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Original Article

Clinical prognostic factors of adjuvant radiation therapy for low-grade gliomas: results of 10 years survival

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Abstract: Objective: Low-grade gliomas compose 5-20% of all glial tumors. The prognosis of the disease can be anticipated by specific clinical factors determined during diagnosis. For this purpose, our study investigated the clinical prognostic factors for low-grade gliomas. Methods: Patients diagnosed with histopathologically confirmed low-grade glioma, followed by Akdeniz University and Süleyman Demirel University School of Medicine, Department of Radiation Oncology between 1999 and 2013 were included in the study. The examination of survival by single variable analyses were performed by log rank test. For the multivariate analysis, independent factors for the prediction of survival by using possible factors determined by previous analyses were examined by using Cox regression analysis. Results: Fifty-five patients were included in the study. The mean follow-up period was determined as 60 ± 57 (4.5-168.1) months. Five-year overall survival was determined as 69% and 10-year overall survival was determined as 40%. When the potential prognostic factors were studied in Cox regression model, pre-radiotherapy age below 40 and gross-total excision were determined as good prognostic factors. Conclusion: We demonstrated that the aggressive surgical resection provided a better survival advantage both in single variable analyses and multivariate analyses. Consequently, although the low number of patients was the most important limitation in our study, we consider that patient age and extent of resection are the most important clinical prognostic factors in low-grade gliomas.

Keywords: Low-grade, gliomas, radiotherapy, prognosis

Introduction

Low grade gliomas (LGG) compose 5-20% of all glial tumors [1]. According to the WHO classification system, grade II diffuse infiltrative low-grade gliomas are classified as astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas [2]. They reach to a peak between 30-40 years of age in young adults and they are more frequent in males (rate of male/female: 1.18/1) [3]. Most of the oligodendroglial tumors originate from white matter of cerebral hemispheres, in particular from the frontal lobe [4]. Symptoms may be generalized (headache, seizures, cognitive dysfunctions) or focal (auditory abnormalities, aphasia or fatigue).

Generally, oligodendroglioma and oligoastrocytoma (mixed gliomas) are clinically and biologically diffuse tumors [5]. The negative prognostic factors include patient age over 40, astrocytoma histology, tumor diameter greater than 6 cm, tumors past the midline, and existence of neurological deficits prior to resection [6]. Cerebral palsy is the most frequent symptom (81%) [7]. Diffuse astrocytomas may become invasive and, mostly, higher grade astrocytomas with poorly defined borders [8].

The prognosis of the disease can be anticipated by specific clinical factors determined during diagnosis. For the patient treatments, laboratory parameters can be employed to determine the intensity of the treatment. For this purpose, our study investigated the clinical prognostic factors for LGG.

Materials and methods

Patient selection

Patients diagnosed with histopathologically confirmed LGG, followed by Department of

Table 1. Patient characteristics

Variable	Value (%)
Patiens	55 (100)
Gender	
Male	35 (63.6)
Female	20 (36.4)
Age at diagnosis (years)	
Mean	39.7 ± 13.2
< 40	29 (52.7)
≥ 40	26 (47.3)
Symptom duration (days)	
Mean	181.6 ± 343.1
≤ 30	22 (40)
> 30	29 (52.7)
Missing	4 (7.3)
Seizures at diagnosis	
Yes	27 (49.1)
No	28 (50.9)
Neurological deficit at diagnosis	
Yes	16 (29.1)
No	39 (70.9)
Karnofsky performance status pre-RT	
≤ 70	11 (20)
> 70	42 (76.4)
Missing	2 (3.6)
Extent of surgery	
Biopsy	4 (7.3)
Subtotal resection	21 (38.2)
Total/gros-total resection	30 (54.5)
Radiotherapy timing	
Postoperative	44 (80)
At progression	11 (20)

Radiation Oncology, Akdeniz University School of Medicine and Department of Radiation Oncology, Süleyman Demirel University School of Medicine between 1999 and 2013 were included in the study. The medical records of the patients were scanned and information on age, gender, disease stage, and treatment was obtained. Patient without histopathological diagnosis or patients for whom a treatment was initiated by another medical center and continue their treatment in our medical center were excluded.

Radiation therapy

A total of 54 Gy in 30 fractions radiation therapy (RT) was planned with a linear accelerator. The RT fields included the preoperative tumor volume as defined by a preoperative MRI. In the first phase of the treatment; 45 Gy in 25 fractions to primary tumor and/or tumor bed and edema plus 2 cm was performed. The boost volume includes the primary tm and/or tumor bed plus 2 cm and is treated 9 Gy in 5 fractions. RT delivered by using 6 and/or 25 MV photon energy to the primary tumor and/or tumor bed and edema, in the two lateral, anterior or posterior areas, 5 days a week with a fraction dose of 1.8 Gy. None of the patients received chemotherapy during RT.

Toxicities were evaluated according to radiation-specific criteria from Radiation Therapy Oncology Group (RTOG) in weekly examinations. In addition, late side effects were assessed every 3 months according to the RTOG criteria.

Response to RT was evaluated by contrast enhanced MRI. RT response was evaluated according to these criteria: complete response (CR) was defined as disappearance of all T2 hypersignal and T1 post-contrast tumor. Partial response (PR) was defined as greater than 50% reduction in the tumor based on perpendicular diameters or a clear reduction in the tumor from baseline. Minimal Response (MR) was defined as 25% to 50% reduction in the tumor size. Progressive disease (PD) was defined as greater than 25% increase in tumor size based on perpendicular diameters, a clear increase in the size of the tumor-related clinical and neurological deterioration [9].

Statistical analysis

The statistical analyses were performed by using software SPSS version 15. The compatibility of disease and other variables to normal distribution were studied by using visual (histogram and probability graphics) and analytical methods (Kolomogorov-Simirnov/Shapiro-Wilk tests). For the Kolmogorov-Simirnov test, *P* value > 0.05 was considered normal distribution.

The survival rates were calculated by using Kaplan-Meier survival analyses. The examination of survival by single variable analyses was performed by log rank test. For the multivariate analysis, independent factors for the prediction of survival by using possible factors determined by previous analyses were examined by using Cox regression analysis. Conditions for which

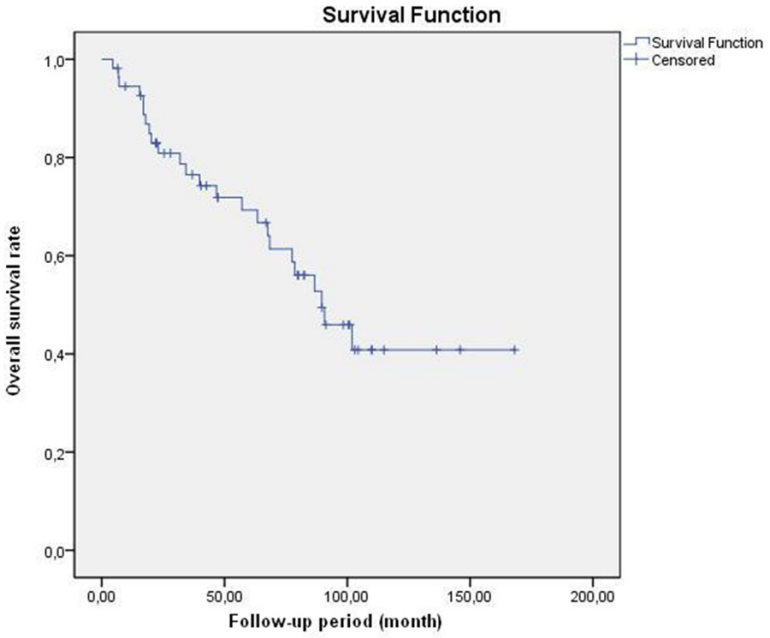

Figure 1. Median survival for all patients.

type-1 error level is < 5% were concluded statistically significant.

Results

A total of 55 patients were included in the study, 35 patients were male (63.6%) and 20 patients were female (36.4%). The mean age of the patients was determined as 39.7 ± 13.2 (10-77) years. Twenty-nine of the patients (52.7%) were < 40 years, 26 of the patients (47.3%) were ≥ 40 years. The median time from the initial symptom of a patient to diagnosis was determined as 181.6 ± 343.1 (1-1825) days. This period was less than 30 days in 22 of the patients (40%), whereas it was more than 30 days in 29 of them (63.8%), and this data could not be provided for 4 patients (7.3%). Twenty-seven of the patients (49.1%) had an epileptic seizure history during diagnosis. Sixteen of the patients (29.1%) had a focal neurological deficit during diagnosis. Karnofsky performance score was ≤ 70 for 11 (20%) patients before RT (**Table 1**).

Diagnoses of patients were performed through biopsy in 4 patients, subtotal resection in 21 patients and total/gross total resection in 30 patients. The histopathological types of patients during diagnosis were grade I astrocytoma for 2 patients (3.6%), grade II astrocytoma for 35 patients (63.7%), oligodendrogliom for 17 patients (30.9%) and ganglioglioma in 1 patient (1.8%). Forty-four patients (80%) received immediate postoperative RT after initial diagnosis, whereas 11 patients (20%) received RT at progression (**Table 1**). All of our patients have completed the scheduled RT program. Following RT, 5 patients (9.1%) received chemotherapy due to malignant transformation. RT response was described as; CR/PR in 4 patients (13.3%) and MR in 16 patients (53.4%). The response could not be estimated for 5 patients (33.3%).

The mean follow-up period was determined as 60 ± 57 (95% confidence interval 4.5-168.1) months. The median survival was determined as 89.5 ± 12.2 (65.5-113.6) months (**Figure 1**). Five-year overall survival was determined as 69% and 10-year overall survival was determined as 40%. Five-year overall survival could not be estimated for grade I astrocytomas. It was determined as 58% for grade II astrocytomas and 85% for grade II oligodendrogliomas.

According to Kaplan-Meier survival analysis and Log-rank test, a statistically significant relationship was determined between survival and age whether or not below 40, history of epileptic seizures before diagnosis, surgery whether or not subtotal or gross-total, and pre-RT Karnofsky performance scores ($P = 0.039$, $P = 0.045$, $P = 0.008$, and $P = 0.023$, respectively) (**Figure 2A-D**). A borderline significance was determined between survival and histological sub-types and existence of neurological deficits during diagnosis ($P = 0.053$, $P = 0.052$) (**Figure 3A** and **3B**).

During the examination of survival by univariate analysis, no statistically significant relation between survival and gender, histologic type, neurological deficit, epileptic attac, and surgey type (**Table 2**).

When the potential prognostic factors were studied in multivariate analysis using by Cox

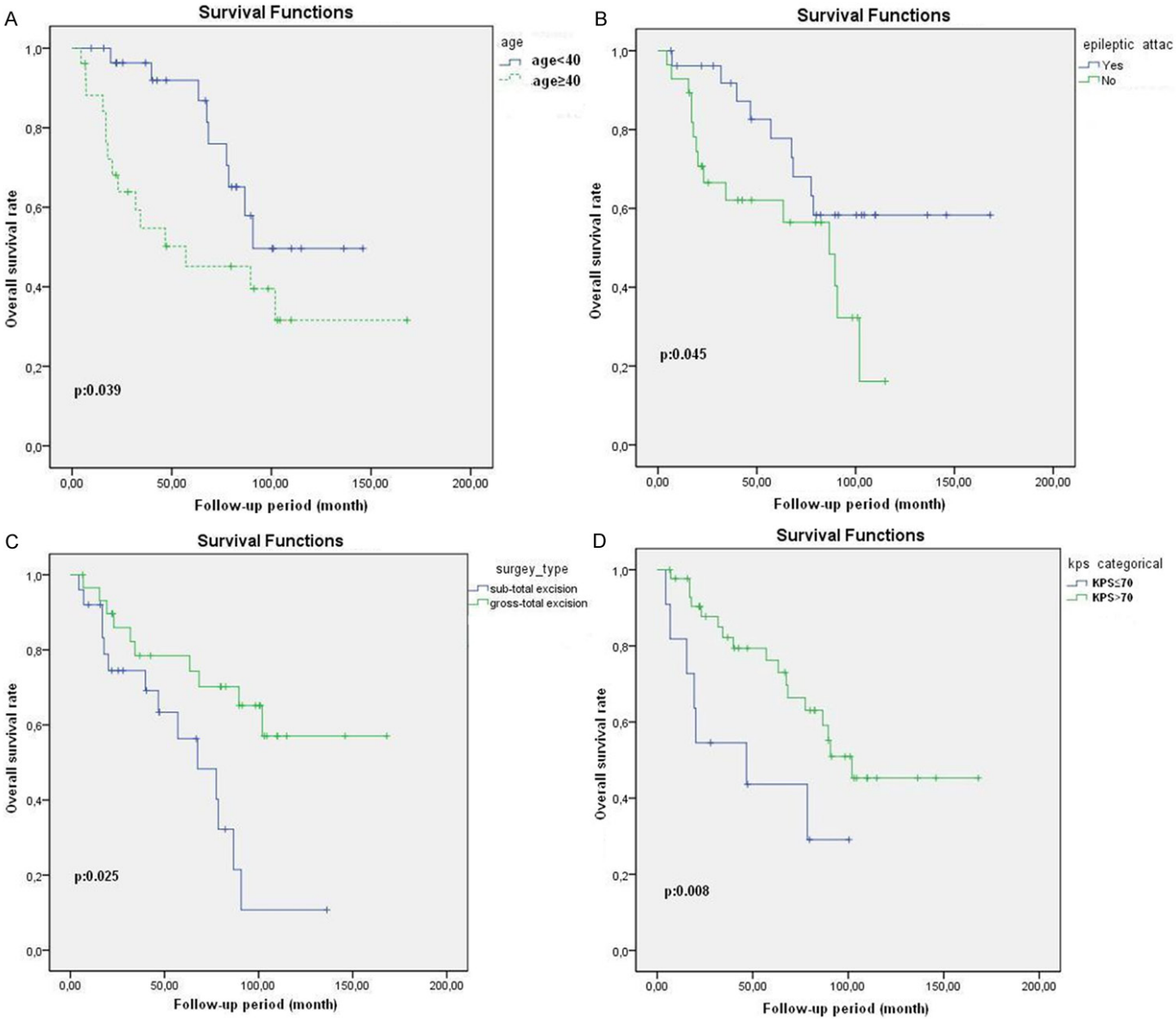
A
Survival Functions
age
age<40
age≥40
Overall survival rate
1,0
0,8
0,6
0,4
0,2
0,0
p:0.039
0,00
50,00
100,00
150,00
200,00
Follow-up period (month)
B
Survival Functions
epileptic attac
Yes
No
Overall survival rate
p:0.045
Follow-up period (month)
C
Survival Functions
surgey_type
sub-total excision
gross-total excision
Overall survival rate
p:0.025
Follow-up period (month)
D
Survival Functions
kps categorical
KPS≤70
KPS>70
Overall survival rate
p:0.008
Follow-up period (month)

Figure 2. A: Overall survival according to age whether or not below 40. B: Overall survival according to history of epileptic seizures before diagnosis. C: Overall survival according to surgery whether or not subtotal or gross-total. D: Overall survival according to karnofsky performance scores.

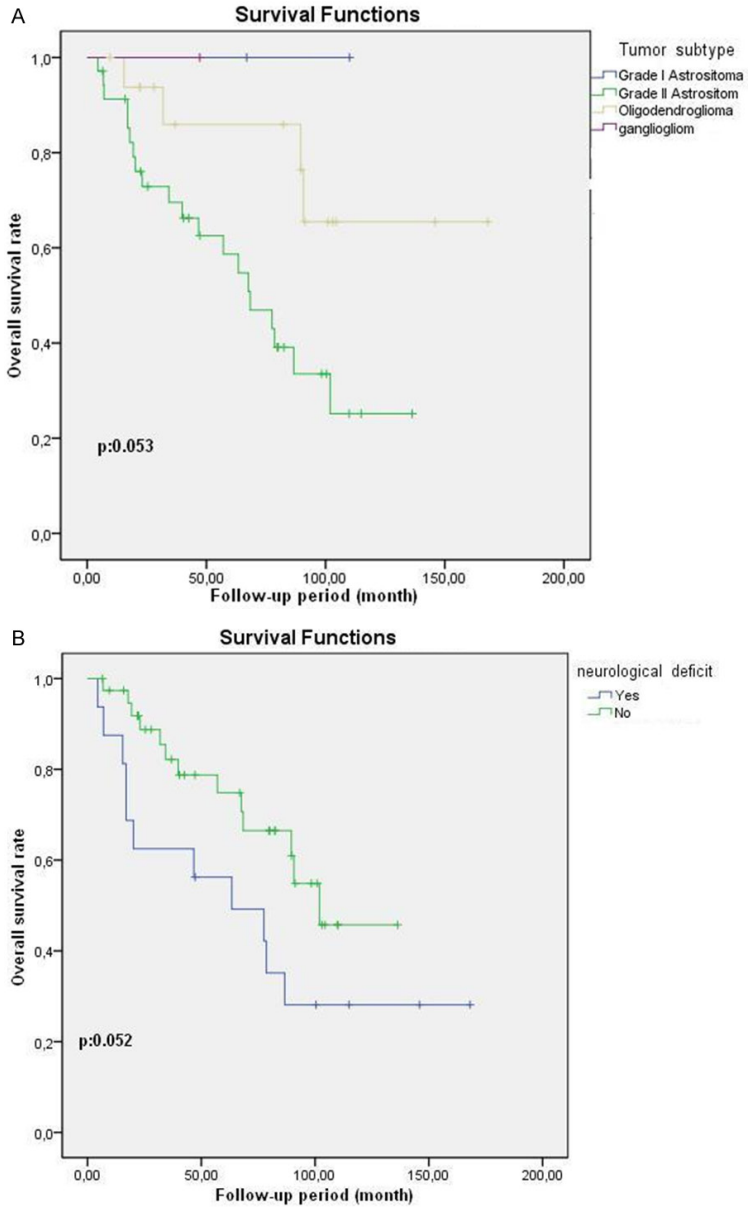

Figure 3. A: Overall survival according to histological sub-types. B: Overall survival according to existence of neurological deficit during diagnosis.

regression model, age below 40 and gross-total resection were determined as favorable prognostic factors (**Table 2**).

Discussion

In our study, patients whether or not below 40 years of age and surgical resections whether or not total/gros-total were determined as independent prognostic factors. For LGG, histological sub-type is a prognostic factor [10, 11]. Oligodendroglial component has been found to be associated with a better prognosis. Our study determined a significant relationship between survival and histological subtype and also determined a *P* value of 0.026. A better prognosis of oligodendroglia component was suggested to be associated with 1p/19q codeletion [12]. Five year survival was reported as 70% for grade II oligodendrogliomas, 56% for mixed gliomas and 37% for astrocytomas [13]. In our study, we determined a 69% of a 5-year survival for all histological subtypes. We also determined that the survival was longer for oligodendrogliomas compared to that of astrocytomas.

In a study where prognostic factors for LGG were examined, Pignatti et al. determined patient age over 40, astrocytoma histology, largest tumor diameter ≥ 6 cm and existence of neurological deficits prior to surgery as bad prognostic factors [6]. Our study determined a borderline significance between survival and existence of a neurological deficit prior to surgery in univariate analysis. The low number of patients may account for this situation.

The time from emerging of symptoms to diagnosis is approximately between 6-17 months. We also obtained similar results in our study. Epileptic seizure is the most frequent symptom observed in 81% of LGG and it is frequently associated with oligodendrogliomas [7]. We determined that epileptic seizures have a lower rate among presenting symptoms, however, we

Table 2. Overall survival rate according to univariate and multivariate analysis

	Univariate Analysis			Multivariate Analysis		
Factor	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Gender	1.415	0.474-2.593	0.813	1.466	0.523-4.113	0.467
Age ≥ 40	2.342	1.020-5.375	0.045	0.310	0.115-0.833	0.020
Histologic Type	0.674	0.439-1.033	0.070	2.299	0-4.210	0.996
Neurological deficit	0.459	0.205-1.026	0.058	1.524	0-7.940	0.444
Epileptic attac	2.297	0.997-5.291	0.051	2.416	0.202-1.192	0.116
Surgey Type	0.675	0.318-1.430	0.305	1.126	0.218-5.827	0.031
Karnofsky performance status pre-Radiothreapy	0.368	0.150-0.905	0.029	1.156	0.342-3.914	0.816

CI, confidence interval; HR, hazard ratio.

also determined a significant relationship between survival and epileptic seizures. Patients presenting with an epileptic seizure had a better survival. This can be accounted for by the epileptic seizures observed more frequently in patients with oligodendrogliomas which have a better prognosis.

The most appropriate treatment for LGG is still controversial. However, surgery is the most important diagnosis and treatment modality [14]. Aggressive or non-aggressive performance of surgery is among the controversial subjects for the treatment of LGG. There are studies demonstrating that maximum safe surgical resection provides a survival advantage, as well as studies suggesting that it has no advantage [15-19]. However, maximum safe surgery was demonstrated to reduce malignant progression and recurrence [20-23]. In our study, we demonstrated both through single variable and multivariate analyses that a better survival advantage is achieved for patients who underwent an extensive surgical resection.

The role of adjuvant RT in LGG, as well as in high-grade glial tumors is not clear. The most critical questions on this topic are RT dose and timing. The first randomized trial performed by EORTC-22844 aimed to find out optimum RT dose in LGG [24]. In EORTC-22844 study, 379 LGG patients with incomplete resection were randomized to receive either 45 Gy in 25 fractions or 59.4 Gy in 33 fractions. The 5-year survival rates were 58% for low dose and 59% for high dose RT, respectively [24].

Another dose escalation study was performed by Shaw et al. in 2002 [25]. In this phase III prospective randomized clinical trial, 203 adult supratentorial LGG patients were randomized to receive low dose (50.4 Gy in 28 fractions) or high dose (64.8 Gy in 36 fractions) RT [25]. Based on the results of this study, lower survival and a slightly higher incidence of radiation neuro-toxicity in the high-dose arm. Increasing the RT doses did not show any contribution in terms of overall survival (OS) and progression-free survival (PFS) in two clinical randomized trials [24, 25]. On the other hand, Shaw et al. reported that; histologic subtype, tumor size, and age, were most consistently and significantly associated with overall survival in multivariate analysis [25]. Likewise in our study; age below 40 and gross-total excision were determined as favorable prognostic factors. The currently accepted treatment for LGG includes a radiation dose of 50-54 Gy in fractions of 1.8 Gy to the tumor bed as well as a 1- to 2- cm surrounding margin [26].

In EORTC-22845 trial, patients were randomized to immediate postoperative RT or delayed RT arm to determine the optimal timing of RT in LGG patients. According to results of this study; increase in time to progression and PFS achieved by immediate postoperative RT. But the same improvement was not achieved in the OS [27]. In our study, 44 patients (80%) received immediate postoperative RT, whereas 11 patients (20%) received RT at progression. Five-year OS rates (69%) of our study are consistent with the literature.

Youland et al. evaluated 852 adult LGG patients who received a diagnosis at Mayo Clinic from 1960 through 2011 in recently [28]. Factors associated with improved OS in multivariate analysis were younger age, nonastrocytoma histology, small tumor size, and gros total or

radical subtotal resection. In this study 10-year OS rate is between 47% and 33%. Similarly, our study showed that 10-year survival is 40% in LGG patients. Consequently, although the low number of patients was the most important limitation in our study, we consider that patient age and extent of resection are the most important clinical prognostic factors in low grade glial tumors.

Disclosure of conflict of interest

None.

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