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Comparison of Molecular Markers and Classical Histopathological Diagnostic Methods in Grade II and III Glial Tumors and Their Prognostic Outcomes

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ABSTRACT

AIM: To demonstrate the changes in Grade II and III glial tumors after WHO 2016 Brain Tumors Classification.

MATERIAL and METHODS: The previous diagnoses and postoperative treatment of the 83 patients were recorded. We used real-time PCR (mutation assay) for the analysis of IDH1 and IDH2, while we used FISH test to determine 1p/19q codeletion. The integrated diagnosis was compared with classical histopathological diagnoses.

RESULTS: We studied 13 oligodendendrogliomas, 41 astrocytomas and 29 oligoastrocytomas patients with classical histopathological diagnosis group. IDH mutation was detected in 51 of the patients after genetic analysis, whereas 1p/19q codeletion was detected in 20 patients. We found that grade II IDH-mut astrocytoma patients had significantly better survival outcomes compared to grade III IDH-mut astrocytoma patients.

CONCLUSION: Grade II and III gliomas are separated into more homogeneous diagnostic groups for survival after molecular marker analyses. Compared to histopathological diagnosis, the WHO 2016 glioma classification with molecular markers provides new perspectives in patient prognosis and treatment. However, due to the costs of using molecular markers, the extent to which it can be used remains questionable.

KEYWORDS: Gliomas, IDH mutation, 1p/19q codeletion, WHO 2016 Brain Tumors Classification

INTRODUCTION

The first comprehensive description of gliomas was provided by Rudolf Virchow (1821 – 1902) in 1865. He identified gliomas as malignant tumor formations that originate from the glial cells of the central nervous system invading healthy brain tissues (31,34). Virchow was also the one who coined the term glioma. The word glia is derived from a Greek word that means glue and has been used to describe cells that produce extracellular matrix (14,25). In 1926, approximately 50 years after glioma was first defined as a pathological condition, Percival Bailey and Harvey Cushing laid the foundations for the modern glioma classification that is used today (13). In 1988, Daumas-Duport et al. proposed a new method to classify brain tumors known as the St. Anne-Mayo grading system (9). WHO updated the CNS tumor classification system in 1993 (18), in 2000 (19), in 2007 (24) and most recently, in 2016 (25).

Gliomas are the most common tumors of the central nervous system. Although the mechanisms of glioma formation remain to be poorly understood, we know that glioma subtypes are associated with different and unique genetic pools (32,38). The current literature states that these pools of genetic conditions develop in a certain schema, not by random chance (6).

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Perhaps the most important findings derived from immunohistochemical and genetic analyses of grade II and III glial tumors is that the mutations in IDH1 and IDH2 genes make up some of the earliest changes in tumor development (2,3). It has also been reported that multiple histopathologically normal cells that surround the IDH1 mutant cells also contain the IDH1 mutation. After IDH mutation is detected in oligodendrogliomas and astrocytic tumors, it is possible to genetically differentiate oligodendrogliomas by determining 1p/19q codeletion (23,30,37).

With the use of genetic markers, the WHO 2016 classification has introduced the concept of layered diagnosis. This novel "layered diagnosis" system has led many cases to be reviewed and rediagnosed (21,25). This study aims to compare previous diagnoses with new results and determine how the new diagnoses correlate to the prognosis in patients that were or were not treated with postoperative adjuvant therapy (15).

MATERIAL and METHODS

Patient Selection

The study includes the retrospective evaluation of patients that were histologically diagnosed with supratentorial grade II and III glial tumors aged ≥ 18 years between 1995 and 2012. Considering the suitability of the pathology samples for genetic analysis, we included patients from between 2004 and 2012. This study was in accordance with the Helsinki Declaration and was granted ethical approval by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (No:375, Date:30.05.2018). Patient data were then retrieved from Akdeniz University Hospital patient archive, Mia-Med and Medi-Patient programs, Akdeniz University Medical Pathology Department archive, and discharge report archives of the relevant years.

Inclusion Criteria

- ≥18 years old
- Supratentorial grade II and III glial tumors operated between 2004 and 2012
- The patient who had accessible information in archive search
- The patient who was available for clinical follow-up
- The patient who had appropriate materials for genetic examination

Exclusion Criteria

- <18 years old
- Infratentorial glial tumors
- WHO grade I and IV glial tumors
- Not enough cells in histopathological preparation
- Pathological preparations were not suitable for genetic studies

The previous diagnoses and treatment and surgery history of the selected patients were recorded. Histopathological diagnoses of all subjects were reevaluated and confirmed by a neuropathology specialist. We evaluated the surgical procedures and postoperative adjuvant treatment decisions according to diagnostic groups. We used real-time PCR (mutation assay) for the analysis of IDH1 and IDH2, while we used FISH test to determine 1p/19q codeletion. We used this data for the integrated diagnosis of the subjects and compared survival and postoperative adjuvant treatment outcomes to those of the original diagnoses.

Data were then analyzed using SPSS version 20. The significance of categorical variables (age, gender, IDH positivity, presence of 1p / 19q codeletion) on overall survival was evaluated using log-rank test. The survival findings of diagnosis groups were evaluated using Kaplan-Meier survival analysis. Significance level was set at $p<0.05$.

RESULTS

A total of 83 conforming patients from the 162 grade II and III glial tumor patients from between 1995 and 2012 were included in the study after determining the suitability of the samples for genetic examination and the availability of follow-up information. The mean age of the patients was 42.4 years (18–71). Included in the study were 54 male patients (65.06%) and 29 female patients (34.94%).

The original histopathological diagnoses of the subjects were as follows: oligodendroglioma, 13 (15.66%); astrocytoma, 41 (49.4%); and oligoastrocytoma, 29 (34.94%). A total of 58 (67.47%) and 27 (32.53%) subjects were originally diagnosed with grade II and grade III glial tumors, respectively. The frequencies and survival rates of the original histopathological diagnoses are presented in Table I. The astrocytoma and oligoastrocytoma diagnostic groups were not found to be significantly different in terms of survival ($p=0.648$).

IDH sequencing and 1p/19q FISH analysis revealed that 51 subjects were IDH positive (61.45%) and 32 were IDH negative (38.55%). Of the 51 IDH-positive patients, 37 were IDH1 positive (72.55%) and 14 were IDH2 positive (27.45%). FISH analysis revealed 1p/19q codeletion in 20 patients (24.10%).

We found that IDH-positive patients had a significantly better survival outcome compared to IDH-negative patients ($p<0.0001$). Furthermore, we found that IDH1 survival outcomes were better than those of IDH2 (progression-free survival [PFS]: 63.3 months, overall survival [OS]: 99.2 months vs. PFS: 61.9 months, OS: 97.9 months). However, this result determined to be not statistically significant ($p=0.0847$). Patients with 1p/19q codeletions had significantly better survival outcomes than patients without 1p/19q codeletions (PFS: 72.7 months, OS: 114.5 months vs. PFS: 34.7 months, OS: 52.71 months, $p<0.0001$).

We reevaluated the original disease classifications after analyzing molecular marker and further repeated the analyses for the new patient groups.The relative frequency and overall survivals of WHO 2016 diagnosis are presented in Table II.

The 29 patients that were originally histopathologically diagnosed with oligoastrocytoma (grade II, n=12; grade III,

n=17) were reevaluated as follows: IDH-mutant (IDH-mut) oligodendroglioma with 1p/19q codeletion, 6 patients (20.69 %; grade II, n=2; grade III, n=4); IDH-mut astrocytoma, 10 patients (34.48 %, grade II, n=6; grade III, n=4); and IDH- wild-type (IDH-wt) astrocytoma, 13 patients (44.83%; grade II, n=4; grade III, n=9) (Figure 1).

Among the 13 patients that were originally diagnosed with oligodendroglioma, only 1 (7.69%) was determined to be IDH-wt. This patient had been treated only with radiotherapy due to partial resection. Among the 41 patients that were originally diagnosed with astrocytoma (grade II, n=32; grade III, n=9), 18

Table I: Relative Frequency and Overall Survivals of Histopathological Diagnosis Before WHO 2016

Histopathological Diagnosis Before WHO 2016	No. of Cases	% of Total	Overall Survival (Months)
Oligodendroglioma	12	14.46	112.1
Astrocytoma	32	38.55	73
Oligoastrocytoma	12	14.46	66.8
Anaplastic Oligodendroglioma	1	-	-
Anaplastic Astrocytoma	9	10.84	17.8
Anaplastic Oligoastrocytoma	17	20.48	52.7
Total	83	100.0	

Table II: Relative Frequency and Overall Survivals of Layered Diagnosis After WHO 2016

Layered Diagnosis After WHO 2016	No. of Cases	% of Total	Overall Survival (Months)
IDH mut 1p/19q Codel Oligodendroglioma	15	18.07	121.2
IDH mut Astrocytoma	25	30.12	95.3
IDH wt Oligoastrocytoma	16	19.28	17.6
Anaplastic IDH mut 1p/19q Codel Oligodendroglioma	5	6.02	88.8
Anaplastic IDH mut Astrocytoma	6	7.23	66
Anaplastic IDH wt Astrocytoma	16	19.28	18
Total	83	100.0	

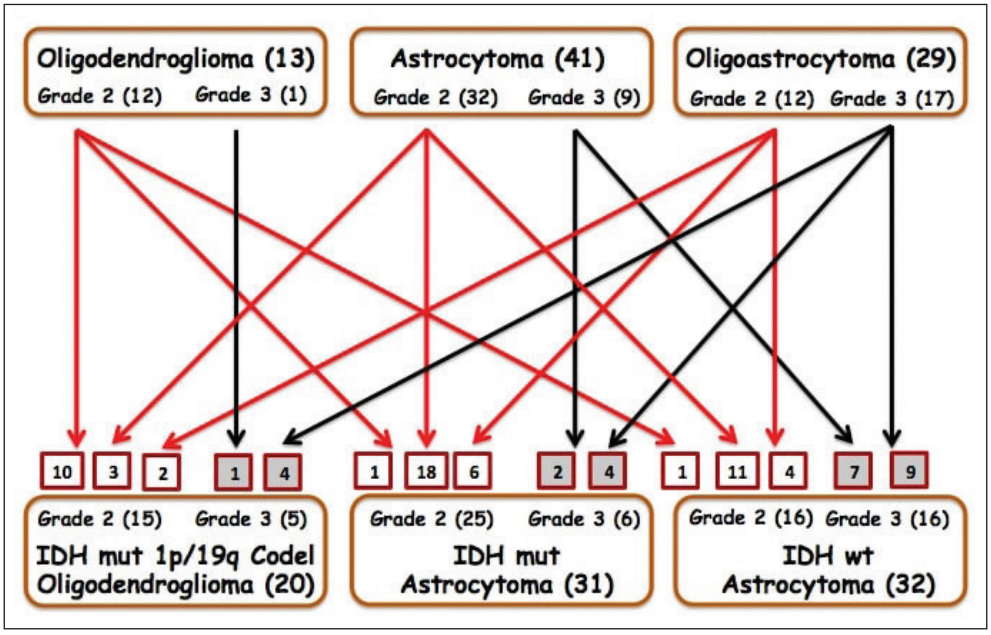

Figure 1: From previous histopathological diagnoses to new layered diagnoses.

were IDH-wt (43.9%; grade II, n=11; grade III, n=7). Of these 18 patients, 8 were treated with chemotherapy (44.4%; grade II, n=7; grade III, n=1), and 6 did not undergo any adjuvant therapy (33.3%; grade II, n=5; grade III, n=3). In total, 8 of the 35 patients that did not receive any adjuvant therapy after their initial diagnosis were IDH-wt (22.9%). Among the 47 patient who received radiotherapy but not chemotherapy (grade II, n=39; grade III, n=8), 13 were IDH-wt (27.6%; grade II, n=9; grade III, n=4).

We found that the PFS of grade II and grade III glial tumors were 50.7 and 29.7 months, respectively. The OS of grade II and grade III glial tumors was 80.1 and 41.8 months, respectively (p=0.0021). We analyzed the survival rates of IDH-mut and IDH-wt patients for grades after layered diagnosis. We found that grade II IDH-mut astrocytoma patients had significantly better survival outcomes compared to grade III IDH-mut astrocytoma patients (p<0.0001). Thus, the survival outcomes of grade II and grade III IDH-wt astrocytoma patients were not significantly different.

We also compared the survival outcomes of patients according to the novel layered diagnosis method that combines molecular marker findings with the histopathological data. We found that the IDH-mut astrocytoma patients (grade II, n=40; grade III, n=11) had significantly better survival outcomes when compared to IDH-wt astrocytoma patients (grade II, 16; grade III, n=16) (p<0.0001, Table II, Figure 2).

DISCUSSION

Recent studies indicate that histopathological diagnosis alone is not sufficient to evaluate grade II and grade III glial tumors and that evaluation of molecular markers such as IDH mutations and 1p/19q codeletion yield more accurate results. Thus, WHO 2016 included molecular markers to integrate diagnosis in the classification of brain tumors (4,25,33,40).

It is proposed that the histopathological grading system will become unimportant in glial tumors as we start to better understand the underlying genetic background (4,16,20,29). Our study aims to contribute to this transition from histopathological to molecular diagnosis of gliomas and to demonstrate the subsequent outcomes through patients' results. We will see whether genetic diagnosis will completely replace histopathological evaluation in the near future. For now, we would like to focus on the impact of the different diagnostic methods on patient outcomes.

We used IDH mutation and 1p/19q codeletion as genetic markers when utilizing the novel integrated diagnosis concept. We found that IDH mutation and 1p/19q codeletion were associated with better prognosis. The early detection of the markers required for the novel layered diagnosis is important since they can provide information about the requirement of adjuvant therapy and overall prognosis. Recent studies argue that IDH-wt astrocytomas can be added to Pignatti classification and evaluated as high-risk tumors and that these patients will benefit from early postoperative adjuvant treatment (11,12).

Our study primarily consists of reevaluating the patients for the transition from classical histopathological diagnostic methods to the novel integrated diagnosis. The novel integrated diagnosis concept utilizes IDH mutation status to further divide the classical astrocytoma diagnosis into two subgroups, which provides a clarification for the formerly vague survival outcomes (1,11,17,27). We observed that the survival

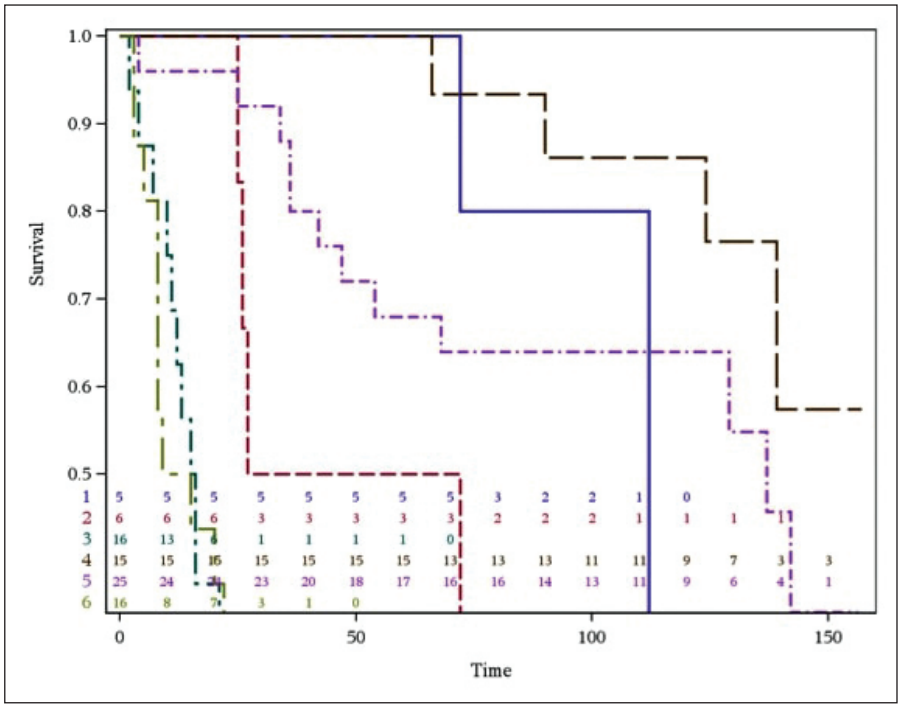

Figure 2: Survival outcomes after layered diagnosis.
1. Anaplastic IDH-mut 1p/19q codel oligodendroglioma (blue)
2. Anaplastic IDH mut astrocytoma (red)
3. Anaplastic IDH wt astrocytoma (green)
4. IDH-mut 1p/19q codel oligodendroglioma (brown)
5. IDH-mut astrocytoma (purple)
6. IDH-wt astrocytoma (yellow).

outcomes of astrocytoma and oligoastrocytoma patients were statistically similar. However, the evaluation of molecular markers showed that survival outcomes were significantly different for patients with and without IDH mutations. This makes it possible to more accurately estimate the prognosis and subsequently determine a more adequate treatment compared to classical diagnostic methods. Molecular marker analysis can clarify the diagnosis and change the course of treatment.

The analysis of relevant studies shows that patients histopathologically diagnosed with oligoastrocytoma have highly variable disease profiles and survival outcomes. While the ratio of patients with astrocytoma and oligodendroglial tumor are similar in different studies, the rate of oligoastrocytoma significantly varies from 15 to up to 30%, as was the case in our study (7,22,35,36,41). We diagnosed approximately half of our oligoastrocytoma patients with IDH-wt mutations. Current resources recommend different adjuvant therapy approaches for oligoastrocytoma patients with and without IDH mutations. Previously, since IDH status was not investigated before WHO 2016, the patients were diagnosed with and treated for the same condition, and thus, none of them were treated with early adjuvant therapy. Now, it is known that certain patients would have benefited from treatment and could have had a better prognosis. It can be considered that adjuvant therapy can be standardized with new diagnostic systems if they become sufficiently available.

The latest brain tumor classification in WHO 2016 recommended abandoning histopathological grading; however, studies suggest that the grading system is still significant for medical practice. Hence, the grading system is still a part of the current integrated diagnostic system (5,28,33,35,39). In our study, we investigated tumor grades together with integrated diagnoses. We found that grading was insignificant for IDH-wt tumors, and the prognosis was poor for both tumor grades (II and III). As for IDH-mut astrocytomas and IDH-mut 1p/19q codeletion oligodendrogliomas, the outcomes of grade II tumors were significantly better than grade III tumors. Hence, the histopathological grading system was significant in terms of PFS and OS.

The primary difference of molecular classification from histopathological grading is access. As utilizing molecular markers can be very costly and time-consuming, researchers are in search of efficient and cost-effective methods (8,10,17,26). We found that one out of every four patients received inadequate treatment when diagnosed with immunohistochemistry, as this method can only determine IDH1 status. This brings about the requirement of more detailed mutation analyses; however, this would further increase treatment costs. Compared to histopathological diagnosis, the WHO 2016 glioma classification with molecular markers provides new perspectives in patient prognosis and treatment. However, due to the costs of using molecular markers, the extent to which it can be used is questionable. WHO may have opened the door to an ethical problem by generalizing an application that can be used with sponsorship supports. We hope that these systems will become more commonly available all over the world in the coming years.

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