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RESEARCH ARTICLE

The Potential Role of Peritumoral Apparent Diffusion Coefficient Evaluation in Differentiating Glioblastoma and Solitary Metastatic Lesions of the Brain

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Abstract: ***Objective*:** Differentiating glioblastoma (GBM) and solitary metastasis is not always possible using conventional magnetic resonance imaging (MRI) techniques. In conventional brain MRI, GBM and brain metastases are lesions with mostly similar imaging findings. In this study, we investigated whether apparent diffusion coefficient (ADC) ratios, ADC gradients, and minimum ADC values in the peritumoral edema tissue can be used to discriminate between these two tumors.

***Methods*:** This retrospective study was approved by the local institutional review board with a waiver of written informed consent. Prior to surgical and medical treatment, conventional brain MRI and diffusion-weighted MRI (b = 0 and b = 1000) images were taken from 43 patients (12 GBM and 31 solitary metastasis cases). Quantitative ADC measurements were performed on the peritumoral tissue from the nearest segment to the tumor (ADC_1), the middle segment (ADC_2), and the most distant segment (ADC_3). The ratios of these three values were determined proportionally to calculate the peritumoral ADC ratios. In addition, these three values were subtracted from each other to obtain the peritumoral ADC gradients. Lastly, the minimum peritumoral and tumoral ADC values, and the quantitative ADC values from the normal-appearing ipsilateral white matter, contralateral white matter, and ADC values from cerebrospinal fluid (CSF) were recorded.

***Results*:** For the differentiation of GBM and solitary metastasis, ADC_3 / ADC_1 was the most powerful parameter with a sensitivity of 91.7% and specificity of 87.1% at the cut-off value of 1.105 ($p < 0.001$), followed by ADC_3 / ADC_2 with a cut-off value of 1.025 ($p = 0.001$), sensitivity of 91.7%, and specificity of 74.2%. The cut-off, sensitivity and specificity of ADC_2 / ADC_1 were 1.055 ($p = 0.002$), 83.3%, and 67.7%, respectively. For ADC_3 – ADC_1, the cut-off value, sensitivity, and specificity were calculated as 150 ($p < 0.001$), 91.7%, and 83.9%, respectively. ADC_3 – ADC_2 had a cut-off value of 55 ($p = 0.001$), sensitivity of 91.7%, and specificity of 77.4, whereas ADC_2 – ADC_1 had a cut-off value of 75 ($p = 0.003$), sensitivity of 91.7%, and specificity of 61.3%. Among the remaining parameters, only the ADC_3 value successfully differentiated between GBM and metastasis (GBM 1802.50 ± 189.74 *vs*. metastasis 1634.52 ± 212.65, $p = 0.022$).

***Conclusion*:** The integration of the evaluation of peritumoral ADC ratio and ADC gradient into conventional MR imaging may provide valuable information for differentiating GBM from solitary metastatic lesions.

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1. INTRODUCTION

The most common malignant lesions of the brain in adulthood are glioblastoma (GBM) and metastasis [1]. In conventional brain magnetic resonance imaging (MRI), glioblastoma and metastases are lesions with mostly similar signal intensities, and they have similar contrast enhancement patterns [2]. Therefore, it is not always clinically and radiologically possible to distinguish between these two common lesions, and in many cases, the diagnosis can only be made after the histopathological examination [3]. Clinically, it is easy to diagnose metastasis if the patient has a known

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primary malignancy and multiple lesions are present in the brain. However, in many cases of a single contrast-enhanced lesion in the brain, the histopathological examination may be necessary even if the patient has a history of a malignant tumor [2, 3]. Since the treatment process of these two lesions is completely different, it is important that these two lesions are differentiated using non-invasive methods.

Brain metastases and GBM may create a large peritumoral vasogenic edema zone on MRI. The term vasogenic edema is traditionally used to refer to the area of pathologically high T2 signal intensity in the white matter surrounding the tumoral lesion. However, the pathological white matter around the contrast-enhanced area in the center is defined as 'peritumoral edema'. The increased permeability of end-capillary membranes due to the deterioration of the blood-brain barrier and the subsequent accumulation of fluid in this area has a role in the pathogenesis of peritumoral edema [4]. Studies in the pathology literature have shown that the peritumoral edema area around metastatic tumors generally consists of pure vasogenic edema and has no infiltrative tumoral structure [5]. In GBM-like high-grade infiltrative lesions, there are tumoral foci showing invasion along the white matter pathways within the peritumoral edema [6]. Therefore, demonstrating this difference between GBM and solitary metastasis in peritumoral edema using imaging methods can contribute to the non-invasive differentiation of both lesions.

Currently, there is no non-invasive imaging method other than histopathology that has proven to be sufficiently reliable to distinguish GBM and solitary metastasis, and the research on advanced MR methods, such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), MR perfusion and MR spectroscopy (MRS) continues [7-11]. DWI is an MRI technique that detects the random Brownian motions of water molecules. Molecules of free water are in continuous random motion. However, the movement of the water molecules within the cellular environment is restricted by different intracellular and extracellular membranes and compartments. The diffusion signal in the examined tissue can be quantified by generating apparent diffusion coefficient (ADC) maps.

Compared to the other advanced MR techniques, DWI has become increasingly easier to apply and access in routine radiology practice; thus, the question of whether GBM-solitary metastasis can be differentiated using DWI has gained more importance. Intratumoral ADC measurements have not been very successful in distinguishing between these two tumors and have produced inconsistent results [12-14]. Therefore, it seems more useful to focus on determining tumor invasion in the peritumoral edema area.

In a study on the role of minimum ADC value in the discrimination of GBM-solitary metastases using peritumoral edema [13], two tumors were successfully delineated based on their statistically significant differences. However, in a more recently published study [7], although Grade IV glial tumors and solitary metastases were differentiated, it was not possible to distinguish solitary metastases from Grade III glial tumors [7, 12]. The suggestion from Lemercier *et al.* [15] that peritumoral ADC gradient can be used to discriminate between the two tumors is relatively new, and there are no other studies in the literature.

For the first time, the current study evaluated the success of proportioning ADC measurements taken from the closest, middle, and furthest segments in the peritumoral edema zone (peritumoral ADC ratios) in differentiating GBM and solitary metastases. Furthermore, as evaluated in other studies, the success of peritumoral ADC gradient and peritumoral and tumoral ADV values in discriminating between these two tumors was assessed.

2. METHODS

The study was approved by the local ethics committee. Due to the retrospective nature of the study, the ethics committee did not find it necessary to obtain written informed consent from the patients.

2.1. Patient Selection

All routine contrast-enhanced brain MR images scanned on the 3 Tesla MR device (Discovery MR750w, General Electric Healthcare, Milwaukee, WI) from May 1, 2013, to May 1, 2016, were retrospectively screened from the imaging archive of the radiology department of our faculty, and the patients that had been histopathologically diagnosed with GBM or solitary brain metastases were included in the study. From the screening process based on the above-mentioned criteria, a total of 53 patients were found, 15 diagnosed with GBM and 38 with solitary brain metastases. However, three patients with GBM and seven patients with solitary metastases were excluded due to the peritumoral edema around the lesions not being sufficient to conduct a quantitative analysis. Therefore, the study was conducted with 43 cases with a histopathological diagnosis. Thirty-one patients (72.1%) had been diagnosed with solitary brain metastases, and 12 (27.9%) with GBM. The primary diagnoses for metastatic brain tumors were as follows: lung carcinoma (n = 23), colon carcinoma (n = 2), parotid carcinoma (n = 1), malign melanoma (n = 1), laryngeal carcinoma (n = 1), thyroid carcinoma (n = 1), renal cell carcinoma (n = 1), and primary unknown cancer (n = 1). Of the two patients with lung carcinoma, the lesions were located in the cerebellum, while the remaining 29 patients with solitary metastasis had lesions in the cerebral hemisphere. For all the patients with GBM, the lesions were located in the cerebral hemisphere.

2.2. MRI Protocol and Image Evaluation

All the MR images were obtained using a standard head coil on a 3 Tesla MR imaging instrument (Discovery MR750w, General Electric Healthcare, Milwaukee, WI). The MRI protocol of our center for patients with a pre-diagnosis of mass lesions is as follows: axial T1-weighted image (TR / TE, 1857 / 36; number of signals acquired, 1; slice thickness, 4.5 mm; intersection gap, 1 mm; matrix, 256 x 224 FOV, 22 x 22 cm), axial T2-weighted image (TR / TE, 5341 / 98; number of signals acquired, 1; slice thickness, 4.5 mm; intersection gap, 1 mm; matrix, 256 x 256; FOV, 22 x

22 cm), coronal FLAIR (TR / TE, 8000 / 90; inversion time, 2300 ms; number of signals acquired, 1; slice thickness, 4.5 mm; intersection gap, 1 mm; matrix, 256 x 192; FOV, 22 x 22 cm), axial DWI (b = 0 and b = 1000), axial ADC map, and axial and sagittal contrast-enhanced T1-weighted images. DWI was performed in the transverse plane using a single-shot SE echo-planar sequence with the following parameters: TR / TE, 8300 / 110; FOV, 22 x 22 cm; slice thickness, 4.5 mm; matrix, 256 x 224; number of signals acquired, 1; intersection gap, 1 mm; diffusion gradient encoding in three orthogonal directions at b values of 0, 1000 s/mm^2. The ADC maps were calculated automatically by computer from isotropic DWI according to the equation: $ADC=-ln(SI_{b=1000}/SI_{b=0})/b$ [16].

The images of the 12 patients diagnosed with GBM and 31 with solitary brain metastasis were randomized and retrospectively evaluated. The evaluation of the images was undertaken by an observer with four years' radiological experience who was blind to the histopathological diagnosis of the lesions. The T2-weighted images, FLAIR, ADC map, T1-weighted images, and contrast-enhanced T1-weighted images were evaluated. Peritumoral edema was considered as the region outside the enhancing part of the lesion with a high signal on the T2-weighted images. We straightened three regions of interest (ROIs) in the peritumoral edema, where edema was most prominent. ADC was quantitatively measured from the peritumoral edema tissue three times, from the closest to the furthest to the tumor (the nearest, middle, and most distant), closest measurement encoded as ADC_1, furthest measurement encoded ADC_3, and ADC_2 was measured right in the middle of this straight line. Furthermore, in all measurements, ROIs that were of uniform size (approximately 10 mm^2) and spherical in shape were used. ROIs were carefully positioned to prevent contamination from neighboring tissues. Then, the ratios of these values over each other (peritumoral ADC ratios: ADC_3 / ADC_1, ADC_3 / ADC_2, ADC_2 / ADC_1) were obtained. Based on the differences between the ADC values, peritumoral ADC gradients were calculated ($ADC_3 - ADC_1$, $ADC_3 - ADC_2$, $ADC_2 - ADC_1$). In addition, for each patient, the quantitative ADC values were calculated from the normal white matter of the ipsilateral hemisphere (ADC_I), contralateral hemisphere (ADC_C), and lateral ventricle (ADC_{CSF}). ADC measurements were performed several times on the lowest signal areas of the tumoral tissue visualized in the ADC map, and the lowest signal was recorded as the minimum ADC value of the tumor (ADC_{TMIN}). Similarly, several ADC measurements were undertaken on the peritumoral tissue at the lowest signal areas visualized in the ADC map, and the lowest signal was recorded as the minimum ADC value of the peritumoral area (ADC_{PMIN}). Then, the ADC_{PMIN} / ADC_C ratio was calculated by dividing ADC_{PMIN} by ADC_C, and ADC_{TMIN} / ADC_C was obtained by dividing ADC_{TMIN} by ADC_C. During the measurement of ADCs, areas with cystic, necrotic, and hemorrhagic signals were avoided. All ADC measurements were performed on a Hewlett Packard Z800 workstation using the dedicated software, AW VolumeShare 5.

2.3. Statistical Analysis

All digital ADC data was converted to 10^{-6} and processed. A total of 43 cases with the histopathological diagnosis were grouped according to tumor type. Thirty-one of the cases (72.1%) were diagnosed with solitary brain metastasis, and the remaining 12 cases (27.9%) were diagnosed with GBM.

The Shapiro-Wilk test was used to evaluate the normal distribution of numerical data. Numerical data such as age, ADC values showed a parametric distribution ($p>0.05$). Normally distributed data were expressed as a mean ± standard deviation (SD). The independent-samples t-test was used to compare numerical data regarding age and ADC with gender between the GBM and solitary brain metastasis groups.

For the evaluation of the ADC ratios and ADC gradients, a receiver operating characteristic (ROC) analysis was undertaken to determine the cut-off value of the statistically significant results obtained from the data on ADC_3 / ADC_1, ADC_3 / ADC_2, ADC_2 / ADC_1, $ADC_3 - ADC_1$, $ADC_3 - ADC_2$, and $ADC_2 - ADC_1$. In the ROC curve analysis, in addition to the significance of the test and the cut-off value, the area under the curve (AUC), the Youden's index, sensitivity, and specificity were calculated. Pearson's Chi-square test was used to evaluate the significance of differences created by gender between the GBM and solitary brain metastasis. SPSS v. 21.0 (IBM Corporation, New York, USA) was used for statistical analysis, with $p \leq 0.05$ being accepted as statistically significant.

3. RESULTS

Table **1** presents the demographic data obtained from the cases included in the study. There was no significant difference between the two groups in terms of ADC_1 and ADC_2 values ($p = 0.162$ and $p = 0.533$, respectively). However, the difference in the mean ADC_3 values was statistically significant between the groups ($p = 0.022$). (Fig. **1**) shows GBM exhibits a positive gradient of ADC values between regions closest (ADC_1) and furthest (ADC_3) from enhancing tumor, but metastasis does not show this kind of correlation. Statistically significant difference was found between the groups concerning the peritumoral ADC ratios; *i.e.*, ADC_3 / ADC_1, ADC_3 / ADC_2, and ADC_2 / ADC_1 ($p < 0.001$, $p = 0.001$, $p = 0.008$). Similarly, there was a statistically significant difference between the groups in terms of the mean values of $ADC_3 - ADC_1$, $ADC_3 - ADC_2$, and $ADC_2 - ADC_1$ that were used to calculate the peritumoral ADC gradient ($p < 0.001$, $p = 0.001$, and $p = 0.001$, respectively) (Table **2**, (Figs. **2** and **3**). There was no significant difference between the groups in the ADC_1 and ADC_2 parameters and ADC_{PMIN} / ADC_C and ADC_{TMIN} / ADC_C ratios (Table **2**). The parameters of ADC_3 / ADC_1, ADC_3 / ADC_2 and ADC_2 / ADC_1 also provided statistically significant results in the ROC analysis ($p < 0.001$, $p = 0.001$, and $p = 0.002$, respectively). The ADC_3 / ADC_1 ratio was the strongest diagnostic parameter compared to the remaining parameters, with the AUC being calculated as 0.898. When the cut-off value was taken as 1.105, the sensi-

Table 1. Demographics for glioblastoma and solitary metastatic lesions.

Variable	-	Metastasis	Glioblastoma	Total
-	n (%)	31 (72.1)	12 (27.9)	43 (100)
Age (year)*	Mean ± SD	61.1 ± 9.80	58.75 ± 9.54	60.44 ± 9.67
Gender** (Men)	n (%)	27 (62.8)	6 (14)	33 (76.7)

*p=0,481; Independent Sample T Test **p=0,01; Pearson's Chi Square Test

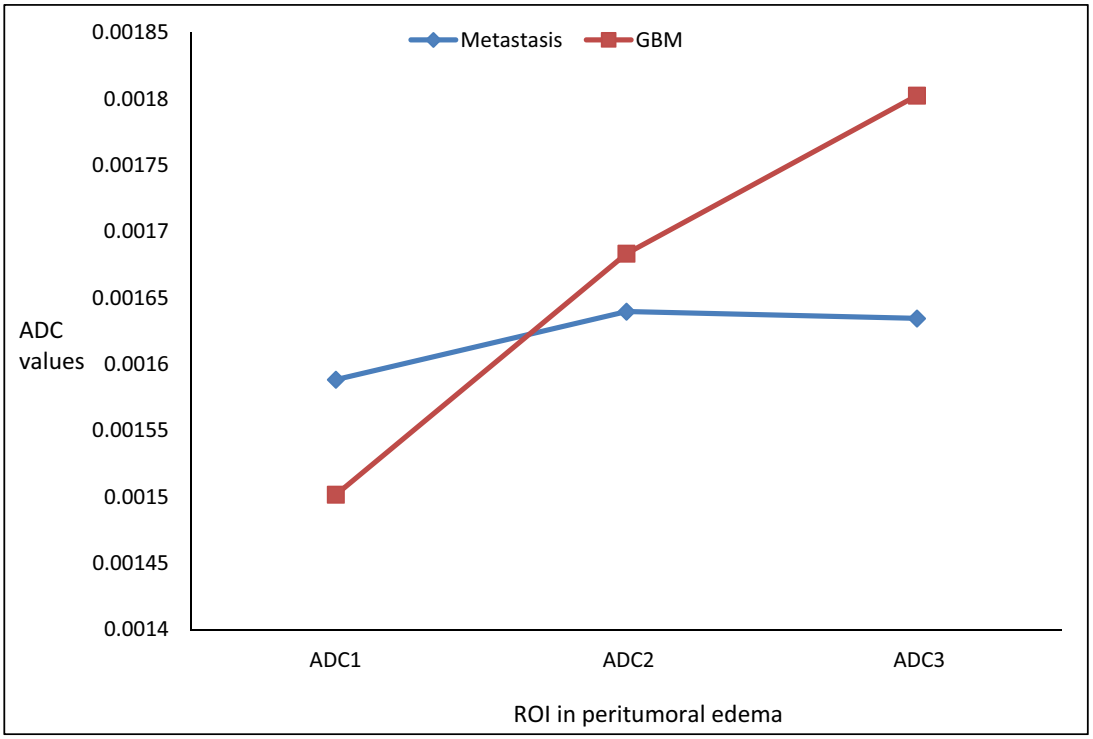

Fig. (1). Line graph shows ADC values for different ROIs (ADC_1, ADC_2 and ADC_3) in peritumoral edema in GBM and solitary metastasis groups. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Peritumoral and tumoral ADC values (x 10^{-6} mm^2/s), ADC ratios and ADC gradient values (x 10^{-6} mm^2/s) for glioblastoma and solitary metastatic lesions.

MRI Findings	Glioblastoma (n=12)	Metastasis (n=31)	p
ADC_1	1501.67 ± 230.57	1588.39 ± 155.99	0.162
ADC_2	1683.33 ± 215.55	1639.68 ± 199.62	0.533
ADC_3	1802.50 ± 189.74	1634.52 ± 212.65	0.022*
ADC_3 / ADC_1	1.21 ± 0.13	1.02 ± 0.07	< 0.001*
ADC_3 / ADC_2	1.07 ± 0.07	0.99 ± 0.06	0.001*
ADC_2 / ADC_1	1.12 ± 0.10	1.03 ± 0.05	0.008*
ADC_3 – ADC_1	300.83 ± 167.79	46.13 ± 121.51	< 0.001*
ADC_3 – ADC_2	119.17 ± 98.67	-5.16 ± 102.30	0.001*
ADC_2 – ADC_1	181.67 ± 132.86	51.29 ± 87.40	0.001*
ADC_{TMIN}	817.25 ± 224.86	785.90 ± 177.61	0.633
ADC_{PMIN}	1495.00 ± 219.86	1559.35 ± 171.91	0.315
ADC_I	776.50 ± 38.01	787.68 ± 64.63	0.489
ADC_C	760.00 ± 26.74	786.94 ± 70.20	0.076

(Table 2) contd....

MRI Findings	Glioblastoma (n=12)	Metastasis (n=31)	p
ADC_{CSF}	3335.83 ± 188.32	3268.39 ± 158.52	0.242
ADC_{PMIN} / ADC_{C}	1.97 ± 0.29	2.00 ± 0.31	0.747
ADC_{TMIN} / ADC_{C}	1.07 ± 0.27	1.01 ± 0.25	0.478

Values are presented as mean ± SD. ADC_1 = ROI closest to the tumor, ADC_2 = ROI in the middle of edema, ADC_3 = ROI furthermost from the tumor, ADC_{TMIN} = minimal ADC value in tumoral lesion. ADC_{PMIN} = minimal ADC value in peritumoral edema. ADC_I = mean ADC value in ipsilateral normal white matter, ADC_C = mean ADC value in contralateral normal white matter. ADC_{CSF} = mean ADC value in the cerebrospinal fluid.

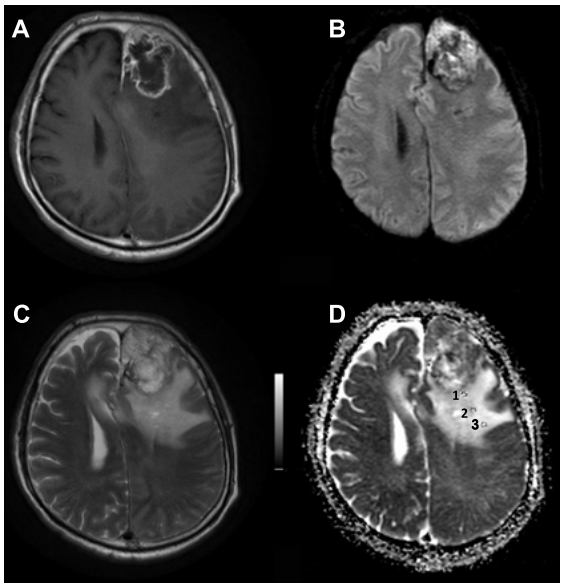

Fig. (2). A 64-year-old male patient with a GBM diagnosis. **A.** Contrast-enhanced T1-weighted image, **B.** DWI (b = 1000), **C.** T2-weighted image, **D.** ADC image showing a large (55.3 mm in dimension) lesion in the left frontal lobe, causing a pronounced peritumoral edema. Note the marked heterogeneous signal in the peritumoral edema zone on T2-weighted image and ADC map. In the ADC map, using ROI 1, 2 and 3, ADC_1, ADC_2 and ADC_3 were calculated as 1620 x 10^{-6}, 1830 x 10^{-6}, and 1900 x 10^{-6}, respectively.

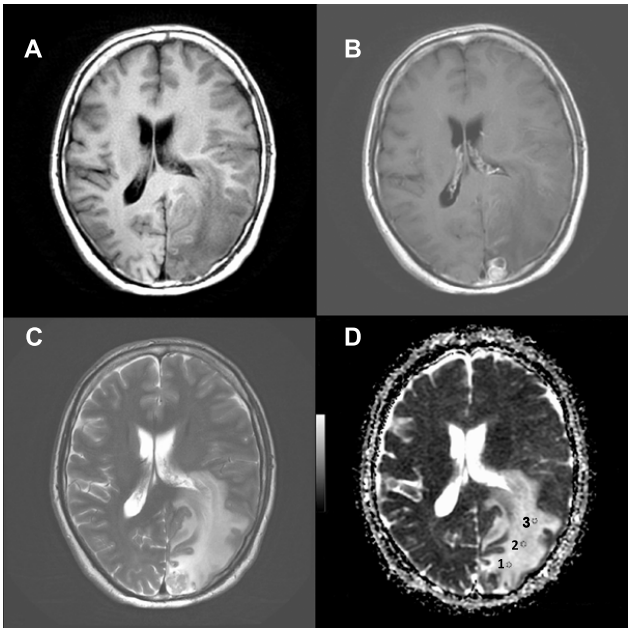

Fig. (3). A 52-year-old man with a diagnosis of colon carcinoma and solitary brain metastasis. **A.** Contrast-enhanced T1-weighted image, **B.** DWI (b = 1000), **C.** T2-weighted image, **D.** ADC image showing a mass lesion measuring 21.7 mm in diameter, located in the left occipital lobe, which caused a significant peritumoral edema. In the ADC map, using ROI 1, 2, and 3, ADC_1, ADC_2 and ADC_3 were calculated as 1590 x 10^{-6}, 1640 x 10^{-6}, and 1650 x 10^{-6}, respectively.

Table 3. ROC analysis for peritumoral ADC ratios and ADC gradient values.

Peritumoral ADC Ratios and Gradient Values	AUC*	p	Youden's Index	Cut-off Value	Sensitivity (%)	Specificity (%)
ADC_3 / ADC_1	0.898	< 0.001	0.788	1.105	91.7	87.1
ADC_3 / ADC_2	0.825	0.001	0.659	1.025	91.7	74.2
ADC_2 / ADC_1	0.810	0.002	0.511	1.055	83.3	67.7
ADC_3 – ADC_1	0.884	< 0.001	0.755	150	91.7	83.9
ADC_3 – ADC_2	0.841	0.001	0.691	55	91.7	77.4
ADC_2 – ADC_1	0.793	0.003	0.53	75	91.7	61.3

*AUC-Area under curve.

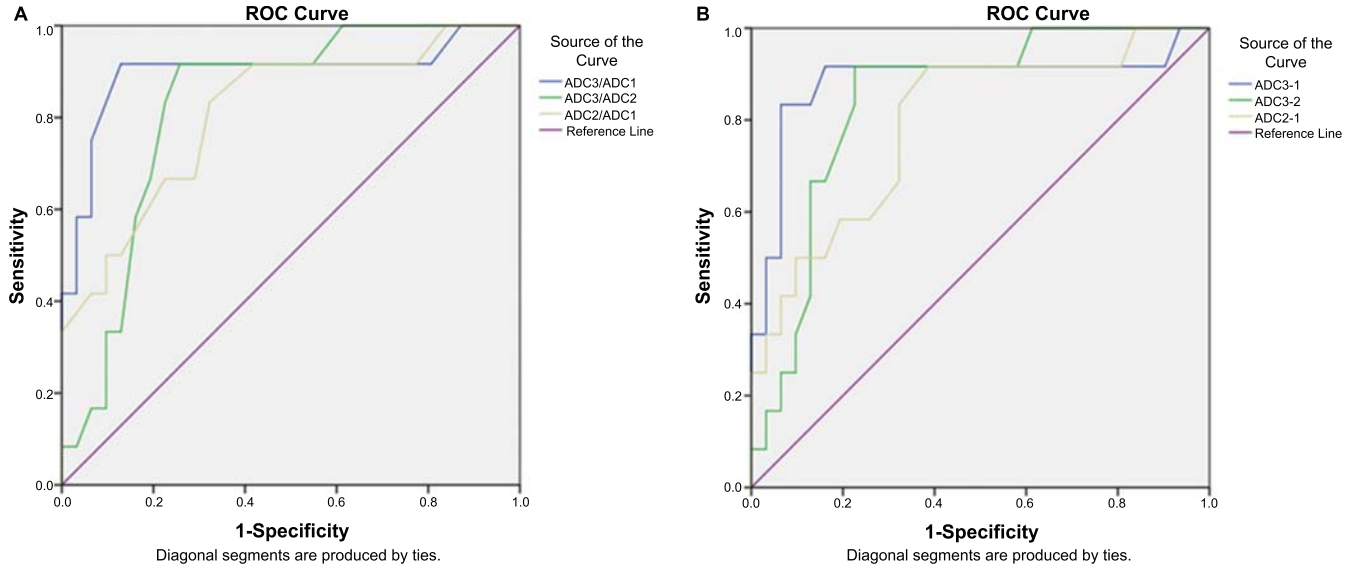

Fig. (4). ROC curves. **A.** For ADC ratios, **B.** For ADC gradients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tivity was 91.7%, and the specificity was 87.1%. The AUC value was calculated as 0.825 for ADC_3 / ADC_2 and 0.810 for ADC_2 / ADC_1. When the cut-off value for ADC_3 / ADC_2 was taken as 1.025, the sensitivity and specificity were 91.7% and 74.2%, respectively. Lastly, for ADC_2 / ADC_1, using the cut-off value of 1.055, the sensitivity and specificity were calculated as 83.3% and 67.7%, respectively (Table **3**, Fig. **4a**).

The parameters of ADC_3 – ADC_1, ADC_3 – ADC_2, ADC_2 – ADC_1, which had significant differences between the groups, were also statistically significant according to the ROC analysis ($p < 0.001$, $p = 0.001$, and $p = 0.003$, respectively). Among the parameters examined, ADC_3 – ADC_1 presented as the second most powerful potential diagnostic tool with an AUC of 0.884. When the cut-off value was taken as 150×10^{-6} mm^2/s, the sensitivity was 91.7%, and the specificity was 83.9%. The AUC value was calculated as 0.841 for ADC_3 – ADC_2 and 0.793 for ADC_2 – ADC_1. Taking the cut-off value as 55×10^{-6} mm^2/s for ADC_3 – ADC_2, the sensitivity, and specificity were obtained as 91.7% and 77.4%, respectively. Lastly, at the cut-off value of 75×10^{-6} mm^2/s for ADC_2 – ADC_1, the sensitivity, and specificity were 91.7% and 61.3%, respectively (Table **3**, Fig. **4b**).

4. DISCUSSION

In the current study, the ADC_3 / ADC_1 ratio was found to be the most powerful parameter in differentiating between GBM and metastasis. To the best of our knowledge, this is the first study to evaluate the ratio of ADC values measured from the nearest and furthest segments in the peritumoral edema tissue. The gradients of ADC_3 – ADC_1, ADC_3 – ADC_2, and ADC_2 – ADC_1 were found to be significantly higher in the GBM group than in the solitary metastasis group, which is similar to the results of a previous study [15]. In patients with GBM, the cause of the findings described above was considered as the presence of tumoral cell groups that histopathologically show invasion in the peritumoral edema tissue, particularly closest to the contrast-enhanced tumor tissue, and the decrease of malignant cells in-

filtrating into the peritumoral edema further from the tumor. The significantly higher ADC gradients in the GBM group support the findings reported by histopathological studies [6].

According to the findings obtained from the current study, undertaking a quantitative ADC analysis in peritumoral edema can provide important clues for the differentiation of GBM and solitary metastasis. In particular, the measurement of the ADC_3 / ADC_1 ratio presented as the strongest diagnostic tool with a sensitivity of 91.7% and a specificity of 87.1% in the discrimination of the two groups of tumors. The findings also indicated that in the delineation of the two tumor groups, the ADC ratios, and ADC gradients were stronger parameters than morphometric analyses and signal intensity measurements on T2-weighted images [17, 18] and had similar sensitivity and specificity to analyses using MRS, DTI, and MR perfusion [19-22]. This means that more successful diagnoses can be achieved with a more practical method.

It is known that the ADC values may vary according to the MR parameters, systems, or software used [23]. This raises doubts about the universal reproducibility of ADC gradients obtained by subtracting intratumoral or peritumoral ADC values or the values measured from the peritumoral area. In this case, it may be necessary to calculate different cut-off points for each MR system and software. However, it is considered that the peritumoral ADC ratios (ADC_3 / ADC_1, ADC_3 / ADC_2, and ADC_2 / ADC_1) that were first introduced in this study may be more universal and repeatable in differentiating GBM and metastasis.

In previous studies, the measurement of ADC_{TMIN} was not found to be useful in distinguishing between GBM and solitary metastasis [12-14]. However, Server *et al.* reported that the ADC_{TMIN} value and the ADC_{TMIN} / ADC_C ratio were statistically significant in discriminating brain metastases from high-grade gliomas [24]. In the current study, no significant difference was observed between GBM and solitary metastasis in terms of the ADC_{TMIN} values and the ADC_{TMIN} / ADC_C ratio. These results can be attributed to the frequent prevalence of intratumoral heterogeneity, hemorrhage and necrosis in GBM and solitary metastases, and the T2* effect and susceptibility artifacts due to these changes.

Lee *et al.* reported that the minimum ADC values measured from the peritumoral edema tissue were useful in discriminating between GBM and solitary metastasis, and the peritumoral ADC values were significantly lower in patients with GBM than in solitary metastases due to infiltrative peritumoral edema [13]. However, Server *et al.* suggested that the ADC_{PMIN} values were not useful in such differentiation [24]. In the current study, the ADC_{PMIN} values were not significantly different in the two tumor groups.

In this study, the ADC value measured from the most distant segment of the peritumoral area (ADC_3) successfully distinguished between GBM and solitary metastasis, while the measurements taken from the nearest and middle segments of the peritumoral area (ADC_1 and ADC_2, respectively) did not support such differentiation. This demonstrates that the peritumoral area should be evaluated in a three-dimensional plane rather than a two-dimensional one. In fact, GBM invasion follows white matter tracts and vascular structures around the tumor [25], and this can also explain why the orthogonal planes examined in this study did not correspond to the invasion pathways.

In a study by Lee *et al.*, the ADC_{PMIN} / ADC_C parameter was found to be significantly lower in GBM than in solitary metastasis, indicating that this parameter could be used to discriminate between these two lesions and to determine the site of biopsy before a stereotactic biopsy [13]. In the current study, there was no significant difference between GBM and solitary metastasis for the ADC_{TMIN} / ADC_C and ADC_{PMIN} / ADC_C parameters.

Conventional MR imaging has an important place in the preoperative evaluation of brain tumors and monitoring response to treatment due to its excellent soft-tissue resolution and superb delineation of anatomical boundaries. However, with conventional MR imaging, it is often not possible to obtain information about the size of the tumor, the true size of the lesion, and the histopathological type and grade [26]. Therefore, studies on advanced MR imaging methods, such as DWI, MRS, MR perfusion, and DTI, continue to distinguish lesions, particularly GBM and brain metastasis that are commonly seen [20, 27-29].

The retrospective design, relatively small number of samples, and the operator-dependent and manual measurement of ROI may be considered as the limitations of this study. Furthermore, the axial sections of ADC measurements may not have always been exactly parallel to the orientation of the peritumoral edema tissue. Also, lesions with histopathologically diagnosed as GBM or metastasis may not form prominent peritumoral edema, especially in the early stages of the disease. In these kinds of cases, ADC measurement techniques can be challenging or even impossible.

CONCLUSION

Quantitative ADC measurement in peritumoral edema is a helpful parameter for differentiating between GBM and solitary brain metastasis. Peritumoral ADC ratios and peritumoral ADC gradients were significantly higher in patients with GBM than in those with solitary metastasis; therefore, these parameters were useful for the differentiation of these two groups of tumors. However, there is a need for further studies of prospective nature with larger case series and multiple observers.

MAIN POINTS

-Differentiation of GBM and solitary brain metastasis often becomes problematic with conventional MRI.

-There is an inverse correlation between cellularity and ADC measurement in tissues.

-Peritumoral ADC ratios and ADC gradients can be used to distinguish between GBM and solitary metastasis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Scientific Research Ethical Committee of the Faculty of Medicine, Osmangazi University, Turkey, (approval number: 2016-239).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All data collection were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Due to the retrospective nature of the study, the ethics committee did not find it necessary to obtain written informed consent from the patients.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declare none.

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