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ORIGINAL ARTICLE

Low-grade glial tumors: The experience of an oncology hospital in Türkiye*

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ABSTRACT

Objective: Several factors are important in the prognosis of low grade gliomas, besides genetic changes. The present study aims to examine the effect of other factors on prognosis except for genetic changes in low grade gliomas (LGGs).

Materials and Methods: Patients diagnosed with "brain malignant neoplasm" who were referred to Hacettepe University Oncology Hospital were screened. Among these patients, 148 patients with a supratentorial low grade gliomas whose data are completely available were included. Patients were followed for at least five years after diagnosis or death within this period.

Results: Mean age of diagnosis was 36.2±10.7 years, and 52.7% of patients (n=78) were females, Most common subtype was oligodendroglioma (n=86, 58.1%). Sixty-two of patients relapsed (41.9%). The 5-year mortality rate was 35.1% (n=52). Kaplan-Meier analysis of the variables, the only difference was between histopathological subtypes (p=0.03). Astrocytoma histology was related to wporse prognosis. Cox regression analysis of factors affecting 5-year mortality, advancing age (HR: 1.03, 95% CI: 1.00-1.06, p=0.03), astrocytoma (HR: 2.59, 95% CI: 1.35-4.98, p=0.004) and oligoastrocytoma (HR: 2.13, 95% CI: 1.02-4.43, p=0.04) were identified to increase the mortality risk.

Conclusion: The age of the patients and the histopathologic subtype of the tumor must be taken into consideration during the follow-up and treatment of low grade gliomas.

Keywords: astrocytoma, glioma, mortality, survival.

INTRODUCTION

Central nervous system tumors are defined according to the type of cell they originate from and the histopathological characteristics of these cells. Gliomas are neuroepithelial tumors arising from glial cells. According to the 2007 WHO classification system, low-grade gliomas (LGGs) are grade I and II tumors [1]. Low-grade gliomas constitute approximately 5% of all primary brain tumors and 15% of all glial tumors [2,3]. They are rare tumors that are more common in the young population [4]. In the diagnosis of LGGs, after it is determined that there may be LGG according to the radiological features of mass by radiological methods, surgical resection or biopsy is performed. Afterward, diagnosis is confirmed by examination for histopathological and molecular changes [5].

Mutations/deletions in various genes are of great importance in the course of the disease [6]. Size, location and histopathological type of tumor, tumor crossing the midline, neurological deficits before surgery, patient's age, and performance status are important in the prognosis of LGGs, besides genetic changes [7,8]. In LGGs, the average life expectancy is shorter than ten years from the time of diagnosis. Median overall survival can be extended to over ten years with aggressive treatment [9].

Low-grade gliomas have been studied primarily in retrospective studies. Data on LGG are also from highly developed countries. [4]. Limited data are available from low- and middle-income countries. The present study serves up information from a middle-income, developing country and aims to examine the effect of other factors on prognosis except for genetic changes in LGGs retrospectively. Molecular study results were not included in the present study, since changes at the molecular level in pathology samples have been understudied.

MATERIAL AND METHODS

Participants

Four thousand nine hundred ninety-one patients diagnosed with "brain malignant neoplasm" who admitted to Hacettepe University Oncology Hospital between 01.01.2008 - 01.01.2017 were screened through the hospital automation recording system. Among these patients, 148 patients with a supratentorial LGG whose data are completely available were included in the study.

Study Protocol

Demographic and clinical data were obtained from the hospital automation recording system. Age of diagnosis, gender, localization of the tumor, crossing the midline, if the surgery was performed, the pathological examination results, presence of primary/adjuvant treatment, relapse situation, and 5-year survival were obtained. During the follow-up period, it was accepted as relapse if the tumor progressed. Patients were followed for at least 5 years after diagnosis if there was no exitus. The exitus status of patients was obtained from the death notification system.

Statistical Analysis

Descriptive statistics were used to show the characteristics of patients. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean and standard deviation or median and interquartile range values according to the normal distribution. Kaplan-Meier was performed for survival analysis. The Log-Rank test was used for comparative analysis of survival rates. Cox regression analysis was applied for examining the factors that affect the 5-year survival rate independently. Variables with a p-value of <0.20 were added to the regression model, and variables that were expected to affect survival rate even if the p-value was not <0.20. In all statistical comparisons, the p-value for significance was accepted as <0.05. Statistical Package for the Social Sciences (SPSS) 24.0 (Armonk, NY: IBM Corp.) was wielded for statistical analysis.

RESULTS

The mean age of diagnosis was 35.0 (Interquartlile range: 30.0-43.5) years, and the number of patients 40 years and over at diagnosis was 56 (37.8%). Fifty-two point seven percent of patients (n=78) were females, 43.9% (n=65) of the tumors were located in the frontal lobe, 14.9% (n=22) in the temporal lobe, 6.1% (n=9) in the parietal lobe, and 35.1% (n=52) in more than one lobe. In 96 patients

information about midline status of the tumor could be obtained, of these 16 (16.7%) had tumors crossing the midline. One hundred thirty-nine (93.9%) patients were operated. On histopathologic examination, most of the tumors were grade II (n=140, 94.6%) therefore we are dealing with mainly grade II tumors in this study. The most common subtype was oligodendroglioma (n=86, 58.1%) and the least oligoastrocytoma(n=23, 15.5%). The number of patients who received primary/adjuvant treatment was 97 (65.5%). Radiotheraphy (RT) was given to everyone who received primary/adjuvant treatment, while chemotheraphy (CT) was given to ten (6.8%) people. Sixty-two of patients relapsed (41.9%). While 40 (64.5%) of them were treated with RT, 45 (72.6%) of them received CT. The 5-year mortality rate was 35.1% (n=52) (Table 1).

The Kaplan-Meier analysis of the variables such as age, gender, localization, crossing the midline, surgery, primary/adjuvant treatment, and relapse status did not show any statistically difference on 5-year mortality rates (Table 2). The only difference was between histopathological subtypes (p=0.03). The 5-year mortality rate for oligodendroglioma was 25.6%, 48.7% for astrocytoma and 47.8% for oligoastrocytoma (Table 2, Figure 1).

Cox regression analysis of factors affecting 5-year mortality, advancing age (HR: 1.03, 95% CI: 1.004-1.066, p=0.03), astrocytoma (HR: 2.59, 95% CI: 1.35-4.98, p=0.004) and oligoastrocytoma (HR: 2.13, 95% CI: 1.02-4.43, p=0.04) were identified to increase the mortality risk. Gender, primary/Adjuvant treatment and relapse status did not have an effect on 5-year mortality (Table 3).

Table 1. Demographic and clinical characteristics of patients.

	N=148 (n, %)
Age of Diagnosis (years) (median, interquartile range)	35.0 (30.0-43.5)
≥40 years	56 (37.8)
Gender (female)	78 (52.7)
Lobe	
Frontal	65 (43.9)
Temporal	22 (14.9)
Parietal	9 (6.1)
≥2 lobes	52 (35.1)
Crossing the Midline (n=96)	16 (16.7)
Surgery	139 (93.9)
Histopathological Examination	
Grade	
I	4 (2.7)
II	140 (94.6)
Undetermined	4 (2.7)
Subtype	
Oligodendroglioma	86 (58.1)
Astrocytoma	39 (26.4)
Oligoastrocytoma	23 (15.5)
Primary/Adjuvant Treatment	97 (65.5)
Radiotheraphy	97 (65.5)
Chemotheraphy	10 (6.8)
Relapse	62 (41.9)
Treatment After Relapse	
Radiotheraphy	40 (64.5)
Chemotheraphy	45 (72.6)
Exitus	52 (35.1)

Table 2. Demographic and clinical characteristics of patients.

	Deaths (N,%)	P*
Age of Diagnosis (years)		0.89
<40	32 (34.8)	
≥40	20 (35.7)	
Gender		0.95
Female	28 (35.9)	
Male	24 (34.3)	
Localization		0.32
Frontal	27 (41.5)	
Temporal	6 (27.3)	
Parietal	1 (11.1)	
≥2 lobes	18 (34.6)	
Crossing the Midline (n=96)		0.59
Present	32 (40.0)	
Absent	7 (43.8)	
Surgery		0.57
Present	48 (34.5)	
Absent	4 (44.4)	
Subtype		0.03
Oligodendroglioma	22 (25.6)	
Astrocytoma	19 (48.7)	
Oligoastrocytoma	11 (47.8)	
Primary/Adjuvant Treatment		0.33
Present	15 (29.4)	
Absent	37 (38.1)	
Relapse		0.37
Present	32 (37.2)	
Absent	20 (32.3)	

*Results from Kaplan-Meier survival analysis

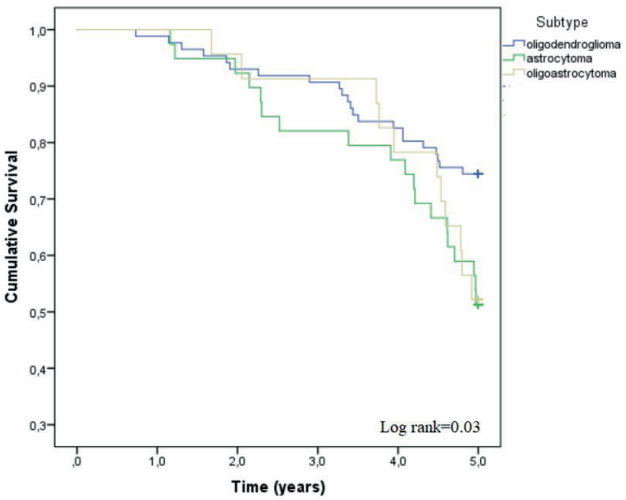

Figure 1. Histological subtypes and 5-year mortality.

Table 3. Multivariate regression analysis of factors affecting 5-year mortality rate.

	HR	95% CI	P
Age of Diagnosis (years)	1.03	1.004-1.066	0.03
Gender (female)	1.01	0.58-1.76	0.96
Subtype			0.01
Oligodendroglioma	Ref	Ref	
Astrocytoma	2.59	1.35-4.98	0.004
Oligoastrocytoma	2.13	1.02-4.43	0.04
Primary/Adjuvant Treatment	1.03	0.54-1.97	0.92
Relapse	0.86	0.48-1.52	0.60

HR: Hazard ratio, CI: Confidence Interval

DISCUSSION

Low-grade gliomas are a rare group of the primary brain tumors. A new classification was made by World Health Organization in 2016 [10] and updated in 2021 [11], but many features from the old classification are similar to the new version. Retrospective follow-up data of 148 patients with LGGs were analyzed in the present study and the results suggest that age and histopathological subtype were related to 5-year mortality rate.

Patients diagnosed with LGG are usually diagnosed at a young age, and the average age at diagnosis is in the range of 35-40 years [12]. In the present study, the mean age at diagnosis was 36.2±10.7, in line with data in other studies. The young age at diagnosis complicates treatment because it involves patients who are fertile and when the tumor is an eloquent area, applying a standardized algorithm becomes more difficult.

The prognosis of LGGs has not improved over the years, despite improved diagnosis and treatment methods. Treatment decisions are generally made according to clinical variables although considerable advances are made at molecular-level [13]. The median survival of LGG patients is between 4.7 and 9.8 years [14]. Overall survival decreases with increasing age at diagnosis [15]. The Pignatti risk score takes age 40 as a threshold and considers age 40 and over as high risk [16]. In addition, in recent studies it is stated that the age limit, which indicates a poor prognosis, is higher [17-19]. Reasons for this are reduced performance score with increasing age, increased frequency of comorbidities, an increase in tumor diameter, and inability to achieve total resection [20]. In the present study, advancing age at the diagnosis was found as a risk factor for 5-year mortality.

Astrocytomas constitute the most common LGG histology [4,21], but in our series oligodendrogliomas were more frequent and astrocytomas were the second. Astrocytoma histology indicates worse prognosis. Pignatti risk score also includes astrocytoma histology [16]. In the North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study, oligodendroglioma or oligo-dominant histology has better survival rates. Histologic subtype and age combined, were particularly powerful indicators of overall survival [22]. In the present study, astrocytoma histology is associated with lower survival rates and the combination of age and histology shows a strong relationship with survival similar to literature.

Early maximum tumor resection within safe limits is the standard treatment in LGG management [23,24]. With early resection, uncertainty in the radiological diagnosis is eliminated, and malignant transformation is delayed, and as a result, survival is increased [24]. Studies comparing follow-up after biopsy with early resection report longer survival with the latter mode [25,26]. On the other hand, there are also contradictory data that early resection does not affect survival compared to the wait-and-

see strategy. By delaying surgical intervention, the patient spends a longer time without impairment in the quality of life [27]. Surgical treatment was not found to have a significant effect on the 5-year mortality rate and there is no satisfactory data on quality of life in the present study. Some studies also indicate that adjuvant therapy does not improve survival [4]. Similar results were found for primary/adjuvant treatment on the 5-year mortality rate in the present study.

Relapse is a significant issue in the follow-up and treatment of these tumors. Patients with low-risk scores are generally followed up without treatment after surgery; high-risk patients receive adjuvant RT and/or CT after surgery. Despite these treatments relapses occur [13,28,29]. In the present study, relapse rate was 41.9% in five years and relapse status did not affect the 5-year mortality rate. This could be because the follow-up was limited to five years.

Some limitations exist due to the retrospective nature of the study. Since patients were lost to follow up for various reasons, data of some patients could not be reached. As studies at the molecular level were not done regularly in the past, data on this subject remained limited. Therefore, molecular study results were not included in the present study. High-grade tumors may have been misdiagnosed due to the possibility of heterogeneity in tumors that underwent subtotal resection and were diagnosed by biopsy. In LGGs, classification of tumors at pathological examination can be difficult, and low level of interobserver concordance may complicate the diagnostic approach further [30]. Because the follow-up period was limited to 5 years, the negative effects of relapse may not have been observed. The present study does not contain information on performance status, quality of life, and toxicity. Another limitation is that the causes of death are unknown. Since the patients were young, their accompanying chronic diseases were few, they were not included in the analysis.

CONCLUSION

Despite the advances in diagnosis, the characteristics of the patients and the histopathological features of the tumor remain to be important. The age of the patients and the subtype of the tumor must be taken into consideration during the follow-up and treatment of the patient.

Author contribution

Study concept adn design: S.C., A.K.; Supervision: N.K., G.Y.; Data collection and interpretation of results: S.C., A.K.; Literature search: S.C., A.K.; Writing: S.C., A.K.; Critical review: N.K, G.Y. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Researches Ethics Board (Protocol no. 17/771-07).

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Conflict of interest

The authors declare that there is no conflict of interest.

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