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Evaluation of the Accuracy of Diffusion-weighted Imaging (DWI) in Differentiating Primary Brain Lymphoma (PBL) of Glial Tumors

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Abstract **Introduction:** Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) map have an important role in the diagnosis and differentiation of brain tumors. Since the use of ADC for differing glioma of primary brain lymphoma (PBL) tumors is controversial and requires further investigation, the aim of this study was to use diffusion-weighted MRI for determining the ADC values of glial tumors and the relationship between glioma and PBL tumors. **Methods:** This cross-sectional retrospective study is carried out by reviewing documents, images, and ADC brain MRIs of 60 patients (26 males, 34 females) admitted to Shohada Hospital from 2006 to 2016 in Tehran after brain biopsy. The ADC values were measured in the tumor area from diffusion images of the brain with b-values of 0 and 1000 s/mm^2. For data analysis, ANOVA and the Tukey post hoc test were used. **Results:** The ADC values of astrocytoma grade 2 were significantly greater than other grades of glioma and PBL tumor ($P < 0.05$). However, there were no statistically significant differences among the ADC values between anaplastic grade 2 and glioblastoma grade 4. In addition, the ADC values of the PBL were significantly lower than those of astrocytoma grade 2 ($P < 0.05$). **Conclusions:** The results of this study showed that the ADC values in the astrocytoma grade 2 were higher than the PBL. Thus, knowledge of the ADC values can be helpful in better diagnostics of astrocytoma and PBL cases and for future studies.

Keywords: *diffusion-weighted imaging, apparent diffusion coefficient, brain, glioma, primary brain lymphoma*

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1. Introduction

1.1. Background

The diagnosis and treatment of brain lesions are very important in controlling actions, human behavior, and internal organs. These lesions form a wide range of diseases and one of the most important lesions is brain tumors. In general, brain tumors are divided into primary and metastatic tumors (metastasis) [1]. Primary brain tumors originate from the brain, while metastatic tumors of the brain are metastases resulting from systemic malignancies. The primary tumors of the central nervous system are the third cause of death in the age group of 15 to 35 [2]. The incidence of brain tumors has increased by over 40% in all age groups over the past 20 years. The diagnosis and treatment of the brain's primary tumors are two major problems for doctors and researchers. There are several types of primary brain tumors; the primary brain tumors are named according to the type of cells or part of the brain in which they begin to grow. One of the most common primary tumors of the brain is the glioma tumor, which is caused by the involvement of glial cells and the malignancy of these cells in the brain. Glial tumors make up about 40% of the brain's primary tumors [3]. Glioma is divided into four degrees based on the severity of the disease. These types of tumors have the worst prognosis among central nervous system cancers and despite all therapeutic measures, including brain surgery and tumor removal, chemotherapy, and radiotherapy, the average survival rate in these patients is 14 months [4,5].

Another primary brain tumor is PBL. Brain lymphoma is a highly malignant tumor of non-Hodgkin's B-cell lymphoma, which is confined to the CNS, the meninges, and the eyes [6]. This tumor originates from the CNS and is limited to it without any systemic disease; this definition does not include systemic lymphoma metastasis to the CNS [6,7]. The tumor manifestation is often extensive, and most of all involves supratentorial parenchyma [8]. Due to the widespread growth of the disease, the symptoms of the disease are mainly cognitive impairment, psychomotor slowness, personality changes,

and disorientation. [9]. PBL is the most common brain tumor in AIDS patients, with two to six percent of patients showing symptoms during their illness [10,11]. The prevalence of this tumor is increasing among patients with immunodeficiency. However, the lack of adequate clinical studies on this disease, and as a result of limited information about it, ultimately causes these patients to have no prognosis with the current therapies and they have an average survival of 10-20 months [12]. The initial identification of this tumor could be very important and vital for the patient [13]. The early diagnosis of lymphoma and its differentiation from other brain tumors can be helpful in choosing the appropriate treatment method [6-14].

The gold standard method for identifying a variety of brain tumors is a biopsy, which is an invasive and high-risk method. The limitations of the amount and location of sampling are other disadvantages of biopsies. An accurate assessment of the type of tumor is important for determining the appropriate treatment method.

A brain tumor is a massive tissue where some of its cells are irreversibly reproduced. It is evident that these cells do not follow the mechanisms that control the natural cells. The growing tumor occupies the intracranial space and disrupts normal brain function [15]. This tumor can exert pressure on the brain tissue and damage it [16]. The apparent symptoms of the disease vary according to the location of the tumor in the brain since the function of each part of the body is controlled by a specific segment of the brain [17].

Glioma is one of the most common primary tumors in the brain that originates from glial cells. This tumor is classified based on location, grading, and the cells that originate from it. Brain glioma tumors are classified into two groups by the World Health Organization, based on histological characteristics such as cellularity, molecular movements, and necrosis. In general, gliomas are classified in four degrees (I, II, III, and IV). Low-grade tumors (I, II) are quite distinct, and although they are not benign, they have a good prognosis for the patient. Tumors with high degrees (III, IV) are non-differentiated and malignant, and are considered to be serious in terms of prognosis [18,19,20].

1.2. Objective of Research

Considering that the differentiation of PBL tumors from glial tumors with routine MRI images is very difficult and the prevalence of these tumors is increasing, the aim of this study was to evaluate the primary lymphoma tumor using diffusion technique and to differentiate it from glial tumors.

1.2.1. General Objective

The aim is to evaluate the accuracy of diffusion-weighted imaging (DWI) in the differentiation of primary brain lymphoma (PBL) of glial tumors.

1.2.2. Specific Objectives

Does ADC have a significant difference in the primary brain lymphoma (PBL) tumor relative to glial tumors?

2. Materials and Methods

2.1. Research Design and Setting

This study was an applied, observational, and retrospective one. The study population consisted of patients with brain tumors who had been referred to Shohadaye Hospital in Tajrish, Tehran during the years 2006-2016.

2.2. Sampling

2.2.1. Sample Size

The number of samples was based on previous studies, and 30 cases were determined depending on the conditions [21,22,23].

2.2.2. Sampling Method

After the stereotaxic biopsy, the results of their pathology confirmed primary lymphoma and glial tumors. The study was based on existing data (routine data base study). The data collection method was observational and based on the review of patient records. Patients with systemic lymphoma were excluded from the study. The subjects of this study were patients with primary lymphoma tumors and patients with glial tumors who were selected based on the results of a confirmed pathology test. For this study, the patients that were selected had diffusion and ADC images were used.

2.2.3. Measurement Tool

Imaging with Siemens, Avanto, 1.5 Tesla was performed by applying diffusion gradients. The eight-channel head coil for head imaging was used in this test.

2.4. Data Collection

To conduct this study, all cases of patients who had been referred to Shohadaye Tajrish Hospital during the period from 2006 to 2016 were evaluated. The medical history of these patients was examined. Age and sex variables in the study were evaluated. For this study, the results of stereotaxic biopsy and pathology were examined. According to the results of pathologic testing, the patients were divided into two groups. The first group comprised patients with primary lymphoma tumors, and the second group consisted of patients with glial tumors. Patients with systemic lymphoma were not entered into the study. The patients who were selected for this study had diffusion and ADC images and used data that had the same imaging parameters. In this study, Syngo software was used for data analysis. At first, all images were entered into the software; T1W and T2W routine images were used to determine the tumor area. Then, from the diffusion images with a b-value of 0.100 s/mm^2, the ADC value for the two groups was calculated. After the research, the aggregated data were analyzed through statistical tests. The Syngo software in the Siemens MRI device was used to examine images and measure ADC values (Figure 1 to Figure 2).

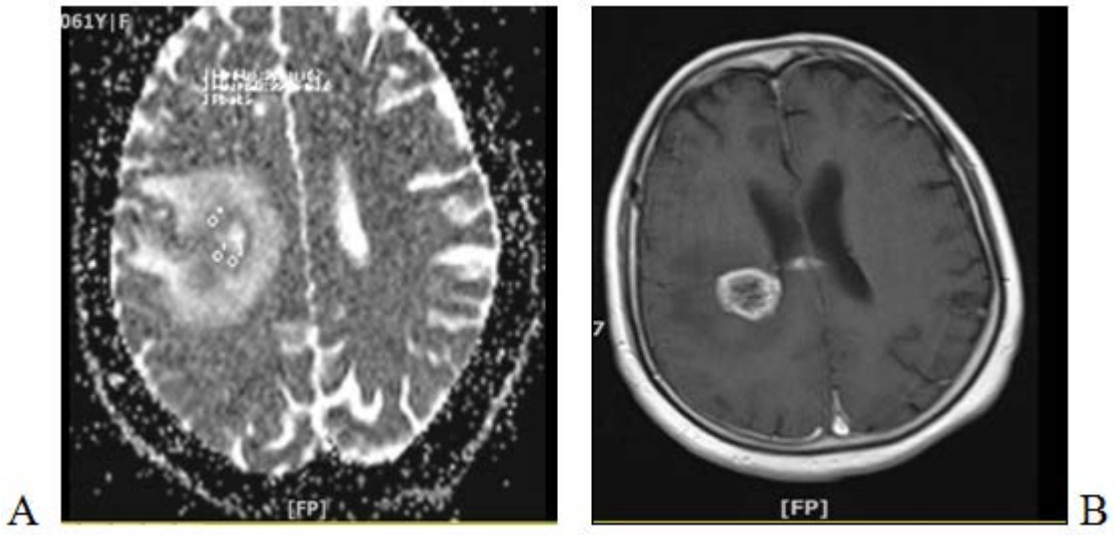

Figure 1. A 61-year-old, ADC-map, measuring ADC with up ROI (A), T1-W + C (B); anaplastic astrocytoma

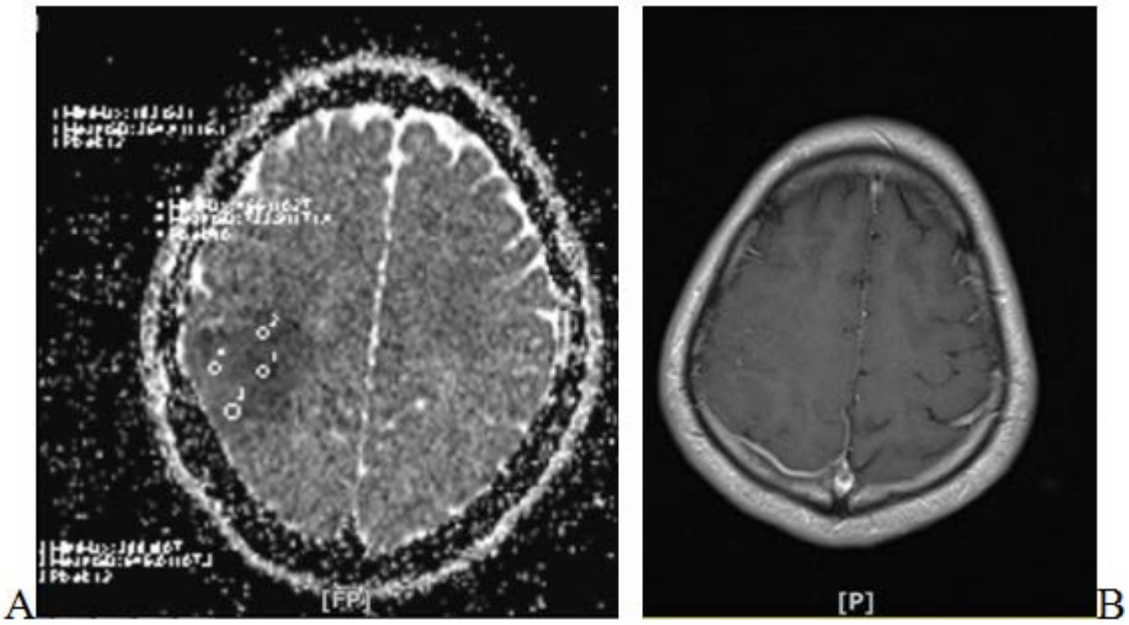

Figure 2. 27-year-old man; ADC-map; ADC measurement with ROI (A); T1-W + C (B); grade II glioblastoma

3. Results

3.1. Result 1

As outlined in Table 1, out of a total of 20 patients in the astrocytoma grade 2 group, 13 were male (35%) and seven were female (65%). Of the 15 patients in the anaplastic grade 3 group, eight were male (46.7%) and seven were female, (53.3%). Of the 13 patients in the glioblastoma grade 4 group, eight were male (38.5%) and five were female (61.5%). Of the 12 patients in the lymphoma group, five were male (58.3%) and seven were female (41.7%). In total, out of 60 patients, 26 patients were male (43.3%) and 34 were female (56.7%). Considering that the P-value for the chi-square test is equal to 0.602 and greater than 0.05, it is concluded that gender distribution is homogeneous between the four groups studied.

As shown in Table 2, the mean age of the patients in the astrocytoma grade 2 group was 38.20 years with a standard deviation of 12.627. The mean age of the patients in the anaplastic grade 3 group was 41.33 years with a standard deviation of 13.129 years. The mean age of the patients in the glioblastoma grade 4 group was 55.92 years with a standard deviation of 12.822 years. The mean age of the patients in the lymphoma group is 48.92 years with a standard deviation of 15.318. Based on the analysis of variance test, the P-value is equal to 0.003, which is less than 0.05, thus indicating the inhomogeneity of the patient's age in the four groups.

In this study, the validated Kolmogorov–Smirnov test was used to check the assumption of the normality of the research data. In this test, according to the following hypotheses, the data is normalized:

H0: Data is a normal distribution.

H1: Data is not a normal distribution.

Table 1. Frequency distribution of respondents in terms of gender

Group	Male	Female	Total
Astrocytoma Grade 2	(%65)13	(%35)7	(%100)20
Anaplastic grade 3	(%53.3) 8	(%46.7) 7	(%100)15
Glioblastoma grade 4	(%61.5)8	(%38.5)5	(%100) 13
Lymphoma	(%41.7)5	(%58.3) 7	(%100) 12
Total	(%43.3)26	(%56.7) 34	(%100) 60
χ^2= 1.859, df = 3, P-value = 0.602			

Table 2. Descriptive statistics of ages of respondents

Group	Age[standard diviation±age]
Astrocytoma Grade 2	12.627 ± 38.2
Anaplastic grade 3	13.129 ± 41.33
Glioblastoma grade 4	12.822 ± 55.92
Primary Lymphoma	15.318 ± 48.92
Total	14.762 ± 44.97
F-value = 5.334, P-value = 0.003	

As shown in Table 3, the significance level of the Kolmogorov–Smirnov test for the ADC variable in each of the four types of tumor is higher than 0.05. As a result, they have normal distribution and the use of parametric statistical methods is possible.

Hypothesis: Does ADC have a significant difference in the primary brain lymphoma (PBL) tumors relative to glial tumors?

To compare the ADC values in glial tumors with three different grades and primary lymphoma tumors, according to the normal data, the analysis of variance test was used. The results of this test are given in Table 4.

As shown in Table 4, the P-value of the test is smaller than 0.05, which indicates a significant ADC difference in the three tumors and the primary lymphoma tumor. This was followed by the Tukey post hoc test that was used to determine the differences.

According to the results of the post hoc test, Figure 1 shows that the ADC value in the astrocytoma grade 2 tumor with an average of 1.37 is the highest and has a significant difference compared to the remaining tumors ($P < 0.05$). Also, the ADC was not significantly different ($P > 0.05$) in the anaplastic grade 3 tumor (0.88), glioblastoma grade 4 (0.80), and primary lymphoma (0.64) tumors. However, the primary lymphoma tumor's ADC value was less than that of the astrocytoma grade 2 tumor and there are significant differences between the two. Hypothesis: Considering the existing data, further studies were conducted on whether the ADC changes in the case of glial tumors. To compare the ADC values in glial tumors with three different grades, analysis of variance was used due to the normality of the data. The results of this test are given in Table 5.

As shown in Table 5, the P-value of the test is less than 0.05, which indicates a significant ADC difference in three tumors; followed by the Tukey post hoc test that was used to determine differences.

According to the results of the post hoc test, Figure 2 shows that the ADC value in the astrocytoma grade 2 tumor with an average of 1.37 is the highest and has a significant difference with the remaining tumors ($P < 0.05$). Also, the ADC was not significantly different ($P > 0.05$) in the anaplastic grade 3 (0.88) and glioblastoma grade 4 (0.80) tumors. However, it was less than the ADC value of the tumor of astrocytoma grade 2 and has significant differences.

Table 3. Kolmogorov-Smirnov test for ADC variable

Type of tumor	P-value	Amount of K-S statistics	standard deviation±age	Results
Astrocytoma Grade 2	0.20	0.104	0.521 ± 1.37	Normal
Anaplastic grade 3	0.074	0.21	0.360 ± 0.88	Normal
Glioblastoma grade 4	0.150	0.202	0.154 ± 0.8	Normal
Primary Lymphoma	0.162	0.208	0.200 ± 0.64	Normal

Table 4. ADC values in glial tumors with 3 different grades and primary lymphoma tumors

P-value	Amount of F statistic	ADC(x 10^{-3} mm^2 /s)±standard diviation	number	Tumor	Indicator
0.001	12.393	0.521 ± 01.37	4	Astrocytoma Grade 2	[ADC]
		0.360 ± 00.88	37	Anaplastic grade 3	
		0.154 ± 00.8	41	Glioblastoma grade 4	
		0.2 ± 00.64	12	Primary Lymphoma	

Table 5. ADC values in glial tumors with 3 different grades

P-value	Amount of F statistic	ADC(x 10^{-3} mm^2 /s)±standard diviation	number	Tumor	Indicator
0.001	10.394	0.521 ±1.37	4	Astrocytoma Grade 2	[ADC]
		0.360 ±0.88	37	Anaplastic grade 3	
		0.154 ± 0.8	41	Glioblastoma grade 4	

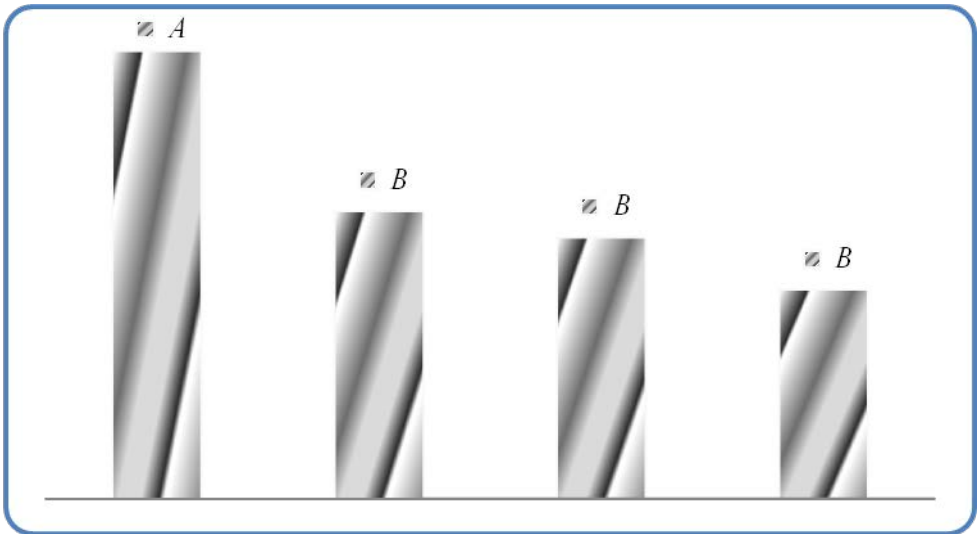

Chart 1. Tukey post hoc test results, ADC's comparison between 3 measured tumors and primary lymphoma tumors

4. Discussion

Technological advances in hardware and software have made possible ultrafast sequence imaging in milliseconds. The ultrafast sequence imaging allows for an almost infinite range of applications that would never have been possible with normal sequence imaging. These are collectively called functional imaging techniques because unlike conventional, straightforward structural imaging, they allow MRI to be used for performance evaluation and physiology, one of which is DWI. The DWI technique is an MRI technique by which information on the propagation of water molecules can be obtained. In this technique, the microscopic emission of water molecules in the tissue can be measured using non-coherent and coherent gradients [24]. Because water molecules change in many pathologies, measuring water release is very important [25]. Using this technique, one can measure the ADC in each tissue, and the ADC measurement can differentiate many different lesions [26,27].

Diffusion is a term used to describe the motion of molecules due to the Brownian thermal motion. This movement is bound by as the likes of ligaments, membranes, and macromolecules. Diffusion imaging is a non-invasive method for investigating the Brownian motion of water molecules in the human body. Changes in tissue structure or cellularity affect the diffusion of water molecules in the human body, which can be quantitatively analyzed using ADC in DWI [28].

Sometimes, depending on the structure of the tissue, the braces of diffusion are oriented. The spreading of molecules also occurs on both sides of the tissues, especially from adherent emission regions to free emission regions. The pure displacement of molecules is called the ADC, and a sequence can be sensitive to this motion by applying two gradients on either side of the pulse of 180 degrees. In diffusion imaging, spin-echo pulse sequences are often used with unipolar gradients. In recent years, a lot of research has been done on this subject. [29,30,31]

In a 2011 study entitled "Differences between glioblastoma, cerebral metastasis, and primary brain lymphoma," Sumeiwang et al., using Diffusion Tractography Imaging (DTI) and Dynamic-susceptibility contrast (DSC), tested 26 cases of glioblastoma, 25 cases of metastasis, and 16 primary lymphoma cases made retrospective diagnoses. The result was that the combination of the DTI and Rcvb tests can be useful in differentiating the glioblastoma from metastasis and PBL. Cheng-Hong Toh et al., (2008) conducted a study titled "Difference of diffusion characteristics in DTI imaging of primary brain lymphoma and multiform glioblastoma." The hypothesis of this study was that there are major differences in the fractional anisotropy (FA) and ADC of lymphoma and gliobastoma (GBM), which allows us to differentiate between them. Before surgery, 10 patients with lymphoma and GBM were subjected to DTI. The target area of the tumor that the ADC and FA measured were made of the solid part of the tumors that were enhanced, as well as the symmetric regions on the opposite side of the brain that had normal tissue. The FA and ADC values of the lymphoma were significantly reduced compared to the normal half-tissue. Also, as the FA and ADC of the primary lymphoma were significantly lower than the GBM, the DTI was able to differentiate the lymphoma from the GBM. [32,33]

In a study titled "PBL differentiation of multiform glioblastoma with arterial spin labeling (ASL), diffusion-weighted imaging (DWI), and ^{18}F-fluorodeoxyglucose positron emission tomography (PET)," Kaji Yamashita et al. retrospectively studied 56 patients, including 19 patients with PBL and 37 patients with GBM. From the ASL data, an adipose tissue blood flow and a relative tissue blood flow (Rtbf) were obtained. From inside the tumor-enhanced region, the lowest ADC (ADC min) and the highest standardized uptake value (SUV max) were obtained from the DWI and FDG-PET data respectively. All four parameters were compared using the Kruskal-Wallis test between PBL and GBM. The absolute tumor blood flow (aTBF), relative tumor blood flow (rTBF), and ADC min were mostly higher in GBMs than PBLs. In addition, the SUV max was significantly lower in the GBM than the PBLs. The area under curve (AUC) for the aTBF was higher than the RTBF, although this difference was not statistically significant. The result is that these techniques are useful for differentiating the PBL from GBM. Argyroxyda et al., in a study titled "Imaging of CT perfusion in internal brain tumors to distinguish High-Grade

Glioma from PBL" in 2010, analyzed the CT perfusion data for 43 patients with brain tumors. Four patients had low-grade glioma, 31 patients had glioblastoma, and eight patients had intracranial lymphoma. In the intended areas the Tumour regions of interest (ROI), cerebral blood flow (CBF), cerebral blood volume (CBV), and permeability were calculated. The average values were calculated and group differences were tested using the Wilcoxon and Mann–Whitney U test. [34,35]

Result: Compared to normal parenchyma, low-grade glioma shows no significant difference in perfusion parameters (p <0/0001) for the CBV and for the CBF (P = 0.002). The mean K^{trans}values showed a significant increase in lymphoma compared with healthy tissue (P = 0.0078) but no increase was observed in the CBV. Therefore, in the present study, we try to increase the knowledge base by using information and studying approved patients.

4.1. ADC Value in Primary Brain Lymphoma Tumor (PBL) Relative to Glial Tumors

The present study showed that the ADC values obtained from diffusion images with b-value of 0.1000 s/mm^2 in astrocytoma grade 2 tumors with an average of 1.37 had the highest value and had a significant difference with the remaining tumors (P < 0.05). Additionally, the ADC values were not significantly different (P > 0.05) in the two anaplastic grade 3 (0.88) tumors and the glioblastoma grade 4 tumor, but they were less than the ADC of the astrocytoma grade 2 tumor and had a significant difference.

In studies conducted by Guo AC et al. in 2002, an ADC with b-values of 0 and1000 s/mm^2 was 0.580 to 0.750 x10^{-3}mm^2/s in patients with lymphoma, and 0.963 to 1.140 x10^{-3} mm^{2}s in patients with glioblastoma [36] The results of our study were in line with the results of this study. Therefore, the comparison between the ADC and cellularity in lymphoma and high-grade astrocytoma showed that higher cellularity leads to diffusion that is more restricted. In addition, our research results indicate that ADC is associated with tumor cellularity.

In addition, in studies conducted by Kono K, Inoue Y, and Nakayama K et al. in 2001, there is an inverse association between tumor cellularity and ADC meningioma and glioma [37], which is consistent with the results of our research.

Depending on the diffusion of intracellular and extracellular diffusion, there is a slow and rapid diffusion. The ADC values primarily indicate rapid diffusion and therefore indicate the diffusion of extracellular space. Therefore, an inverse relationship between cellularity, tumor, and ADC in b-value may be due to changes in the release of extracellular water. [37]

The authors of this study showed that the difference between the mean ADC values of ADC in the astrocytoma grade 2 tumor with the mean of 1.37 was the highest and had a significant difference with the remaining tumors (P < 0.05). Also, the ADC was not significantly different (P > 0.05) in three anaplastic grade 3 tumors (0.88), glioblastoma grade 4 (0.80), and primary lymphoma tumor (0.64). However, the ADC of the primary lymphoma tumor was less than the astrocytoma grade II tumors, and they have significant differences.

According to the findings of "Server A" in 2002, the difference between ADC glioblastoma and lymphoma was not significant, although the ADC of lymphoma was less than that of high-grade glioma, which was not consistent with the results of our study. This could be due to the low sample volume of our study.

In our study, the ADC values of lymphoma were lower than those of astrocytoma grade 2, which is due to the inverse relationship between cellularity and ADC as well as more extracellular space. As a result, higher changes in extracellular water release in high-grade tumors lead to low ADC. The diffusion of water molecules may be influenced by tissue density, voxel perfusion, or T2-shine through effect, where ADC values are independent of its effect. [33,35,36]

In fact, due to ADC values, it is difficult to differentiate glioblastoma tumors from lymphoma. The results of our study were in line with the results of research conducted by Yamasaki, Kitis, and Server A in 2005 and 2009. [32-37]

Based on the findings of this study, the differentiation between primary lymphoma and astrocytoma grade 2 using ADC values with a b-value of 0.1000 s/mm^2 can be helpful.

According to studies conducted on healthy and pathologic brain tissue using ADC, Meyer et al. found that relaxed diffusion represents the concentration of macromolecules adhering to water, cell size, and extracellular space. Therefore, tissue complexity may increase the extracellular space in malignant lesions [38].

5. Conclusion

The purpose of this study was to evaluate the role of DWI in differentiating the primary lymphoma tumor from glial tumors. The information based on the ADC values can be used to better detect astrocytoma from the PBL, as well as in future studies.

Our studies were performed by examining medical records and images in which b-values of 0 and 1,000 s/mm^2 were used. Therefore, further studies with more b-values are suggested. Also, the suggestion to other researchers in this field would be to explore the scope of research in future studies and to consider other variables that may affect research results.

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