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Correlation of morphologic findings and apparent diffusion coefficient values with Ki-67 proliferation index in patients with glioblastoma

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ABSTRACT

Objectives: Glioblastoma is the most common primary neoplasm of the central nervous system (CNS) and has a very poor prognosis. Ki-67 proliferative index is a value that reflects the mitotic index of the tumor and is associated with poor prognosis. The radiological features of the tumors can predict the course of the disease. The aim of this study is to evaluate the relationship between the morphology and the apparent diffusion coefficient (ADC) values of the tumor with the Ki-67 index on preoperative magnetic resonance imaging (MRI).

Methods: Preoperative MRI images of 52 patients with pathological diagnosis of glioblastoma were evaluated retrospectively. A score ranging from 1 to 3 was assigned to each of the morphological features of the tumors (peritumoral edema, necrosis, contrasting pattern, heterogeneity, hemorrhage, mass effect, tumor contour irregularity), and was added up to obtain the total score. In addition, the ADC values of each tumor were measured at the workstation. ADC value and total score of each tumor, and Ki-67 values obtained histopathologically were compared.

Results: There was a negative correlation between Ki-67 index of tumors and ADC values (r = -0.895, p = 0.0001). A significant positive correlation was found between the morphological features of the tumors and their total scores (r = 0.772, p = 0.0001). A statistically significant negative correlation was found between total score and ADC values (r = -0.780, p = 0.0001). Heterogeneity and necrosis were the features most closely associated with Ki-67. These were followed by mass effect, hemorrhage and contour irregularity, respectively.

Conclusions: The morphological findings and ADC values obtained from preoperative MRI are related to the Ki-67 value, and thus can be used to predict prognosis and guide treatment in the early period.

Keywords: Glioblastoma, Ki-67, magnetic resonance imaging, prognosis

Glioblastoma is the most common and aggressive malignant brain tumor, classified as high grade according to the World Health Organization (WHO) classification in adults. It constitutes approximately 12-15% of all intracranial tumors. It is the most malignant form of astrocytomas with poor prognosis [1-

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3]. It is very important to know the histological features and grade of astrocytic tumors in order to determine the treatment approach and predict the prognosis [4]. Ki-67 protein is a cellular marker associated with ribosomal RNA transcription and cell proliferation. Ki-67 proliferation index; it can objectively reflect the proliferation and malignancy of tumor cells [5]. It has been shown in previous studies that increased Ki-67 expression is positively correlated with an increased degree of malignancy and poor prognosis in glioblastoma patients [6]. However, defects in tumor sampling, particularly inadequate stereotactic biopsies and heterogeneity of astrocytomas, may lead to an underestimation of the degree of malignancy [7]. Also, histological examination cannot show tumor effects on adjacent brain tissue.

Magnetic resonance imaging (MRI) can accurately assess the macroscopic features of the tumor associated with clinical symptoms. Morphological findings such as peritumoral edema, necrosis, enhancement pattern, heterogeneity, hemorrhage, mass effect, tumor contour irregularity, and apparent diffusion coefficient (ADC) values obtained in diffusion-weighted imaging (DWI) represent the biological behavior of the tumor. Therefore, the integration of histological data with MRI findings may provide a better evaluation of the clinical outcomes of patients with astrocytoma [8]. Recently, many study evaluated advanced MRI or morphological imaging. However, as in this study, there are only few study in the literature assesing both advanced MRI or morphological imaging [9-11].

In this study, we compared the quantitative values obtained by scoring the morphological findings according to their severity and ADC values with the Ki-67 proliferative index. Thus, we wanted to reveal the prognostic importance of morphological findings and ADC values.

METHODS

Patients

The study included 52 patients who were diagnosed with glioblastoma histopathologically and had preoperative MRI (34 males and 18 females; mean age: 52.4 years; and age range: 5-81 years). Patients with a known history of malignancy and the solid component of the tumors smaller than 1 cm were excluded from the study. The patients included in the study had not undergone any previous tumor-related operation and did not receive chemotherapy or radiotherapy. The ethical approval was obtained from a local commitee (Decision No: 2019.12.2.08.098, Date: 27.12.2019).

MRI Protocol

All examinations were performed with a 1.5 T (Achieva, Philips, Netherlands) MRI device with an 8-channel head coil. The MRI protocol consists of the following sequences: Axial, coronal, and sagittal T2-weighted turbo spin-echo sequence (TR/TE=4800/100; FA:90; slice thickness: 5.5 mm; interslice gap, 1 mm; FOV 23 cm, NEX: 1), axial T1 weighted spin-echo sequence (TR/TE=450/15; FA:69; slice thickness: 5.5 mm; interslice gap, 1 mm; FOV 23 cm; NEX: 1), axial FLAIR sequence (TR/TE =7000 /97; FA:90; section thickness: 5.5 mm; interslice gap, 1 mm; FOV 23 cm; NEX: 1), sagittal T1-weighted gradient echo sequence after intravenous injection of 0.1 mmol/kg of contrast medium (TR/TE: 25/4 ms; FA: 30; slice thickness 1 mm; interslice gap, 1 mm; FOV 23 cm; NEX: 1). DWIs were obtained with single-shot SE echo planar imaging sequence (EPI) by applying gradient in three directions in the axial plane (TR/TE=2800/72; FA: 90; slice thickness 5 mm; interslice gap, 1 mm; FOV 23 cm) ; NEX: 2; b-values; 0 and 1000 s/mm2). The ADC map is automatically generated by the device.

Evaluation of Images

Images were evaluated by a radiologist with 13 years of neuroradiology experience (İ.Ş.). Ki-67 proliferation index values were not known during the evaluation. The following MRI morphological findings were scored between 1-3 according to their severity, and a total score was obtained by summing these scores for each tumor (Table 1).

DWI images were evaluated on the workstation of the MRI device company (IntelliSpace Portal, version 7.0.1, Philips Healthcare, Best, The Netherlands). While ADC mapping, which was created automatically by the MRI device, 3 ROIs (region of interest) were drawn manually within the non-cystic or non-necrotic, non-hemorrhagic and enhanced solid components of the tumors. The average of the values of

Table 1. Scores given to MRI characteristics of tumors

Edema	1: no or little edema
	2: there is edema, smaller than the tumor volume
	3: there is edema, more than tumor volume
Necrosis	1: no necrosis
	2: located less than half of the tumor
	3: located more than half of the tumor
Hemorrhage	1: no
	2: yes
Enhancement	1: no enhancement
	2: poor or nodular
	3: pronounced and heterogeneous
Heterogeneity	1: homogeneous tumor
	2: tumor is heterogeneous on T2WI
	3: the tumor is heterogeneous in both T1WI and T2WI
Mass effect	1: lost of subarachnoid space
	2: compression to the ventricular system
	3: midline shift
Irregular contour	1: well-circumscribed
	2: Irregular contour

MRI = magnetic resonance imaging, T1WI and T2WI = T1-and T2-weighted axial imaging

these 3 measurement was recorded as the final ADC value. On ADC mapping, ROIs drawn manually to the lowest ADC areas. Then automatically minimum, maximum and mean ADC values were obtained from measured area within ROI.

Ki-67 Expression Analysis

Ki-67 was assessed by immunohistochemistry using paraffin-embedded tissue samples which were cut into 5 μm thickslices. Briefly, all sections were deparaffinized and rehydrated, then antigen retrieval wasperformed. Non-specific binding sites were blocked by serum at 37 °C for 15 min (Beijing Zhongshan Golden Bridge Biotechnology Company, Beijing, China).The sections were stained with monoclonal-mouse anti-human Ki-67 antibody (Beijing Zhongshan Golden Bridge Biotechnology Company) was incubated in a humidified chamber at 37°C for 120 min. Then the specimens were incubated with secondary goat anti-mouse antibody, respectively (Beijing Zhongshan Golden Bridge Biotechnology Company, China) at 37 °C for 30 min. Ki-67 expression were visualized using 3,3′-diaminobenzidine (DAB)followed by counterstaining with hematoxylin. The expression of Ki-67 was determined in an area with the highest frequency of immunohistochemically stained nuclei on the assumption that it represent best the proliferation potential within a tumor. At least, 1000 cells were 400×counted at amagnification. Ki-67 was considered positive when the cell nuclei were stained brown-yellow. Ki-67 index was calculated as the percentage of positive cells.

Statistical Analysis

The statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In the evaluation of the data, besides the descriptive statistical methods (mean, standard deviation), the distribution of the variables was examined with the Shapiro-Wilk normality test. In the intergroup comparisons of the normally distributed variables; one-way analysis of variance, in comparison of paired groups; independent t test, in determining the relations

Table 2. Demographic distribution of the cases included in the study, minimum-maximum values and averages of Ki-67 and ADC values and total score

		n	Mean ± SD	Minimum	Maximum
Age (years)	**Man**	34	51.44 ± 16.96	5	81
	Woman	18	54.17 ± 13.07	32	79
	Total	52	52.38 ± 15.65	5	81
Ki-67		52	38.13 ± 17.64	8	90
ADC (× 10^{-3} mm^2/s)		52	0.8 ± 0.21	0.36	1.2
Total Score		52	15.56 ± 2.25	10	19

ADC = apparent diffusion coefficient

of variables with each other; Pearson correlation test was used. P value less than 0.05 was considered as significant.

RESULTS

Of the patients included in the study, 34 (65.38%) were male and 18 (34.62%) were female. The mean age of males was 51.44 ± 16.96 years, and the mean age of females was 54.17 ± 13.07 years. The mean age of all patients was 52.38 ± 15.65) years.

The lowest ki-67 value of tumors with pathological diagnosis of glioblastoma was 8, while the highest value was 90. The mean ki-67 value was found to be 38.13 ± 17.648). The lowest ADC value was 0.36 × 10-3 mm^2/s and the highest was 1.2 × 10-3 mm^2/s. The mean ADC value was 0.8 ± 0.21 × 10-3 mm^2/s. The total score obtained by scoring the morphological features of the tumors was found to be 10 as the lowest

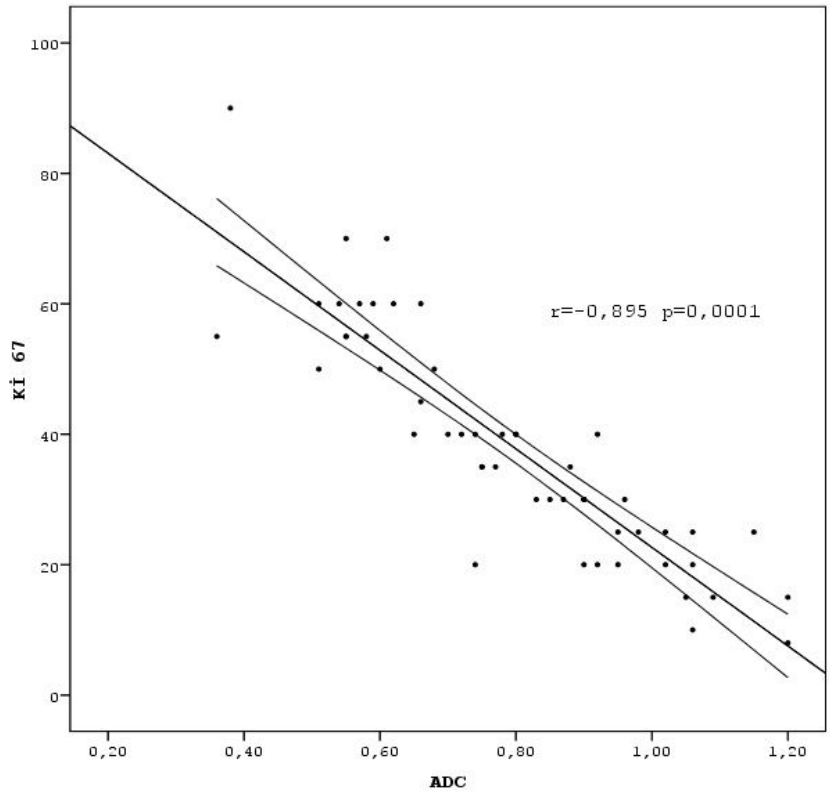

Fig. 1. Negative correlation graph between Ki-67 and ADC values. ADC = apparent diffusion coefficient

Table 3. Relationship of Ki-67, ADC and total score values in tumors with each other and patient age

		Ki-67	ADC	Total Score
Ki-67	**r**		-0.895	0.772
	***p* value**		**0.0001**	**0.0001**
ADC	**r**	-0.895		-0.780
	***p* value**	**0.0001**		**0.0001**
Total Score	**r**	0.772	-0.780	
	***p* value**	**0.0001**	**0.0001**	

ADC = apparent diffusion coefficient, Pearson Correlation Test

and 19 as the highest. The mean total score value was found to be 15.56 ± 2.25. (Table 2).

Pearson correlation test was used to determine the relationships between Ki-67 proliferation index, ADC and morphological total score values. There was a negative correlation between Ki-67 index values and ADC values (Fig. 1), and a positive correlation between Morphological Total Score values (r=-0.895, p = 0.0001), (r = 0.772, p = 0.0001). A statistically significant negative correlation was observed between ADC values and morphological total Score values (r = -0.780, p = 0.0001) (Table 3 and Figs. 2 and 3).

Morphological Features and Ki-67 Index

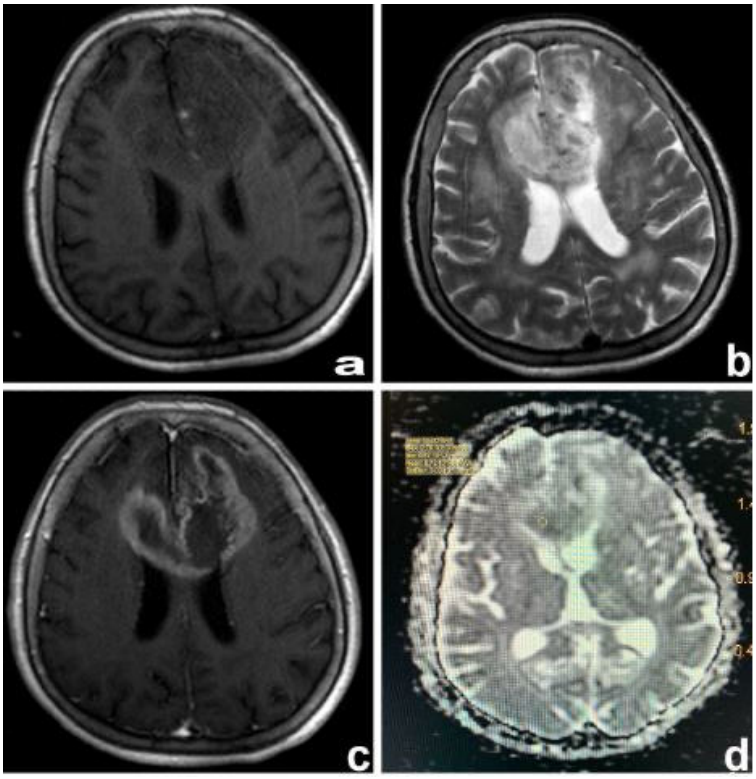

Fig. 2. A 73-year-old female patient has a lesion with a diameter of 62 mm located at the frontal region. Hyperintense foci determined as hemorrhage are seen in T1WI (a). It is observed that the lesion is shifted on contrast-enhanced T2W and T1W images, extends from the midline to the opposite hemisphere, contains large areas of necrosis, has irregular contours, shows intense contrast enhancement, has a small amount of peritumoral edema, and is heterogeneous only on T2W (b, c). A total of score was 17 obtained from their morphological features. ADC value of 0.72 × 10-3 mm2/sec was obtained (d) from the areas showing tumoral enhancement. T1WI and T2WI = T1-and T2-weighted axial imaging, ADC = apparent diffusion coefficient.

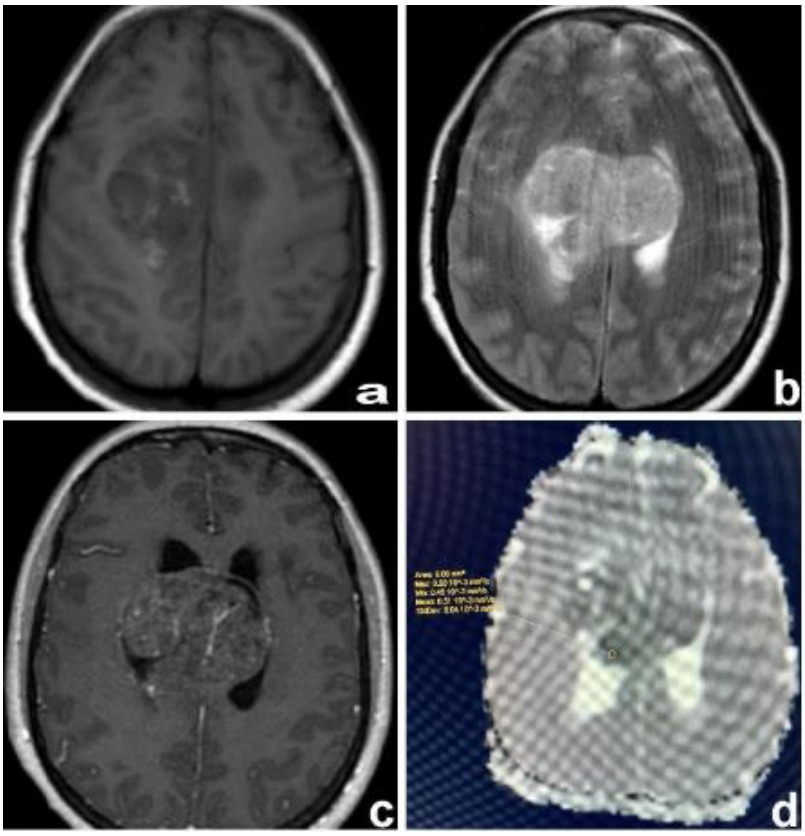

Fig. 3. A 37-year-old female patient has a lesion located at the cingulate gyrus- corpus callosum region with a 57 mm diameter. On T1W images, hyperintense foci evaluated as hemorrhage are seen (a). It is observed that the lesion shifts and extends to the opposite hemisphere on contrast-enhanced T2W and T1W images, contains necrosis less than half of the tumor volume, has regular contours, shows little contrast, has little peritumoral edema, and is heterogeneous in both T1W and T2W (a, b, c). A total of score was 15 obtained from their morphological features. ADC value of 0.51 × 10-3 mm2/sec was obtained (d) from the areas showing tumoral enhancement. T1WI and T2WI = T1-and T2-weighted axial imaging, ADC = apparent diffusion coefficient.

Heterogeneity and necrosis were the features that were most closely associated with Ki-67 proliferation index values ($p = 0.0001$). Tumors heterogeneous on both T1 and T2W had a higher Ki-67 mean than tumors heterogeneous on T2W only ($p = 0.0001$). In addition, mean Ki-67 values of tumors where more than half of the tumor volume is necrosis; were higher compared to tumors with less necrosis ($p = 0.0001$). These were followed by mass effect, hemorrhage and contour irregularity, respectively. There was no statistically significant correlation between the amount of edema and Ki-67 ($p = 0.058$) (Table 4).

DISCUSSION

Ki-67 protein is a cellular marker associated with cell proliferation and can objectively reflect tumor aggression [12, 13]. It has been shown in many studies that increased Ki-67 expression shows poor prognosis in glioblastoma patients [14, 15]. Tissue sampling and histopathological examination used in glioblastoma grading and selection of treatment algorithms have some limitations. Inadequate tissue sampling, especially during stereotactic needle biopsy and after tumor resection, causes inaccurate evaluations in some patients due to the inability to examine every section of the tumor and the dependency of the practitioner [16, 17].

MRI, on the other hand, provides information about the macroscopic features and degree of diffusion that histological examination can not evaluate. Therefore, MRI findings of tumors can be used to contribute to classification and predict prognosis. In previous studies, it was shown that there may be a correlation between the morphological features of gliomas (pe-

Table 4. The relationship of morphological features with the Ki-67 index

		n	Ki-67	*p* value
Edema	1: No or little edema	3	33.33 ± 20.21	0.058‡
	2: There is edema, smaller than the tumor volume	20	31.40 ± 15.47	
	3: There is edema, more than tumor volume	29	43.28 ± 17.69	
Necrosis	1: No necrosis	1	25	**0.0001***
	2: Located less than half of the tumor	26	28.19 ± 11.70	
	3: Located more than half of the tumor	25	49.00 ± 16.77	
Hemorrhage	1: No	30	31.93 ± 14.59	**0.002***
	2: Yes	22	46.59 ± 18.22	
Enhancement	1: No enhancement	1	10	**0.011***
	2: Poor or nodular	11	27.09 ± 13.19	
	3: Pronounced and heterogeneous	40	41.88 ± 17.12	
Heterogeneity	1: Homogeneous tumor	4	19.50 ± 11.45	**0.0001‡**
	2: Tumor is heterogeneous on T2WI	30	33.67 ± 16.55	
	3: The tumor is heterogeneous in both T1WI and T2WI	18	49.72 ± 13.56	
Mass effect	1: Lost of subarachnoid space	8	23.75 ± 8.35	**0.002‡**
	2: Compression to the ventricular system	14	32.00 ± 16.00	
	3: Midline shift	30	44.83 ± 17.15	
Irregular contour	1: Well-circumscribed	14	27.14 ± 6.99	**0.005***
	2: Irregular contour	38	42.18 ± 18.69	

‡ One-Way Analysis of Variance
* Independent t test

ripheral edema, mass effect, degree of enhancement due to blood-brain barrier destruction, degree of intratumoral necrosis, heterogeneity, hemorrhage) and the grade of tumor in these features [18-20]. The role of MRI findings and ADC values in predicting prognosis in glioblastoma patients can be investigated by revealing their relationship with the Ki-67 proliferation index, which is another important prognostic marker. Studies have shown that ADC values are associated with tumor grade, proliferation status and prognosis. Shahmohammadi *et al*. [21] found a negative correlation between ADC values and Ki-67 values in glioma patients (r = −0.634, p = 0.027). Calvar *et al*. [22] showed an inverse relationship between ki-67 and ADC values in glioblastoma patients. Higano *et al*. [23] found a negative correlation between Ki-67 and ADC values among malignant astrocytic (anaplastic astrocytoma and glioblastoma) patients, but no significant association was found in the glioblastoma group. Oh *et al*. [24] investigated the relationship between ADC values and survival by examining the images before surgery and chemoradiotherapy in glioblastoma patients. They showed that patients with low ADC values have a shorter average life expectancy (11.2 and 21.7 months, respectively) [24]. In our study, we found a negative correlation between ADC values and Ki-67 values of glioblastoma patients, which is consistent with the literature (r = -0.895 p = 0.0001). Our results parallel to the literature findings that there is a significant relationship between ADC values and Ki-67 and thus life expectancy in glioblastoma patients.

Highly malignant cerebral tumors are usually associated with significant amounts of necrosis [25]. Detection of necrosis on MRI scanning is a necessary criterion to include glioblastoma in the differential diagnosis. Hasse *et al*. [26] showed that patients with high Ki-67 values had a higher rate of necrosis on MRI examinations. Hammoud *et al*. [27] found that as the amount of necrosis increased in glioblastomas, the mean life expectancy decreased. Lacroix *et al*. [28]

showed that as the amount of necrosis increased in glioblastoma patients, median survival decreased. Among the 52 patients included in our study, we found that the mean of Ki-67 of the patients with necrosis volume more than half of the tumor volume was higher than the other patients, and the mean ADC was lower ($p = 0.0001$ and $p = 0.001$). In addition, in our study, we found that necrosis and heterogeneity were MRI findings that showed the best correlation with the Ki-67 proliferation index ($p = 0.0001$). In the light of these data, detection of necrosis and lesion heterogeneity in preoperative MRI evaluations can provide information about histological grade and prognosis.

It is known that the mass effect formed by the tumors adversely affects the prognosis. Steed *et al*. [29] showed that lateral ventricular compression adversely affects the prognosis. Park *et al*. [30] showed that patients with glioblastoma with tumor volume greater than 50 cm3 had poor postoperative survival. Gamburg *et al*. [31] showed that the life expectancy of shifting tumors was shorter. In another study, the Ki-67 values of the midline shifting group were higher than the Ki-67 values of the tumors causing ventricular compression and causing lost in the subarachnoid space [32]. We think that tumor volume and mass effect should be evaluated and clearly stated in MRI reports, since they affect the treatment method in glioblastoma patients and provide valuable information about prognosis. On MRI, glioblastomas are generally seen as necrotic centrally and enhanced as peripheral rims [33-35]. The contrast may be minimal, nodular, or prominent. In our study, the mean Ki-67 of the significantly enhanced group was statistically significantly higher compared to the minimally enhanced group ($p = 0.011$). Tervonen *et al*. [36] was found that significant contrast enhancement was associated with advanced tumor grade and high cellularity. Although neglected compared to other morphological features of glioblastoma, tumor surface features can also provide important information about tumor progression. Surface irregularity is an important prognostic marker [37, 38]. In our study, we found that the ki-67 values of tumors with irregular borders were significantly higher ($p = 0.005$).

A large amount of edema around the glioma suggests a more malignant phenotype [39, 40]. Levin *et al*. [41] showed that the presence of a large peritumoral low-density area (edema) on CT scan was associated with favorable tumor progression. In contrast to these, Taillandier *et al*. [42] showed that the amount of peritumoral edema had no effect on clinical outcome. In our study, when we classified the patients according to the amount of peritumoral edema, we could not find a statistically significant difference between the ki-67 values ($p = 0.058$).

Hemorrhage represents bleeding within the tumor matrix. Hypertension, anticoagulation, surgical intervention, angiogenesis and invasion of blood vessels by malignant cells may cause hemorrhage [43]. McGahan *et al*. [44] showed that the presence of hemorrhage in glioblastomas had no effect on prognosis. Contrary to this result, we found that the mean Ki-67 values of hemorrhagic tumors is higher than the non-hemorrhagic ($p = 0.002$).

We created a total score by summing the scores we obtained from each MRI finding. When we compared the total scores with the Ki-67 values, there was a positive correlation. Tumors with a high total score also had high Ki-67 values ($r = 0.772$, $p = 0.0001$). Semiquantitative evaluation of morphology findings in MRI examinations of glioblastomas can give us very important clues about the course and prognosis of the disease, which may support histopathological classification and help choose the right treatment methods.

Limitations

Our study had some limitations. The patient age was not included as contributing parameter in the multivariate analysis is not included. We did not measure the morphological findings with computerized systems in order to be fast and practical. Naturally, this may cause subjective results. In addition, we used only Ki-67 values histopathologically to determine the prognostic value of the scores we obtained from the morphological findings. For more accurate results, future studies should compare MRI morphological findings with other histopathological markers that have been shown to have an effect on prognosis. The measurements were made by a single reader, which reduces the reliability of the study.

CONCLUSION

In conclusion; despite the advances in diagnosis and

treatment methods in glioblastomas in recent years, delayed diagnosis and treatment, inadequate histopathological examination may occur. Preoperative MRI findings can be used to prevent delayed diagnosis and to contribute to the histopathological examination. With MRI scoring, radiologists can easily determine the possible pathological grade of the tumor. Thanks to the scoring, where we can get information about almost every patient non-invasively, we can predict the prognosis in the early period and shape the treatment process in glioblastoma patients.

Authors' Contribution

Study Conception: SÖ; Study Design: FZA; Supervision: FZA; Funding: SÖ; Materials: SÖ; Data Collection and/or Processing: İŞ, FZA, MK; Statistical Analysis and/or Data Interpretation: SŞ, GGK, ATC; Literature Review: FZA; Manuscript Preparation: FZA and Critical Review: FZA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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