

Differentiation of glioblastoma, brain metastases and central nervous system lymphomas using amount of vasogenic edema and diffusion MR imaging of tumor core and peritumoral zone- Searching for a practical approach

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Ethics Committee Approval

The study was approved by institutional review board of Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital (2022-04/75).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The differential diagnosis of solitary brain tumors poses challenges for clinicians and radiologists, often leading to invasive biopsy procedures. Therefore, this study aimed to evaluate the variations in edema volume and diffusion characteristics between the tumor core and peritumoral zone in cases of glioblastoma, brain metastasis, and central nervous system lymphoma. The aim was to identify additional parameters for conventional magnetic resonance imaging (MRI) that could aid in the differential diagnosis.

Methods: A total of 39 patients (13 with central nervous system lymphoma, 13 with glioblastoma, and 13 with brain metastases) were included in this retrospective cohort study. Apparent diffusion coefficient (ADC) values were calculated from the ADC maps obtained from Brain MRI for both the lesion and peritumoral region. Additionally, the largest diameter of the vasogenic edema-mass complex was measured using T2 sequences. In the contrast-enhanced series, the largest diameter of the metastatic lesion was measured. The edema-mass ratio was determined by dividing the diameter of the edema-mass complex by the diameter of the mass.

Results: There was a statistically significant difference in the edema-mass ratio among the tumor types ($P=0.008$). Further analysis using Bonferroni correction revealed that this difference was primarily due to glioblastoma. Compared to patients with lymphoma and brain metastases, lesions diagnosed as glioblastoma exhibited a lower edema-mass ratio. Additionally, a statistically significant difference was observed in the ADC value measured from the lesion according to the tumor type ($P=0.017$). It was determined that lesions associated with central nervous system lymphoma had lower ADC values than those with glioblastoma.

Conclusion: Including lesional and perilesional ADC values obtained through diffusion-weighted examination and edema mass ratio measurements may enhance the accuracy of differential diagnosis. Utilizing these imaging characteristics in a multiparametric approach, as suggested by this research, can improve the accuracy of diagnosing malignant cancers, thereby enabling better patient management and treatment decisions.

Keywords: magnetic resonance imaging, brain edema, brain neoplasms, neuroimaging

Introduction

Pre-treatment characterization and differential diagnosis of malignant brain tumors remain problematic in daily clinical practice, particularly when distinguishing between glioblastoma, metastasis, and central nervous system lymphomas (CNSLs) in solitary brain lesions using conventional magnetic resonance imaging (MRI) [1].

Accurate initial diagnosis and appropriate subsequent treatment are crucial factors that significantly impact patient monitoring and management. The treatment choice can vary significantly depending on the type of brain lesion, emphasizing the importance of accurate differential diagnosis [1-3]. Currently, many patients undergo invasive biopsy procedures to aid in the differential diagnosis process.

Standard MR imaging offers valuable information for the differential diagnosis of solitary malignant brain tumors. For instance, CNSLs typically appear as homogeneously enhanced masses on contrast-enhanced T1-weighted sequences, particularly in immunosuppressed patients. In contrast, glioblastomas often exhibit ring-like lesions with central necrosis. However, it is important to note that solid-enhancing glioblastoma lesions lacking necrosis can resemble CNSLs, while atypical CNSLs with necrosis may mimic glioblastoma lesions [4,5]. Metastatic tumors, conversely, can present with a wide range of distinct imaging features.

Despite the availability of publications on advanced MR techniques, such as diffusion-weighted imaging (DWI), dynamic susceptibility-weighted contrast-enhanced perfusion-weighted imaging (DSC-PWI), and susceptibility-weighted imaging, the accurate characterization and differential diagnosis of malignant brain tumors remain a significant challenge in current radiology practice [6-8].

By quantifying physiological differences in water diffusion, DWI assists in detecting microscopic structural changes that may not be apparent in conventional MR examination. The apparent diffusion coefficient (ADC) provides a quantitative measure of diffusion characteristics. Tumors with high cellularity often exhibit restricted diffusion and consequently have low ADC values. As a result, ADC is considered a valuable marker for tumor cellularity [9,10].

Primary or secondary malignant brain tumors are often accompanied by perilesional vasogenic edema. While the precise pathophysiology of peritumoral edema remains unclear, it is recognized that the extent of peritumoral edema can vary depending on the histopathological and clinical characteristics of the tumor [11].

Our objective was to assess the disparities in edema volume and diffusion characteristics between the tumor core and peritumoral zone among cases of glioblastoma, brain metastasis, and central nervous system lymphoma. This evaluation aimed to identify supplementary parameters for conventional MR examination that could aid in the differential diagnosis.

Materials and methods

Our institutional review board, at the Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital, has approved this retrospective study (2022-04/75). Prior to contrast-

enhanced imaging, informed consent was obtained from the patients.

We retrospectively evaluated patients who underwent brain MRI at our radiology clinic between January 2019 and January 2022. The inclusion criteria for this evaluation were patients diagnosed with a supratentorial solitary brain tumor, whose diagnosis was pathologically confirmed, and who underwent follow-up.

Patients meeting the following criteria were excluded from the study: those who did not undergo brain MRI prior to surgery or radiation therapy, those for whom clinical information could not be obtained, those without a definitive diagnosis, and those diagnosed with a neurodegenerative disease.

Consequently, the study included a total of 39 patients, consisting of 13 cases of CNSL, 13 cases of glioblastoma, and 13 cases of brain metastases. All the identified lesions were located in the supratentorial region and were accompanied by perilesional edema.

MRI Examination and Post-processing

All imaging procedures were conducted using a 1.5 T MR scanner (Signa Exp, GE Medical Systems) equipped with a 16-channel HNS (head-neck-spine) coil. A standard MR examination was performed prior to contrast administration, which included axial T1-weighted images, axial, coronal, and sagittal T2-weighted images, and axial FLAIR images. Additionally, as per the standard protocol, a post-contrast 3D T1W sequence was acquired. Throughout the entire MR examination, patients were instructed to keep their eyes closed, and no sedation or anesthesia was administered to any of the patients.

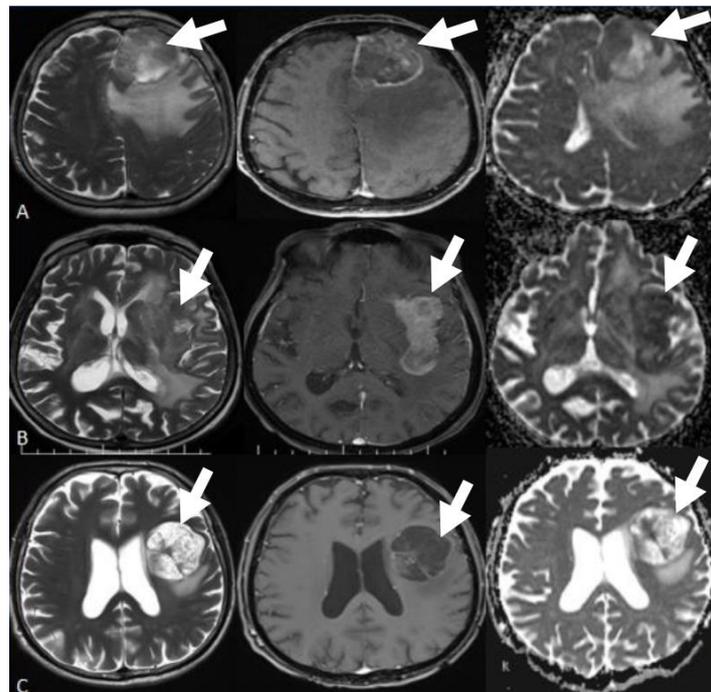
DWI was conducted using a transverse single-shot echo-planar sequence with the following parameters: TE (Echo Time) of 89.9 ms, TR (Repetition Time) of 8000 ms, a slice thickness of 5 mm, FOV (Field of View) of 26 cm, matrix size of 128×128 , NEX (Number of Excitations) of 1, and diffusion-sensitive gradients with b-values of 1000 s/mm^2 in three orthogonal directions.

Two experienced radiologists, each with over ten years of Brain MRI expertise, assessed the MRI images. ADC values were derived from the central and peritumoral regions of the lesions, specifically within a 1 cm distance from the lesion border, using the ADC maps of the patients. Calculations were made using a similar and small ROI (5 mm^2).

When necrosis was present, measurements were conducted excluding the necrotic area. The smallest ADC value was determined based on three measurements for each lesion, and the corresponding peritumoral region was documented.

Furthermore, the T2 sequences were utilized to measure the largest diameter of the vasogenic edema-mass complex. In the contrast-enhanced series, the largest diameter of the metastatic lesion was measured. Lastly, the edema-mass ratio (EMR) was determined by dividing the diameter of the edema-mass complex by the diameter of the mass. The case samples were presented in Figure 1.

Figure 1: T2, contrast-enhanced T1 and ADC maps of supratentorial, solitary brain tumors (arrows); (A): Glioblastoma, (B): CNSL, (C): Solitary metastasis.



CNSL: central nervous system lymphoma

Statistical analysis

For the statistical analysis of the study findings, the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) software was utilized. Descriptive, graphical, and statistical methods were employed to assess the distribution of scores obtained from each continuous variable. The Shapiro-Wilk test assessed the normality of scores derived from continuous variables. Descriptive statistical methods, such as numbers, percentages, means, medians, standard deviations, were employed to evaluate the research data. Additionally, for comparisons involving more than two groups in quantitative data with a normal distribution, ANOVA (variance) analysis was performed. Data that did not exhibit a normal distribution were analyzed using the Kruskal-Wallis test.

The Bonferroni test was employed to identify the specific groups from which the differences originated. Pearson’s chi-square tests were conducted for qualitative group comparisons. ROC (Receiver Operating Characteristic) analysis was utilized to determine the most suitable edema mass ratio and lesion ADC for differentiation in the presence of a glial brain tumor. The significance level was set at a 95% confidence interval with a threshold of $P < 0.05$.

Results

The mean age of the 39 patients included in the study was 58.00 (13.41) years, ranging from 24 to 80 years. Of the participants, 64.1% were male. No statistically significant difference was observed in age distribution and gender representation across different tumor types ($P=0.705$ for age, $P=0.120$ for gender).

A statistically significant difference in EMR was found among different tumor types ($P=0.008$). Further analysis using the Bonferroni method revealed that this difference was primarily driven by glioblastoma. Patients diagnosed with glioblastoma exhibited lower EMR than those with lymphoma and brain metastases.

A statistically significant difference was observed in the ADC value measured from the lesion based on tumor type ($P=0.017$). The Bonferroni analysis indicated that this difference specifically existed between patients with glioblastoma and lymphoma. Consequently, it was determined that lesions associated with CNSL exhibited lower ADC values than those with glioblastoma. There was no significant difference in peritumoral ADC values according to tumor type ($P=0.098$). Patient and lesion characteristics according to tumor types are summarized in Table 1.

Table 1: Distribution of Patient Characteristics by Tumor Type (n=39)

	All (n=39)	Glioblastoma ¹ (n=13)	CNSL ² (n=13)	Metastasis ³ (n=13)			
Variables	n(%)	n(%)	n(%)	n(%)	$\chi^2/F/K-W_{z2}$	P-value	dif
Gender					$\chi^2=4.234$	0.120	
Female	14(35.9)	2(15.4)	7(53.8)	5(38.5)			
Male	25(64.1)	11(84.6)	6(46.2)	8(61.5)			
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)			
Age	58.00(13.41)	60.08(13.49)	55.62(16.00)	58.31(10.98)	F=0.352	0.705	
EMR	2.24(0.75)	1.73(0.46)	2.46(0.79)	2.53(0.72)	K-W _{z2} =9.633	0.008*	1<2,3
Lesion ADC	0.74(0.21)	0.85(0.18)	0.62(0.16)	0.77(0.22)	F=4.569	0.017*	1>2
Perilesional ADC	1.36(0.25)	1.47(0.23)	1.26(0.23)	1.34(0.25)	F=2.478	0.098	

* $P < 0.05$, CNSL: central nervous system lymphoma, EMR: edema-mass ratio, F: One-Way ANOVA (analysis of variance); χ^2 : Chi-Square Test; $K-W_{z2}$: Kruskal-Wallis-H Test, SD: Standard deviation, dif: difference

The results of the ROC analysis revealed that the area under the curve (AUC) for EMR in determining the presence of glioblastoma was 0.81 (95% CI: 0.66-0.95). This indicates a statistically significant diagnostic value of EMR in identifying the presence of glioblastoma ($P=0.002$).

Following the ROC analysis, the optimal EMR value for glioblastoma was determined to be 1.82. At this cutoff value, the sensitivity was 69.2%, specificity was 84.6%, positive predictive value (PPV) was 69.2%, negative predictive value (NPV) was 84.6%, and overall accuracy was 79.5%.

Furthermore, the AUC for the lesion ADC value in diagnosing glioblastoma was determined to be 0.71 (95% CI: 0.54–0.88). Consequently, the lesion ADC value exhibited statistical significance in its ability to diagnose glioblastoma ($P=0.037$).

Following the ROC analysis, the optimal ADC value for glioblastoma was determined to be 0.83. At this cutoff value, the

sensitivity was 53.8%, specificity was 84.6%, PPV was 63.6%, NPV was 78.6%, and overall accuracy was 74.4% (Table 2).

Table 2: Optimal Cut off Value for EMR and Lesion ADC min Value in Determining the Presence of GBM (ROC Analysis Results)

	Glioblastoma		Lesion ADC Value	Glioblastoma	
	Cutoff value	↓1.82		↑0.83	0.707(0.536-0.878)
EMR	AUC(%95 CI)	0.805(0.660-0.950)		0.707(0.536-0.878)	
	P-value	0.002		0.037	
	Sensitivity	69.2%(9/13)		53.8%(7/13)	
	Specificity	84.6%(22/26)		84.6%(4/26)	
	PPV	69.2%(9/13)		63.6%(7/11)	
	NPV	84.6%(22/26)		78.6%(22/28)	
	Accuracy	79.5%(31/39)		74.4%(29/39)	

GBM: glioblastoma

Discussion

Our study unveils that the diffusion characteristics and the extent of edema might offer certain advantages in the differential diagnosis of solitary malignant brain tumors with perilesional edema, a task that proves challenging using standard conventional MR examination. Consequently, our study evaluated the diffusion characteristics of the lesion, the perilesional region, and the extent of edema, aiming to determine their diagnostic value.

In the present study, we identified a statistically significant distinction in the measured ADC values from the lesion based on the tumor type, specifically between lymphoma and glioblastoma. Notably, lymphoma patients exhibited significantly lower ADC values. Previous studies in the literature have predominantly focused on evaluating ADC values for the differential diagnosis of glioblastoma (GBM) and metastasis. While some studies have reported significant differences in ADC values [10,12], others have found no substantial variance [13]. Furthermore, literature reports indicate lower ADC values in lymphoma cases than other malignant tumors attributed to the tumor's histology. Lymphomas are characterized by giant cells and a reduced extravascular space, which has been postulated as the underlying reason for restricted diffusion and lower ADC values [3].

Glioblastoma, known for its high aggressiveness and extensive infiltration, is recognized to exhibit infiltration in both the perilesional area and the contrasting tumor cortex. On the other hand, in metastasis cases, perilesional edema is typically attributed to pure vasogenic edema resulting from compression of the surrounding tissue. Previous studies have consistently demonstrated that the perilesional area in glioblastoma cases is associated with low ADC values, whereas metastases tend to display higher ADC values [14-17].

The study involved 74 cases of solitary malignant brain tumors, consisting of 27 glioblastomas, 30 metastases, and 17 CNSLs. The findings revealed a notable disparity in the ADC values measured from the perilesional area between metastasis and glioblastoma cases, indicating a significant difference. Conversely, no significant distinction was observed in CNSLs.

In contrast to the existing literature, our study did not identify a statistically significant difference in ADC values within the perilesional region among these three tumor types.

In contrast to the previous studies in the literature that examined perilesional edema regardless of lesion size, our study focused on assessing the significance of the EMR in the context of the differential diagnosis. By comparing the extent of perilesional edema, we observed that lesions diagnosed with

glioblastoma exhibited lower EMR values than patients with lymphoma and brain metastases.

To our knowledge, no other publication in the English literature has compared cases of GBM, metastasis, and lymphoma based on the extent of perilesional edema.

Limitations

Despite the encouraging results, the research has several restrictions. First, the study's sample size was relatively small, restricting the data's capacity to be generalized. Second, the analysis only included individuals with glioblastoma, brain metastases, and CNSLs as their sole histologically confirmed diagnoses; this may not accurately reflect the complete range of brain malignancies seen in clinical practice. Third, since the research was retrospective, it had biases and limitations. Fourth, the study did not assess the diagnostic efficacy of other imaging modalities, which may be complementary in the differential diagnosis of these malignancies, such as perfusion-weighted imaging or magnetic resonance spectroscopy.

To confirm the results of this investigation and provide more precise diagnosis algorithms for these brain tumors, more extensive prospective trials that include a wider variety of imaging modalities are required.

Conclusion

In conclusion, our study demonstrates that the combination of lesional and perilesional ADC values measured by diffusion-weighted examination and edema mass ratio measurements can potentially increase the accuracy of differential diagnosis between glioblastoma, brain metastases, and central nervous lymphoma. Furthermore, the study suggests that a multiparametric approach utilizing these imaging parameters may improve the diagnostic accuracy of these malignancies, enabling better patient management and treatment decisions.

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