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The Value of Immunohistochemical Methods and Preoperative Magnetic Resonance Imaging Findings in Diagnosis of IDH1 Mutant Glioblastomas

Umay KIRAZ[1], Cigdem VURAL[1], Gupse TURAN[1], Burcu ALPARSLAN[2], Elmire DERVISOGLU[2]

[1]Kocaeli University, Faculty of Medicine, Department of Pathology, Kocaeli, Turkey
[2]Kocaeli University, Faculty of Medicine, Department of Radiology, Kocaeli, Turkey

Corresponding author: Cigdem VURAL ✉ dr.cvural@gmail.com

ABSTRACT

AIM: To assess the presence of isocitrate dehydrogenase (IDH) 1 mutation in glioblastomas using real-time polymerase chain reaction (RT-PCR), which is the gold standard in the diagnosis of IDH1 mutation; by immunohistochemistry (IHC), which is available in most of the pathology laboratories; and by preoperative magnetic resonance imaging, which is a non-invasive method. We also investigated the relationship between these methods and their usability in routine practice.

MATERIAL and METHODS: RT-PCR was performed to evaluate the presence of IDH1-R132H mutation on the blocks of 70 patients diagnosed with glioblastoma, and IDH1 stain was applied to the same blocks as IHC. Radiologically, preoperative magnetic resonance images of the patients were reviewed in terms of tumor size, localization, and presence of non-contrast-enhancing solid tumor component.

RESULTS: Evaluation by RT-PCR revealed that 15 (21.4%) patients were IDH-mutant, whereas IHC examination revealed 13 (18.6%) and radiological evaluation revealed 11 (15.7%) patients were IDH-mutant. There was a statistically significant difference between the IDH1 mutation detected by RT-PCR and by IHC or radiological methods (p=0.034 and p=0.000, respectively). The sensitivity and specificity of IHC method in detecting IDH1 mutation were 86.6% and 100%, respectively, whereas those of radiological methods were 33.3% and 89%, respectively.

CONCLUSION: Conclusively, radiological and IHC methods can be used in cases where RT-PCR cannot be applied for detecting IDH1 mutation. However, the results need to be confirmed by RT-PCR when necessary as these methods may sometimes overlook some IDH-mutant patients.

KEYWORDS: Glioblastoma, IDH1 mutation, Immunohistochemistry, Polymerase chain reaction, Magnetic resonance imaging

INTRODUCTION

Glioblastoma is a high-grade glioma displaying astrocytic differentiation (18), and is the most common malignant brain tumor in adults. It accounts for 15% of intracranial tumors and 45%–50% of primary malignant brain tumors (22,25). Although its incidence is the highest between the ages of 55 and 85 years, it can be detected at any age (20). It is frequently localized in the subcortical white matter and deep gray matter of the cerebral hemispheres (14). The most frequently involved sites are the temporal, parietal, frontal, and occipital lobes, respectively (17).

Isocitrate dehydrogenase (IDH) is an enzyme that catalyzes the oxidative decarboxylation reaction that provides the conversion of isocitrate to *α*-ketoglutarate in the citric acid cycle. This reaction results in the formation of reduced NADP (NADPH), which plays a role in the cellular control of oxidative

Umay KIRAZ : 0000-0002-6721-4877
Cigdem VURAL : 0000-0002-9405-9112
Gupse TURAN : 0000-0002-4207-2833
Burcu ALPARSLAN : 0000-0002-5518-341X
Elmire DERVISOGLU : 0000-0002-2431-048X

damage (36). IDH mutation occurs in the early stages of glioma tumorigenesis and affects glial precursor cells. It is acquired before TP53 mutation and 1p19q coding (34). The presence of a large number of spontaneous mutations in the gene encoding the cytosolic $NADP^{+/-}$-dependent IDH1 enzyme in diffused gliomas has been demonstrated by many studies. Mutation of the gene encoding the mitochondrial $NADP^{+/-}$-dependent IDH2 enzyme is less common (36). Studies have shown that the majority (more than 70%) of low-grade astrocytomas, oligoastrocytomas, oligodendrogliomas, and secondary glioblastomas carry the IDH1 mutation (28).

The diagnostic system integrated with the World Health Organization (WHO) 2016 classification, which is the latest and updated classification of central nervous system tumors, has begun to be used for glioblastoma classification. Although glioblastoma is diagnosed on the basis of histopathology, the actual denomination is based on molecular characteristics. Accordingly, glioblastomas are classified in two groups based on IDH mutation status, which forms the core of their classification (18). According to the IDH mutation, tumors without mutation, which account for 90% of tumors, are classified as IDH-wild-type glioblastomas, and tumors showing mutation, which account for the remaining 10%, are classified as IDH-mutant-type glioblastomas (20). In addition, in case the methods that detect IDH mutation are not available at some laboratory centers, the term "not otherwise specified," which indicates the absence of sufficient information to make a diagnosis, is used (18). IDH-mutant- and IDH-wild-type glioblastomas differ from each other biologically and clinically, and making this discrimination is critical in predicting clinical progress. Previous studies reported that IDH-mutant tumors are associated with younger age, frontal lobe localization, larger tumor size, and better clinical course (14,20).

IDH1-R132H is the most common mutation seen in IDH-mutant tumors. Presence of this mutation can be either determined by real-time polymerase chain reaction (RT-PCR), which is the gold standard method, or demonstrated immunohistochemically (4). However, although the specificity of immunohistochemical detection of IDH1 positivity is 100%, its sensitivity is lower (5).

IDH mutation can be determined by radiological imaging methods as well. Various studies reported that presence of IDH mutation can be detected by preoperative assessment of some parameters, including tumor localization and size, presence of cysts, size of contrast/non-contrast areas, presence of necrosis and edema, and so on, by magnetic resonance imaging (MRI) (15).

In the present study, we investigated the relationship between RT-PCR method, which is the gold standard in determining IDH mutation, and immunohistochemical method, which is widely used. In addition, we aimed to investigate whether there is a correlation with preoperative assessment of tumor characteristics by MRI, which is a non-invasive method, as well as to identify sensitivity and specificity of all these methods.

MATERIAL and METHODS

Patient Selection and Data Collection

In the present study, a total of 109 patients diagnosed with glioblastoma between 2009 and 2019 at Kocaeli University Faculty of Medicine, Department of Medical Pathology, were investigated. The study was approved by the Research Ethics Committee (08/05/2019, Project No: KU GOKAEK 2019/198). Patients' clinical information such as age and gender were retrieved from their files and from the hospital automation system. Pathology reports of all the patients diagnosed with glioblastoma were reviewed, and patients' biopsy preparations stained with Hematoxylin & Eosin were re-examined. Only the initial biopsies of eight patients with relapse were included in the study group. Moreover, patients without preoperative imaging findings, as well as the patients with paraffin blocks unavailable in our archive, were excluded from the study group. Accordingly, a total of 70 patients, on whom evaluation by immunohistochemistry (IHC) and RT-PCR could be performed together with radiological evaluation, were included in the study.

Real-Time PCR Method and Evaluation

IDH-R132H mutation was evaluated by RT-PCR in all the 70 patients in the study group. Formalin-fixed and paraffin-embedded tissue specimens with the highest tumor burden were chosen for DNA isolation. Clinic SV mini kit was used (GeneAll, Seoul, South Korea).

Briefly, PCR was done in a total volume of 20 μl comprising 7.5 μl of DNA template, 0.25 μl of TaqMan™SNP Genotyping Assay (ThermoFisher), 10 μl of 2X qPCR Probe MasterMix (ABT™), and 2.25 μl water, with an initial denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 10 s and annealing at 60°C for 60 s.

Allelic discrimination analysis technique was chosen on ABI 7500 Fast RT-PCR (Applied Biosystems, ThermoFisher) device to analyze the IDH-R132H mutation. Accordingly, amplification curves in FAM and VIC wavelengths were obtained from each SNP probe. Samples displaying amplification in only FAM wavelength were classified as *Genotype TT*, those displaying amplification in only VIC wavelength were classified as *Genotype CC*, and those displaying amplification in both wavelengths were classified as *Genotype CT*.

Genotype CC indicates the absence of IDH1 mutation, whereas *Genotype CT* indicates the presence of the same.

Since RT-PCR is the gold standard method in detecting IDH1 mutation, patients with IDH1 mutation detected by RT-PCR were considered and coded as "IDH-mutant," whereas the patients without mutation were considered and coded as "IDH-wild-type."

Preoperative MRI Evaluation

Preoperative radiological images of the patients were re-evaluated by Kocaeli University Faculty of Medicine, Department of Radiology. The Visually AcceSAble Rembrandt Images (VASARI) feature set was used for the assessment. The VASARI features were interpreted by one radiologist who was

blinded to the IDH status based on pre-contrast- and contrast-enhanced T1WI, T2WI, FLAIR, and DWI images. According to the guide (Vasari MR Feature Guide v1.1) published by The Cancer Imaging Archive (1), 12 VASARI features were scored that include "tumor location, tumor epicenter side, enhancement quality, proportion enhancing, proportion non-enhancing, proportion necrosis, cysts, thickness of enhancing margin, definition of enhancing margin, proportion of edema, hemorrhage, and diffusion." These VASARI properties were chosen because of their high reproducibility and demonstration that they can provide important information for the diagnosis of gliomas according to previous studies (27,33,37). Assuming that the entire lesion was composed of the following: [1] an enhancing component (CET); [2] a non-enhancing component (nCET); [3] a necrotic component; and [4] an edema component, a non-enhancing tumor is defined as a T2 hyperintense region (lower than cerebrospinal fluid on T2W and hypointense on T1W) that is related to mass effect, architectural distortion, and blurring gray–white matter interface. Necrosis is defined as the central part of the tumor that does not enhance or show markedly diminished enhancement, is hyperintense on T2W and proton density images, is hypointense on T1W images, and has an irregular border. Signal of edema should be higher than nCET signal and lower than CSF signal. Pseudopods are characteristic of edema (11). They are scored on the basis of the percentage of total abnormal tissue (2 = 0%, 3 = <5%, 4 = 6%–33%, 5 = 33%–67%, 6 = 68%–95%). Largest perpendicular (*x-y*) cross-sectional diameter of T2 signal abnormality is measured on a single axial image for tumoral size.

Immunohistochemical Staining Method and Evaluation

Among the 10% formalin-fixed paraffin-embedded tissue samples, the 3 μm sections prepared from the blocks with high tumor burden and that underwent RT-PCR were transferred onto positive-charged slides for immunohistochemical examination. The biopsy preparations were stained by automated immunohistochemical staining method in closed Ventana Benchmark XT device using anti-isocitrate dehydrogenase 1 (IDH1, Clone: H09, Dilution 1:20-50) antibody. The sections obtained from diffused astrocytoma were used as the positive control. Patients with granular cytoplasmic staining of the tumor cells were considered as "IDH1 positive (+)," regardless of the intensity and expansiveness of staining, and patients with no staining were considered as "IDH1 negative (–)" (9).

Statistical Analysis

Statistical analysis was performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. Suitability for normal distribution was assessed by Kolmogorov–Smirnov test. Normally distributed numerical variables were presented as mean±standard deviation, numerical variables not normally distributed were presented as median (min–max), and categorical variables were presented as frequency (percentage). The difference between the two groups was determined by "student-*t*" test for numerical variables that were normally distributed. The difference between multiple groups was analyzed by Kruskal–Wallis test for numerical variables that were not normally distributed, whereas χ^2 analysis was used for categorical variables. Consistency between the categorical variables was determined by κ consistency coefficient. For two-sided hypothesis, $p<0.05$ was considered adequate for statistical significance.

RESULTS

Of the 70 patients diagnosed with glioblastoma, 49 (70%) were male and 21 (30%) were female. Male/female ratio was 2.3/1. In the present study, in which the age ranged from 20 to 79 years, the mean age was 53.33 ± 10.94 years and the median age was 54.00 (29–79) years. The mean age of patients with IDH-wild-type was 53.85 ± 10.80 years, while the mean age of patients with IDH-mutant was 51.40 ± 11.61 years. Although IDH-mutant patients were seen at a relatively younger age, no statistically significant result was obtained between the mean age of the patients, according to the IDH1 mutation status detected by RT-PCR (p=0.445).

The smallest tumor size was 3 cm and the largest was 13 cm, with a mean tumor size of 7.33 ± 2.15 cm. In IDH-mutant patients, the mean tumor size was 7.63 ± 2.39 cm and the median was 7.7 (4–13) cm. In IDH-wild-type patients, the mean tumor size was 7.24 ± 2.10 cm and the median was 7.4 (3–11.8) cm. No statistically significant relationship was determined between the tumor size and the presence of IDH1 mutation (p=0.615).

RT-PCR method revealed that 15 (21.4%) of the patients had *Genotype CT* (IDH-mutant) and 55 (78.6%) had *Genotype CC* (IDH-wild-type). In the present study, amplification images of the patients are illustrated in Figure 1, and the graph of allelic discrimination image is illustrated in Figure 2.

The tumor was localized to the cerebellum in only 2 (2.9%) of the overall 70 patients, whereas it was localized to the cerebrum in the other 68 (97.1%); the site of localization was the frontal lobe in 28 (40.0%), temporal lobe in 27 (38.6%), parietal lobe in 10 (14.3%), insular region in 2 (2.9%), cerebellum in 2 (2.9%), and occipital lobe in 1 (1.4%) of these patients (Figure 3).

There were 17 patients (24.3%) with a nCET ratio of >33%, whereas nCET was <33% or none in 53 patients (75.7%) (Figure 4A, B).

Radiologically, 59 (84.3%) patients were considered as IDH-wild-type and 11 (15.7%) were considered as IDH-mutant type, according to the localization and nCET ratio. Of these 11 patients, 5 were evaluated as mutants radiologically, as well as by RT-PCR. There was statistically significant relationship between IDH-mutant type/wild-type that was assessed radiologically, and the presence of IDH1 mutation was determined by RT-PCR (p=0.034) (Table I). Moreover, the sensitivity and specificity of preoperative radiologic imaging in detecting IDH1 mutation by MRI was 33.3% and 89%, respectively.

Immunohistochemically, positive staining with IDH was determined in 13 (18.6%) patients (Figure 5). Whereas all of these patients were found positive also with RT-PCR, only 2 of the 57 not stained with IHC were positive with RT-PCR.

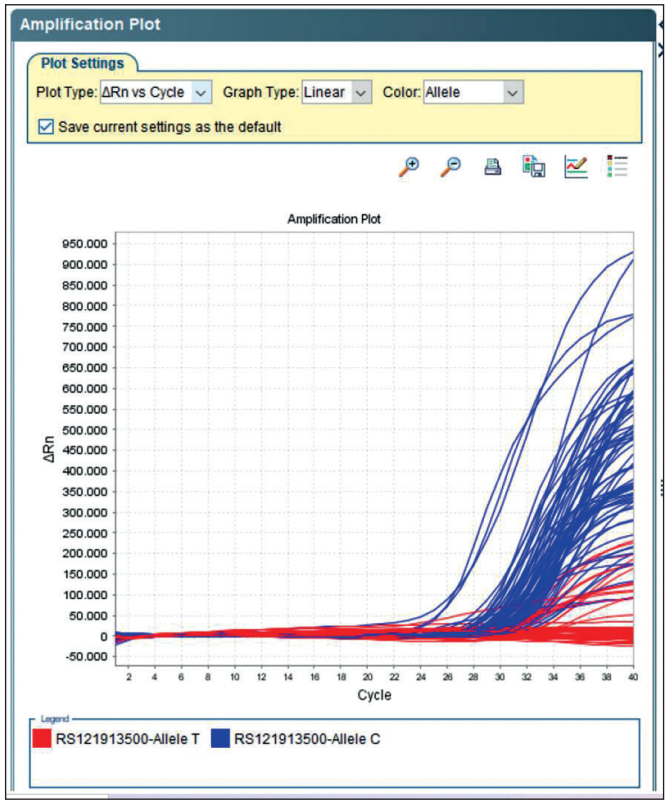

Figure 1: Amplification image of the patients.

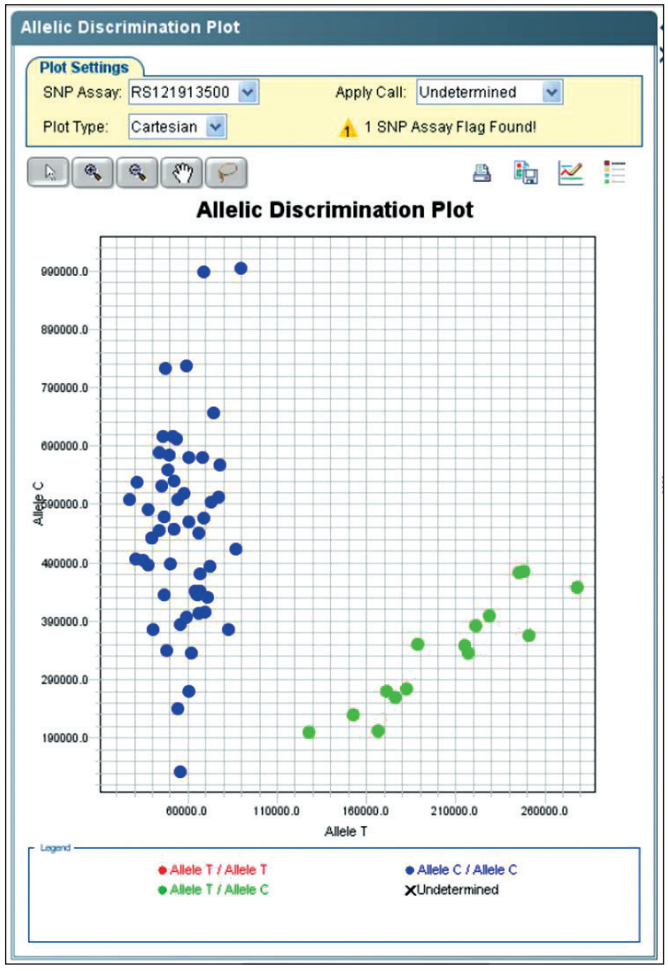

Figure 2: Allelic discrimination image of the patients.

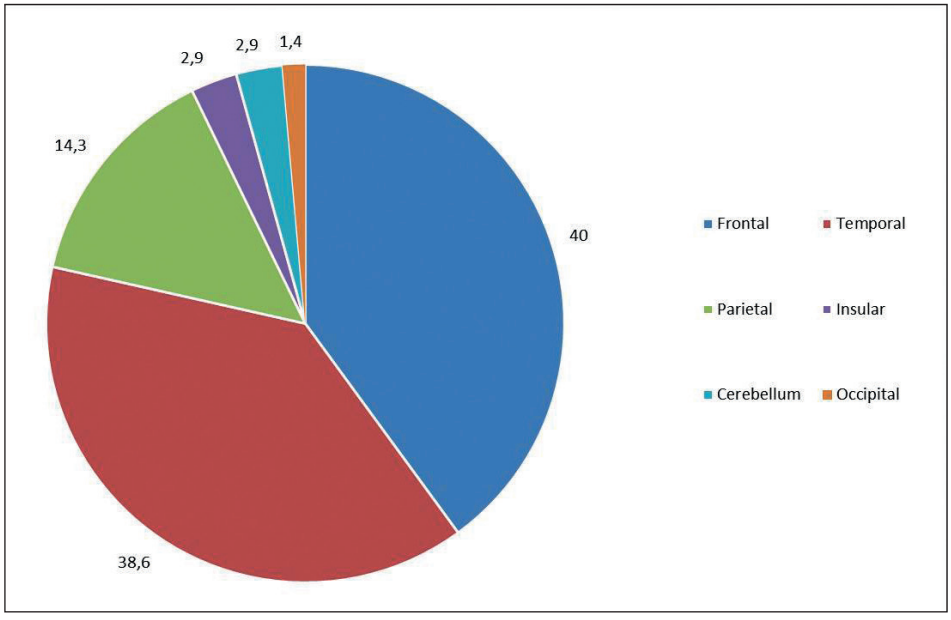

Figure 3: Localization of tumors.

Table I: The Relationship Between Radiological Presence of IDH1 Mutation and IDH1 Staining with IHC Method and Presence of IDH1 Mutation with RT-PCR

	RT-PCR		Total (%)	p
	Positive (%)	Negative (%)		
Radiological evaluation of IDH1 mutation				
IDH-mutant	5 (45.5)	6 (54.5)	11 (100.0)	**0.034**
IDH-wild type	10 (16.9)	49 (83.1)	59 (100.0)	
Total	15 (21.4)	55 (78.6)	70 (100.0)	
IDH1 staining with the IHC method				
IDH positive	13 (100.0)	0 (0.0)	13 (100.0)	**0.000**
IDH negative	2 (3.5)	55 (96.5)	57 (100.0)	
Total	15 (21.4)	55 (78.6)	70 (100.0)	

IDH: *Isocitrate dehydrogenase,* ***IHC:*** *Immunohistochemistry*

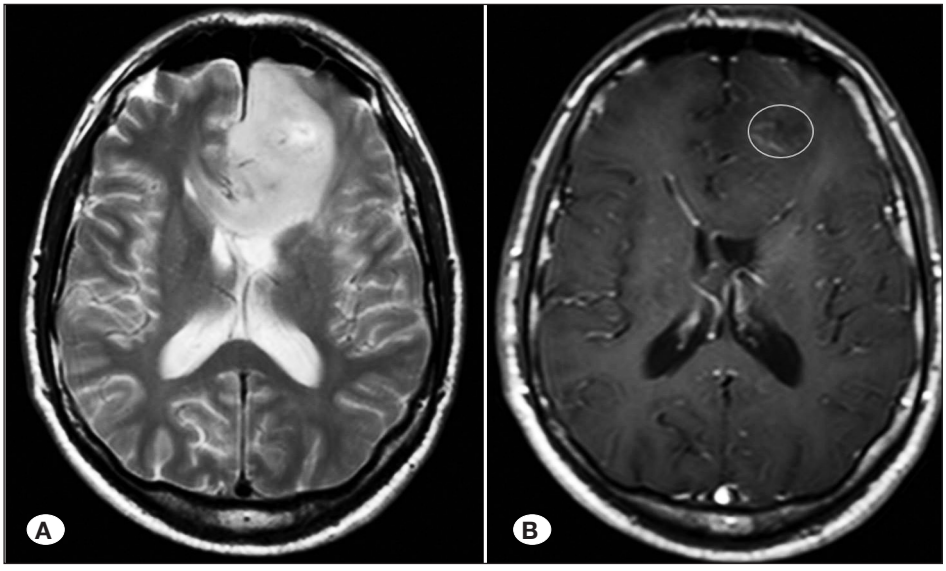

Figure 4: A patient evaluated in favor of isocitrate dehydrogenase-mutant in preoperative magnetic resonance imaging. A) Mass lesion localized in the left frontal lobe on axial T2W section. B) Non-enhancing solid tumor ratio 34%–67%, necrosis rate <5% on axial post-contrast T1W section (the contrasting area is marked).

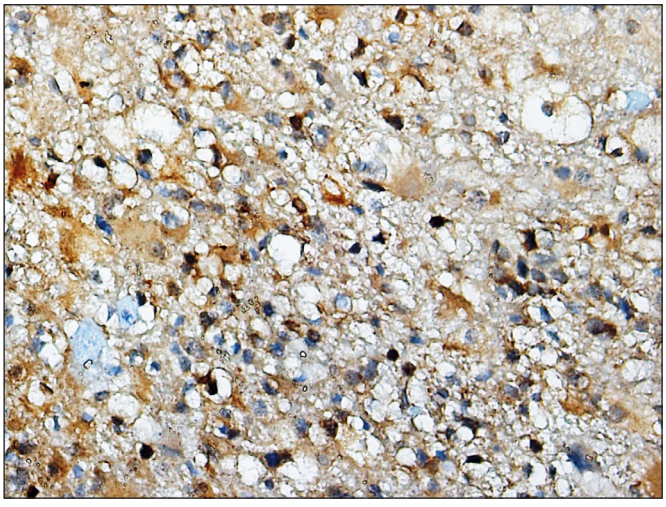

Figure 5: Immunohistochemically; cytoplasmic IDH1 immunoreactivity (IDH×400).

Strong correlation was determined between RT-PCR method and IHC method in detecting IDH1 mutation (p=0.000) (Table I). The sensitivity and specificity of detection of IDH1 mutation by IHC method was 86.6% and 100%, respectively.

DISCUSSION

Glioblastoma is the most prevalent primary malignant tumor among the tumors of the brain and central nervous system. These tumors, which were formerly classified as "glioblastoma multiforme" as they show various histopathological characteristics, took place as glioblastoma alone in the WHO 2016 classification (9,17,18). Although glioblastoma is seen at any age, it is more prevalent between the ages of 55 and 85 years. It is rarely encountered under the age of 40 years and is quite rare in children (18,25). The mean age reported in several studies in the English literature ranged between 48 and 58.8 years (7,16,19,29); in the present study, the age of

the patients ranged from 29 to 79 years with the mean age of 53.33 ± 10.94 years, which was consistent with the literature.

While the mean age during diagnosis of IDH-wild-type glioblastomas is 62 years, it is stated that IDH-mutant glioblastomas are observed at a younger age and the average age during their diagnosis is 45 years (18,23). Similar results were obtained in the study of Nobusawa et al. According to their studies, the mean age of IDH-wild-type patients was 60 years, and the mean age of IDH-mutant patients was 47 years (21). In our study, the mean age of diagnosis of IDH-wild-type patients was 53.85 ± 10.80 years, and the mean age of diagnosis of IDH-mutant patients was 51.40 ± 11.61 years. Although there is no age difference as much as in the literature and this is not statistically significant, it has been noted that IDH-mutant patients are at a younger age.

Although there are variations among countries, male/female ratio in glioblastomas is approximately 1.6/1 (18,25). Although rare, there are studies reporting male–female equality (M/F:1/1) or female dominance (M/F:0.8/1) in glioblastomas (16,19). In the present study, 49 (70%) of the 70 patients were male and 21 (30%) were female, and the male/female ratio was 2.3/1; male dominance was consistent with the literature.

Macroscopically, glioblastomas form unilateral large masses with irregular border (17). Glioblastoma is frequently localized in the subcortical white matter and deep gray matter of the cerebral hemispheres. In the present study, the site of localization of tumor was the cerebrum by 97.1%. The study from Zurich University Hospital evaluating 987 glioblastoma patients reported the most common sites of involvement as the temporal lobe by 31%, parietal lobe by 24%, frontal lobe by 23%, and occipital lobe by 16%; similar localizations were reported from the United States of America (17,24). In the present study, the mean tumor size was 7.33 cm and the most common site of localization was the frontal lobe (40%), followed by the temporal lobe (38.6%).

Glioblastomas are histologically Grade IV tumors according to the WHO 2016 classification; although the classification is based on histopathology, the tumors are named according to their molecular features. IDH mutation forms the core of the classification. The gold standard methods in detecting IDH1/2 mutations include Sangers sequencing and PCR amplification (18). IDH1 sequencing yielded 161 somatic mutations on R132 residue, which are R132H, R132C, R132S, R132L, and R132G mutations. The most common IDH1 mutation is R132H mutation that occurs at codon 132 by replacing the amino acid arginine with histidine (12,20,31,34,36). We also assessed the presence of IDH1-R132H mutation in all patients by RT-PCR.

Earlier studies reported that primary glioblastomas account for 90%–95% of overall glioblastomas, whereas secondary glioblastomas account for a little proportion of 5%–10% (16,20,23). In a study, however, it was reported that primary glioblastomas were seen by 80% and secondary glioblastomas were seen by 20% (26). Although the incidence of IDH1 mutation is low in primary glioblastomas, it is seen in 60%–80% of the secondary glioma patients (28,34). Parsons et al. performed genomic analysis of 20.661 protein-coding genes in glioblastomas and found the rate of IDH1 mutation to be 12% (28). Again, in the studies using DNA sequencing method, IDH1 mutation was determined in 8.8% by Nobusawa et al. (21), in 12.3% by Senhaji et al. (31), and in 7% by Kurian et al. (13). In the present study, we determined IDH1 mutation in 21.4% of the 70 patients, which was closer to the upper limit of the varying ratios reported in various studies in the literature.

It is stated that immunohistochemical methods can be used in determining IDH mutations as they are fast and economic methods that can be performed in most pathology laboratories (2). In the studies using immunohistochemical methods, staining with IDH1 marker was detected in 11% of the glioblastoma patients by Popova et al. (29), in 10.4% by Chaurasia et al. (6), in 6.0% by Ichimura et al. (12), and in 10.7% by Sanson et al. (30). In the present study, we detected immunohistochemical IDH1 staining in 13 (18.6%) patients as well.

In earlier studies, it was determined that IDH1-R132H mutation-specific antibody is immunohistochemically compatible with DNA sequencing methods in determining IDH1 mutation (2,5). Nobusawa et al. found the sensitivity and specificity of immunohistochemical method to be 73.3% and 96.3%, respectively, in terms of using IDH1 mutation as the molecular marker of discrimination between primary and secondary glioblastomas (21). Capper et al. compared DNA sequencing method and immunohistochemical method in terms of IDH1 mutation; they found the sensitivity and specificity of IHC to be 94% and 100%, respectively, and concluded that IHC is a valid method (5,10). In addition, Kurian et al. found that IHC method and DNA sequencing method are completely coherent in the presence of IDH1-R132H mutation (13). In the present study, we compared RT-PCR method with IHC in detecting IDH mutation; IHC method revealed IDH1 positivity in 13 (18.6%) of the 15 (21.4%) patients with IDH1 mutation detected by PCR method. While two patients in the present study had IDH1 mutation, we observed no immunohistochemical staining and found the sensitivity and specificity of immunohistochemical method to be 86.6% and 100%, respectively. We concluded that immunohistochemical IDH1 staining can be routinely used in detecting IDH-mutant-type glioblastomas and for glioblastoma subtyping; however, false negativity may occur. Hence, these findings need to be supported and confirmed by RT-PCR, particularly in clinically suspected IDH1 mutation patients.

Glioblastoma is a heterogenous tumor containing tumoral areas of different grades within the same tumor mass (18). Genetic mutations may also display differences within tumor (21). It is thought that histopathological and genetic evaluation may be faulty because of this heterogeneity and that imaging techniques, particularly imaging of the tumor and the brain by magnetic resonance (MR), could be the solution of problems that potentially arise from the errors during tumor sampling phase. There are numerous studies on IDH1 mutation and imaging techniques. Measuring 2-HG (oncometabolite 2-hydroxyglutarate) levels in MR spectroscopy is still challenging in glioma imaging. It needs special techniques

and optimization; besides, it is too sensitive to magnetic field inhomogeneity and motion artifacts (32,35). Therefore, we could not implant it to our tumor protocol yet. In this study, our aim was to evaluate a radiologist's diagnostic ability to distinguish between IDH-mutant and wild-type glioblastomas only with conventional MR images; for this reason we only used VASARI scoring of conventional MRI. We are also preparing another manuscript where we are comparing the VASARI scoring and machine learning techniques' contribution with detection of IDH mutation.

Carrillo et al. determined significant relationship between nCET and IDH1 mutation; they determined IDH mutation in 97.5% using MR images and reported significant relationship between IDH1 mutation and frontal lobe localization, larger tumor size, and presence of cyst and satellite (3). Ellingson et al. also determined significant relationship between frontal or temporal tumor localization and IDH mutation (8). Lasocki et al, however, reported that the tumor is more likely to be IDH-wild-type if the tumor localization site is not the frontal lobe and the nCET ratio is <33% (15). In our study, we took this criterion as the basis (i.e., we considered the tumors with nCET > 33% and with frontal lobe localization as IDH-mutant type); we categorized 11 patients (15.7%) as IDH-mutant based on preoperative MR images and determined statistically significant relationship comparing with the PCR findings.

In the literature, the sensitivity and specificity of assessing IDH mutation by preoperative imaging methods were found to be 71.4% and 99.5%, respectively, by Carrillo et al. (3), whereas to be 81% and 96%, respectively, by Su et al. (33). In the present study, we found the sensitivity as 33.3% and the specificity as 89.0%, and we concluded that preoperative imaging methods can be used in predicting IDH1 mutation. However, they need to be confirmed by immunohistochemical or molecular methods that would be used in postoperative specimens because the imaging methods may be associated with false-positive or false-negative results.

Study Limitations

The study was planned to be performed on a total of 109 patients that were diagnosed at our department; however, we were able to include only 70 patients, on whom immunohistochemical examinations and RT-PCR could be performed and the images could be re-evaluated because paraffin blocks/preparations of some patients could not be obtained as they have been consulted us, and also because of lacking preoperative images of some of the patients in the hospital automation system.

In addition, only IDH-R132H mutation was evaluated in the tumor by RT-PCR method, but other mutations that are seen more rarely were not investigated or sequenced.

CONCLUSION

As a result of the present study in which we investigated the methods to detecting IDH1 mutation, in cases where RT-PCR cannot be applied to every patient to detect IDH1 mutation, MRI method, which is a non-invasive method, can be used. In addition, immunohistochemical method can also be used for this purpose, as it is a fast, inexpensive method and is available in many pathology laboratories. However, it should be kept in mind that IDH-mutant patients can sometimes be missed in evaluation with these methods with lower sensitivity. In patients that might be clinically IDH-mutant (young patient, large tumor size, history of prior low-grade glial tumor, etc.), the results of these methods should be confirmed by RT-PCR, which is the gold standard method.

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AUTHORSHIP CONTRIBUTION

Study conception and design: UK, CV, BA

Data collection: UK, ED

Analysis and interpretation of results: CV, BA, GT

Draft manuscript preparation: UK, CV

Critical revision of the article: CV, GT

Other (study supervision, fundings, materials, etc...): UK, CV, GT

All authors (UK, CV, GT, BA, ED) reviewed the results and approved the final version of the manuscript.

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