Apparent diffusion coefficient (ADC) values are obtained from a series of DWIs with different gradients.⁹ Previous studies had shown that ADC measurement could distinguish several certain types of brain and cerebral tumors, including malignant and benign meningiomas, high-grade and low-grade gliomas, brain metastasis, and vestibular schwannomas.^{10–12}

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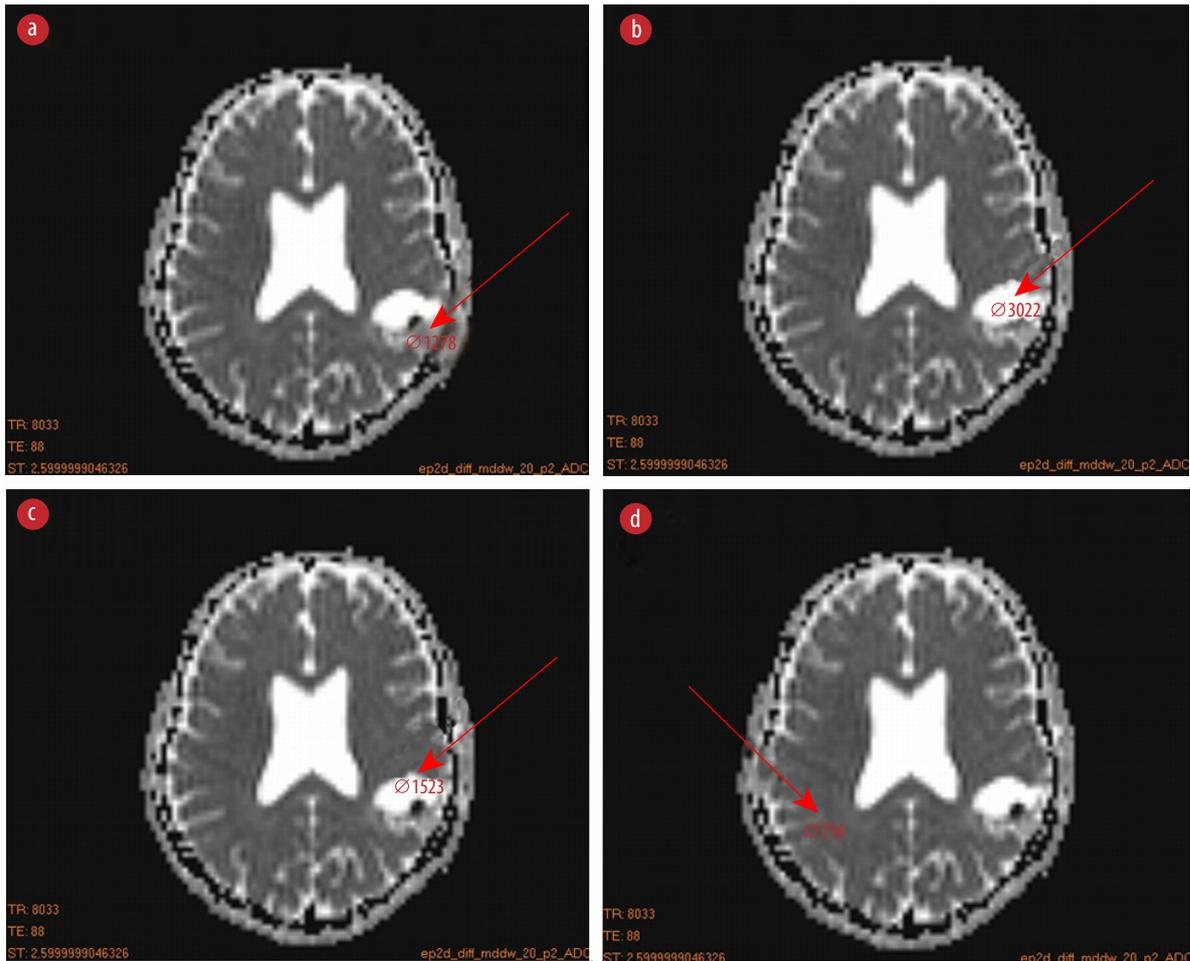


Figure 1: Region of interests (ROIs) placement for measuring the apparent diffusion coefficient values in various sites of the brain. (a) ROI at the center of the tumor, (b) the tumor edema but not at the center, (c) the boundary of tumor edema with surrounding normal tissue, and (d) ROI at the normal tissues located in the healthy hemisphere.

The use of ADC values to differentiate low- and high-grade gliomas have been assessed in previous studies.^{4,7,8,13} However, the ADC values in different areas like the tumor center, edema, boundaries between normal tissue and edema have rarely been investigated for differentiating high- and low-grade gliomas. Therefore, our study aimed to measure the ADC values at various brain regions of the patients with glioma tumors to quantify the differences between high- and low-grade gliomas.

METHODS

We conducted a multicenter, retrospective study conducted from September to December 2019 following national research ethics board approval. The calculated ADC map and pathological results of 56 patients with brain tumors were recorded

for analysis. The patients had an average age of 45.0 ± 7.0 years, including 34 men (16 with malignant glioblastoma multiform and astrocytoma grade III tumors, and 18 with astrocytoma grade I and II tumors), and 22 women (12 with malignant glioblastoma multiform and astrocytoma grade III tumors, and 10 with astrocytoma grade I and II tumors). The patients were divided into two groups with equal size including low-grade (I and II) and high-grade (III and IV) gliomas based on the pathological results. The MRI images were acquired using a 1.5-Tesla Siemens Emotion scanner (Siemens Healthcare GmbH, Erlangen, Germany) applying diffusion gradients in three independent directions. All of the images were taken by three gradient b-values of 0, 500, and 1000 mm^2/s . Dicom Works software (DicomWorks v1.3.5 2000, 2002; License: Freeware Free; Publishers: Phillippe Puech and Loic Boussel) were used to obtain the ADC values

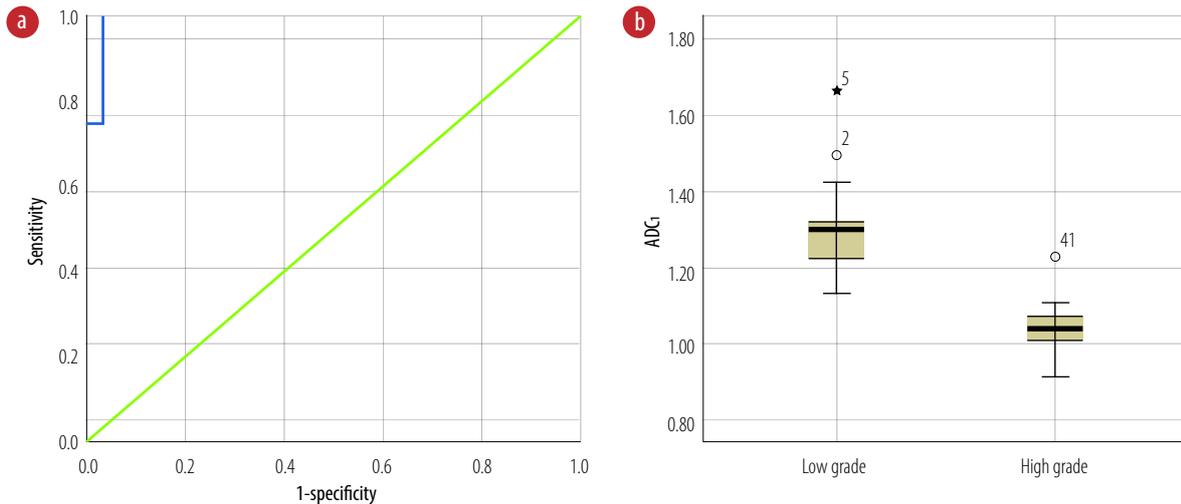


Figure 2: (a) Receiver operating characteristic curve of apparent diffusion coefficient (ADC) values contracted the tumor's center (ADC_1) to differentiate benign from malignant glioma tumors. (b) Comparison of ADC_1 values between benign and malignant glioma tumors.

in different regions of MRI DWIs. Four region of interests (ROIs) were drawn on the ADC map for each patient's image including: 1) ROI at the center of the tumor [Figure 1a]; 2) the tumor edema but not at the center [Figure 1b]; 3) the boundary of edema with surrounding normal tissue [Figure 1c]; and 4) ROI at the normal tissues located in the healthy hemisphere [Figure 1d].

The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic ability of the ADC value to differentiate between high- and low-grade glioma tumors. The cut-off value was chosen to maximize the Youden index.¹⁴ Furthermore, sensitivity and specificity values were calculated using the ROC curves.

SPSS statistical software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.) was employed to distinguish tumor types and obtain the ADC cut-off values. Furthermore, we used the Mann-Whitney statistical test to compare the ADC values of different regions between the high- and low-grade gliomas groups.

RESULTS

The clear area under the ROC curve related to low-grade glioma tumors was equal to 99.1%, as demonstrated in Figure 2a and Table 1. Diagnostic ADC threshold for tumor center (ADC_1) was $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 100% and specificity = 96.0%) with the diagnostic threshold phase error of 1.0%. Figure 2b shows ADC_1 values for patients with high- and low-grade tumors. There is no overlap between the quartiles for each group. The ADC_1 values of high-grade tumors are significantly lower compared to those in low-grade tumors ($p < 0.001$). The median, mean, and range for ADC_1 are shown in Table 2.

The results of quantitative and ADC analysis of tumor edema areas (ADC_2) revealed the area under the curve was equal to 72.3%, as demonstrated in Figure 3a and Table 1. The diagnostic threshold was $1.15 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 75.0% and specificity = 64.0%) with the diagnostic threshold phase error of 7.0%. Figure 3b shows the ADC_2 for patients with low- and high-grade tumors. The ADC_2 values of high-grade tumors

Table 1: Area under the receiver operating characteristic curve of ADC_1 , ADC_2 , ADC_3 , and ADC_4 values.

ROC curve	Area, %	Standard error, %	p-value	Asymptotic 95% confidence interval
ADC_1	99.1	1.0	< 0.001	0.97–1.00
ADC_2	72.3	7.0	0.004	0.58–0.86
ADC_3	41.5	7.7	0.272	0.26–0.56
ADC_4	38.9	79.0	0.157	0.23–0.54

ADC: apparent diffusion coefficient.

Table 2: Mean, median, confidence interval, and range of tumor edema of the apparent diffusion coefficient (ADC) of four regions with scale of $10^{-3} \text{ mm}^2/\text{s}$.

Statistical values	Mean	Median	Asymptotic 95% confidence interval	Minimum	Maximum
Low grade (ADC ₁)	1.2	1.29	1.26–1.33	1.13	1.67
High grade (ADC ₁)	1.0	1.04	1.02–1.07	0.92	1.23
Low grade (ADC ₂)	1.5	1.61	1.47–1.70	0.79	2.17
High grade (ADC ₂)	1.4	1.41	1.34–1.47	0.98	1.72
Low grade (ADC ₃)	0.7	0.84	0.73–0.85	0.08	0.98
High grade (ADC ₃)	0.8	0.84	0.80–0.87	0.67	1.04
Low grade (ADC ₄)	0.8	0.82	0.78–0.82	0.62	0.87
High grade (ADC ₄)	0.8	0.83	0.78–0.84	0.61	0.91

are significantly lower than low-grade tumors ($p = 0.004$). Table 2 shows the median, mean, and range of ADC₂.

The diagnostic threshold for quantitative and ADC analysis in areas between the tumor and normal tissue (ADC₃) values was $0.84 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 50.0% and specificity = 50.0%). Figure 4a indicates the curved-boundary between tumor and normal tissue ADC values. The area under the curve was equal to 41.5%, with a 7.7% error. Figure 4b represents the range of ADC values on the border between the tumor edema and surrounding normal tissue in both low- and high-grade groups. Diagnosis of low- and high-grade tumors, based on the ADC₃ values, seems to be difficult due to no significant differences in ADC₃ values between the groups (Figure 4b). The ADC₃ values in high-grade tumors did not show any significantly higher values than those in low-grade tumors ($p = 0.272$). The

median, mean, and range of the ADC₃ are shown in Table 2.

Results of quantitative and ADC analysis of normal tissue located in the healthy hemisphere (ADC₄) revealed an area under the curve and error in the implementation phase of 38.9% and 79.0%, respectively [Table 1]. Figure 5a shows the ROC curve of ADC values of normal tissue located in the healthy hemisphere (ADC₄) to differentiate between low- and high-grade glioma tumors. Figure 5b indicates the comparison of ADC₄ values between both glioma tumors. There were not any significant differences in the ADC₄ values between the groups ($p = 0.157$). Table 2 shows the median, mean and range of ADC₄. The diagnostic ADC threshold value in normal tissues located in the healthy hemisphere (ADC₄) for differentiating low and high grade gliomas was $0.76 \times 10^{-3} \text{ mm}^2/\text{s}$ (sensitivity = 89.3% and specificity = 22.2%). Regarding the quantitative

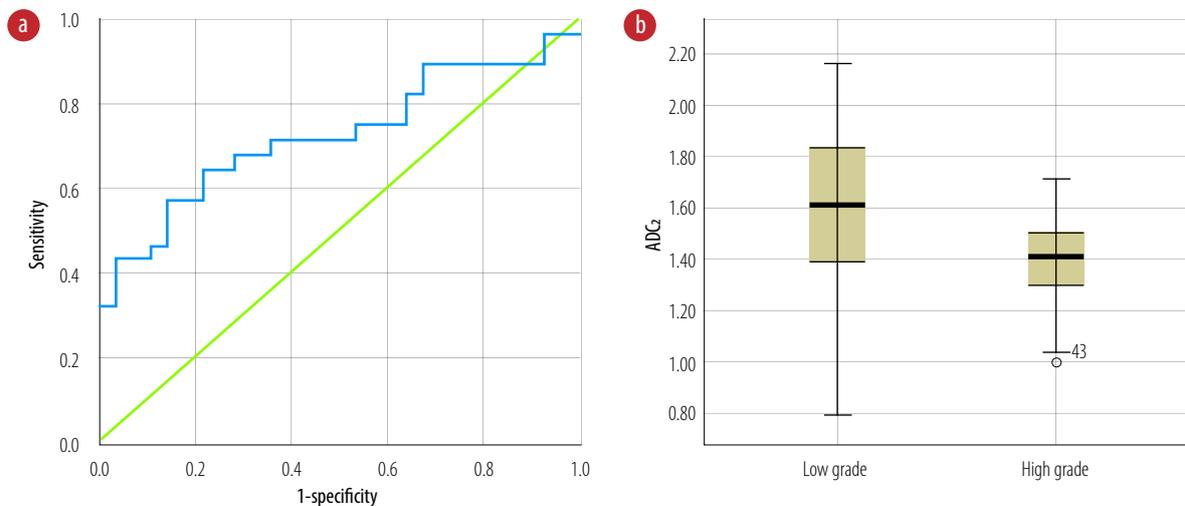


Figure 3: (a) Receiver operating characteristic curve of apparent diffusion coefficient (ADC) values contracted tumor edema (ADC₂) to differentiate benign from malignant glioma tumors. (b) Comparison of ADC₂ values between benign and malignant glioma tumors.

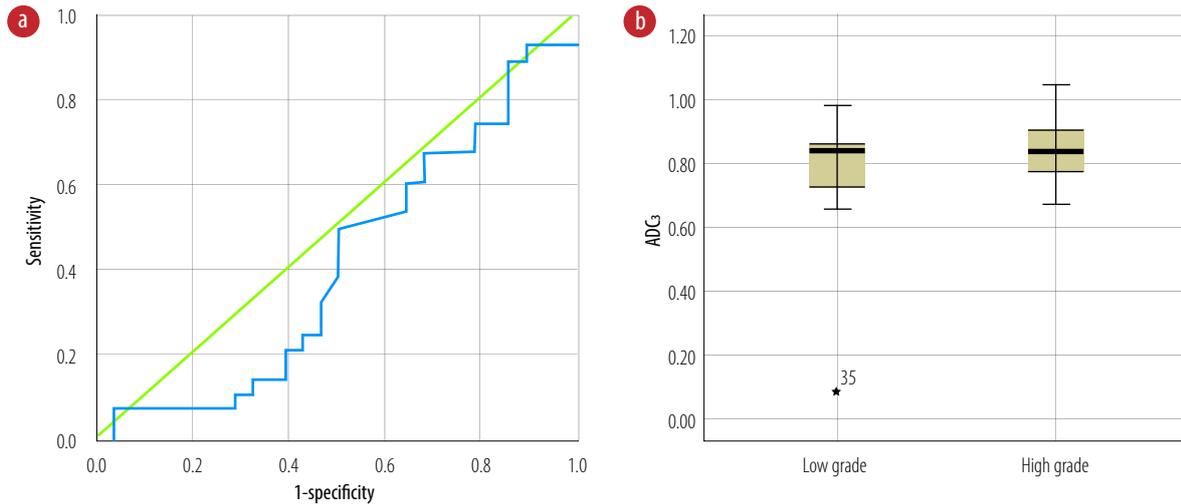


Figure 4: (a) Receiver operating characteristic curve of apparent diffusion coefficient (ADC) values between normal tissue and tumor border (ADC_3) to differentiate benign from malignant glioma tumors. (b) Comparison of ADC_3 values between benign and malignant glioma tumors.

analysis, it is worth to mention that there was no significant differences between the low and high grade gliomas in healthy brain.

DISCUSSION

We evaluated the ability of DWI and ADC values obtained from four various brain regions in differentiating between high- and low-grade brain glioma tumors. We found that ADC cut-off values were able to distinguish these tumors.

MRI has been used to evaluate patients with brain tumors.¹⁵⁻¹⁷ In DWI, the random movement of water molecules that are aligned with fiber tracts in the

central nervous system was determined to find the susceptible tumor tissues. Different degrees of field gradients are applied for quantification of diffusion for calculating the ADC values in tissue.¹⁸⁻²⁰

Our results showed significantly lower ADC values at tumor center and edemas (ADC_1 and ADC_2) in patients with high-grade tumors than those with low-grade tumors. Furthermore, the ADC values at the boundaries between tumor edema with normal tissue and healthy brain hemisphere (ADC_3 and ADC_4) indicated no significantly higher values in patients with low-grade glioma tumors. Lower values of ADC_1 and ADC_2 might be explained by the increased cellularity and higher tumor density

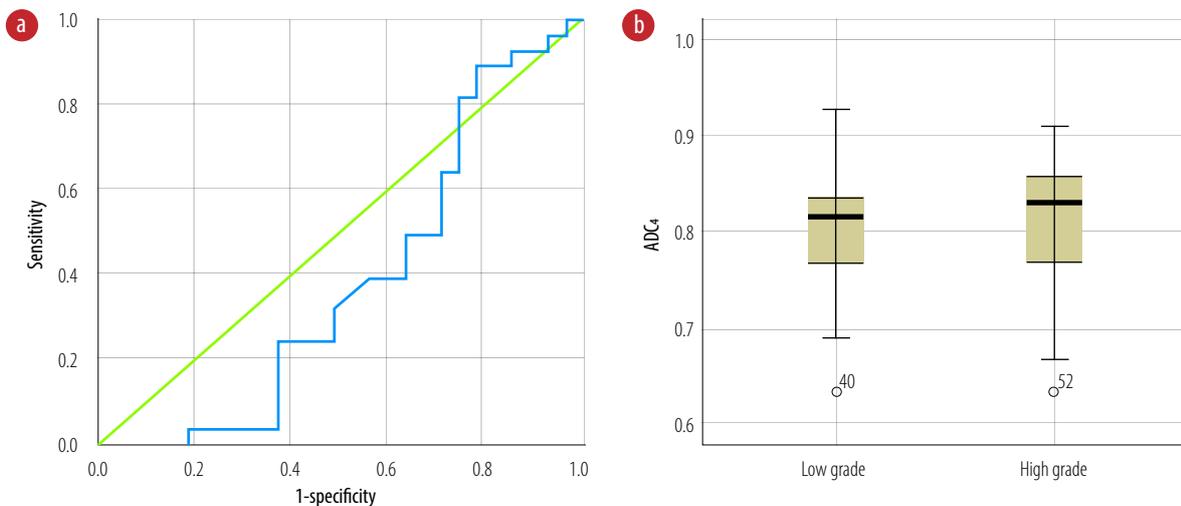


Figure 5: (a) Receiver operating characteristic curve of apparent diffusion coefficient (ADC) values of normal tissue located in the healthy hemisphere (ADC_4) to differentiate benign from malignant glioma tumors. (b) Comparison of ADC_4 values between benign and malignant glioma tumors.

in these areas in patients having high-grade glioma tumors, as well as malignant tumors clutter tissue and the increased curvature of the space between the cells, which slow down water molecules and reduce their ADC.^{4,7,8} Not significantly higher values of ADC₃ and ADC₄ in patients with high-grade glioma tumors can be due to microcystic degeneration, necrosis foci, and overproduction of extracellular matrix components of glioma cells at the boundary of tumoral tissue, edema, and in healthy tissues.^{7,21} A meta-analysis review study provided clinical evidence regarding the relationship between ADC and cellularity in different tumors.²² The correlation coefficient between ADC and cellularity in glioma was $R = -0.66$, which was the strongest correlation among various tumors. Therefore, the ADC values could be a useful tool for differentiating low- and high-grade glioma tumors.

The lower intratumoral ADC values have been linked to increased cellularity; therefore, the regions with minimum ADC reflect the highest tumoral density in this regard.⁸

Several studies investigated the DWI ability to distinguish the various types of brain tumors,^{23–25} whereas some other studies have shown that intratumoral ADC value is not useful to differentiate between some of the brain or cerebral tumors.^{26–28} For example, some studies have found higher intratumoral ADC values in brain metastasis compared to high-grade gliomas, but they have several limitations, such as a small number of patients.^{29,30}

The cut-off values of ADC₁ and ADC₂ had higher sensitivity and specificity than those for ADC₃ and ADC₄. The ROIs of ADC₁ and ADC₂ were contoured inside the tumor regions, while the ROIs of other ADC values were defined outside the tumor. Therefore, it was expected that ADC₁ and ADC₂ values could have better differentiation between low- and high-grade tumors.

The ability of ADC measurement for detecting malignant and benign tumors has been investigated in previous researches.^{8,24,25} Woodhams et al,³¹ expressed that ADC values lower than 1.6×10^{-3} mm²/s were related to invasive ductal carcinoma. They also reported that the sensitivity of this method was 95%.

Sui et al,³² indicated that MRI DWI with high b-values can differentiate various low- and high-grade pediatric brain tumors

(medulloblastomas, glioblastoma multiformes, germinomas, pineoblastomas, anaplastic ependymomas, anaplastic astrocytomas, etc.) with high accuracy. The fractional-order calculus model was used in this study to improve the accuracy of differentiating among low- and high-grade pediatric brain tumors.

We evaluated the ADC values obtained from four different brain regions; however, in previous studies^{4,6,7,12} the ADC values inside the tumor region were assessed to differentiate low- and high-grade tumors. The ADC cut-off values for differentiating low-grade glioma tumors from high-grade ones at the tumor center and edema were 1.12×10^{-3} mm²/s (sensitivity = 100% and specificity = 96.0%) and 1.15×10^{-3} mm²/s (sensitivity = 75.0% and specificity = 64.0%), respectively. In a study by Sasaki et al,³³ the ADC values were evaluated for differentiating benign and malignant tumors in the head and neck. They did not assess the ADC differences between the malignant and benign glioma tumors. However, they showed that the mean ADC of malignant lymphomas (0.66×10^{-3} mm²/s) was significantly smaller than that of carcinomas. The mean ADC of carcinomas (1.13×10^{-3} mm²/s) was significantly smaller than that of benign solid tumors. The mean ADC of benign solid tumors (1.56×10^{-3} mm²/s) was significantly smaller than that of benign cystic lesions (2.05×10^{-3} mm²/s). The ADC values $< 1.22 \times 10^{-3}$ mm²/s were used for predicting malignancy, having an accuracy of 86%, with 84% sensitivity and 91% specificity.

In addition to the DWI and ADC measurement, which we used in our study, other MRI methods can be used to differentiate glioma tumors. For example, arterial spin labeling (ASL) is a perfusion imaging technique that uses arterial blood water as an intrinsic magnetic tracer. This technique can be applied to evaluate the cerebral blood flow in tumor tissue.^{34,35} Several studies reported the clinical ability of ASL to differentiate glioblastoma from metastasis depending on the peritumoral part.^{36,37} Another technique, diffusion tensor imaging (DTI) has been used to differentiate glioblastomas from brain metastases using diffusion tensor metrics, such as mean diffusivity and fraction anisotropy.^{36–38} As subjects for future research, other MRI techniques with the ability of tumor differentiation, like MR spectroscopy as a useful technique in the differential diagnosis of brain tumors,⁷ DTI, and ASL^{34,35,38–40} could be used along with the ADC results to find

the appropriate MRI protocol for distinguishing the various brain tumors and grades.

The sample size of our study was relatively small, therefore, further studies are needed to confirm these results. Furthermore, it is possible to better differentiate tumor grades (I, II, III, and IV) having bigger sample sizes.

CONCLUSION

ADC measurement in tumor and edema can be very efficient in differentiating low- and high-grade glioma tumors. The ADC values of low-grade tumors were larger than high-grade ones because of higher cellularity of malignant tumors and inverse relationship between ADC and cellularity. By comparing the ROC curves of ADC values in various regions, it can be noted that the ADC values in the tumor center and edema had better sensitivity and specificity for reliable differentiating between low- and high-grade glioma tumors compared to ADC values of edema boundaries and surrounding healthy tissues. The ADC values at tumor center and tumor edema higher than $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$ and $1.15 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively, could be classified as low-grade, and tumors with lower values could be classified as high-grade tumors.

Disclosure

The authors declared no conflict of interest.

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