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Orginal Article

Prognostic factors for survival in adult patients with grade II glial tumors

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Abstract

Aim: To investigate survival results of patients with low grade gliomas (LGGs) and to evaluate the predictive role of clinico-pathologic prognostic factors on survival.

Material and Methods: Between 2003 and 2014, the adult patients with Grade II glial tumors were evaluated retrospectively. Several variables were investigated to find prognostic factors related with the overall survival (OS) and progression-free survival (PFS).

Results: This study involved in 124 patients with median 40 (range; 6-132) months follow up. The average OS for the all patients was 7.8 years. 2-, 5- and 10- year OS ratios were 91%, 73% and 55%, respectively. Patients with low pignatti risk score had a longer OS than high pignatti risk score (p=0.01). Patients with seizure had a better OS (p=0.03). Patients with biopsy/partial resection had a poorer OS (p=0.02). Patients with residue after initial surgery had a worse OS (p=0.03). If the patients had recurrence or progression, the patients had poorer OS (p=0.01). Tumor with malignant transformation (p=0.01) and glioblastoma subtype after second surgery (p=0.003) had a poorer OS. The Pignatti risk score and seizure were the independent prognostic factors for PFS.

Conclusion: The extent of surgery and recurrence or progression of Grade II glioma were the independent prognostic factors for OS. The Pignatti risk score and seizure were the independent prognostic factors for PFS.

Keywords: Grade II glioma; Prognostic factors; Progression Or Recurrence Free Survival; Radiotherapy; Survival.

INTRODUCTION

Low grade gliomas (LGGs) are relatively rare and consist nearly 15% of primary central nervous system cancers (1,2). They have a heterogeneous clinical behavior although slow growing primary brain tumors in general (3). The median survival rate varies from 5 to 10 years (2,4) and the average 10-year survival is 30% (5). It's important to know prognostic factors for the decision of treatment, as they seen at young age and as they have long survey (6,7). The patient age, gender, performance status, tumor site, presence of seizure, tumor size, extent of surgery, histological subtype are the some prognostic factors (3,6,7).

Otherwise, there is significant disagreements among clinicians regarding the best treatment modality for LGGs because of the heterogeneity of histopathological subtypes. Despite standard treatment is surgery, LGGs often arise in eloquent areas therefore it is difficult to resect tumor radically (8). Surgery can be performed as gross total resection (GTR), subtotal resection (STR), partial resection (PR) or biopsy (BX). GTR is correlated with a delay in disease recurrence and malign transformation as well as with better survival outcomes (4,6,9). Radiotherapy (RT) indications are still controversial. In general, RT is performed for patients with tumors which can not be resected grossly or for patients with high risk characteristics (10). High risk factors were identified by Pignatti and colleagues; these factors were defined as tumor size ≥ 6 cm, age ≥40 years, astrocytoma histology subtype, tumor crossing the midline, and preoperative neurologic deficit existence. Presence of ≥3 of these factors are defined as high-risk (3). The prognosis of patients with LGGs can differ based on some clinical factors although this classification can be helpful for clinicians when deciding the optimal individualized treatment. The aim of this study was to investigate survival results of patients with LGGs and to evaluate the predictive role of clinico-pathologic prognostic factors on survival.

MATERIAL and METHODS

Patient population

Between 2003 and 2014, the patients with Grade II glioma who had been followed up at our radiation oncology departments were evaluated in this retrospective study.

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Eligibility criteria for this study: histopathologically proven Grade II glioma, age ≥16 years and the availability of patients records. Patients with another concurrent cancer and follow-up period < 6 months were excluded. Magnetic resonance imaging (MRI) scans were obtained preoperatively; tumor size and presence of crossing midline confirmed from MRI reports. Patients were divided low risk and high risk groups as Pignatti's risk factors (3).

This research was approved by the institutional ethic board and carried out according to the Declaration of Helsinki.

Radiotherapy

In our departments, postoperative early-RT frequently applied for patients with LGGs which can not be resected grossly or who have high risk characteristics; delayed-RT frequently applied for patients with recurrence or progression. A total dose (median=54 Gy, range; 50-66 Gy) delivered with a conventional fractionation schemes (1.8-2 Gy fraction doses/five days a week) to the tumor or tumor bed with 1-2 cm margin. Conventional RT was applied exclusively from 2003 to 2010. Three dimentional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) gradually replaced with conventional RT for all patients after 2010. The early-RT group was defined as patients who received RT within 4 months from the diagnosis, without clinical or radiological progression. The delayed-RT group was defined as patients who observed after the surgery, and had RT at progression or recurrence. The group of patients who observed postoperative period and had no RT yet, defined in the second group.

Clinical evaluation and follow-up

Following RT or after surgery, patients were followed up 3 months intervals for two years, 6 months intervals for 3 to 5 years, and yearly thereafter. At each follow-up, a physical examination was performed, and cranial MRI were obtained.

The end points

To assess the overall survival (OS) and progression-free survival (PFS) were the primary end points of this study. The time from diagnosis to the date of the patient's death or last follow-up was defined as OS. The time from diagnosis to the date of the documented progression or recurrence was defined as PFS. The secondary end points were to evaluate the predictive effect of clinico-pathologic prognostic factors on survival.

Statistical analysis

Patients, disease and treatment characteristics were analysed with descriptive statistics. The mean, the median and the proportion values, the ranges and the standard deviations were measured for descriptive statistics. Pearson's Chi-square test was used to compare the categorical variables. Independent sample t-test and ANOVA test were used to compare continuous variables. Kaplan-Meier survival analysis was performed to evaluate the survival analysis and 2-sided long rank test was carried out to compare the survival curves of subgroups. Hazard ratios (HR) and 95% confidence intervals (CIs) were estimated by using Cox regression analysis. Variables with statistical significance in univariate analysis ($p < 0.05$) were added as covariates in multivariate analysis. A p- value of ≤0.05 was defined as statistically significant. Statistical Package for Social Sciences software, v 13.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Patients and tumor characteristics

This study specified 124 patients with median 40 (range; 6-132) months follow up period. Patients, treatment and tumor characteristics are summarized in Table 1.

Table 1. Patients, tumor and treatment characteristics

Variables	No. of patients (total:124)	%
Age (years)		
Median	38	
Range	16-68	
<40	66	53
≥40	58	47
Gender		
Male	75	60
Female	49	40
Tumor size (cm)		
Median	5	
Range	1-9	
Surgery type		
Biopsy or partial resection	32	26
Subtotal resection	50	40
Gross total resection	42	34
Residue		
No	42	34
Yes	82	66
Histopathology		
Grade II astrositoma	87	70
Grade II oligodendroglioma	25	20
Grade II oligoastrositoma	12	10
Neurologic deficit existence at diagnosis		
No	73	59
Yes	51	41
Tumor crossing the midline at diagnosis		
No	82	66
Yes	42	44
Seizures at diagnosis		
No	66	53
Yes	58	47
Headache at diagnosis		
No	83	67
Yes	41	33
Pignatti risk scale		
Low risk	79	64
High risk	45	36
Timing of RT		
Early RT	76	61
Delayed RT	48	39
Malignant transformation		
No	101	81
Yes	20	16
Unknown	3	3

Abbreviations: RT= Radiotherapy

Thirty seven patients had second surgery, 2 patients had Gamma-knife therapy and 12 patients had second-line radiotherapy because of recurrence or progression of LGGs. Malignant transformation was pathologically proven in 20 patients (16%); 10 patients had glioblastoma, 7 patients had anaplastic astrositoma, 2 patients had anaplastic oligoastrositoma and 1 patient had anaplastic oligodendroglioma.

Malignant transformation was much lower in patients with GTR than patients with non-GTR but the results did not reach to statistically significant (p=0.059).

Treatment characteristics

Seventy-six patients (61%) were in early-RT group and 48 patients (39%) were in delayed-RT group. Table 2 shows the difference between the characteristics of patients according to timing of RT. Postoperative residue after initial surgery was much higher in early-RT group than delayed-RT group however the differences were not statistically significant (p=0.06). Recurrence or progression of disease during the follow- up was much lower in early-RT group as compared with delayed-RT group (p=0.002). The early-RT and delayed-RT groups were similar in terms of the other parameters.

Table 2. Patients, tumor and treatment characteristics according to timing of RT

Variables	Early-RT (n=76) N	%	Delayed-RT (n=48) N	%	p-value
Age (years)					
Median	40		37		0.1
Range	18-68		16-60		
<40	36	47	30	63	0.1
≥40	40	53	18	37	
Gender					
Female	34	45	15	31	0.1
Male	42	55	33	69	
Tumor size (cm)					
Median	5		5		0.6
Range	1-9		1.8-8		
Surgery type					
Biopsy or partial resection	24	31	8	10	0.1
Subtotal resection	31	41	19	40	
Gross total resection	21	28	21	44	
Residue					
No	21	28	21	44	0.06
Yes	55	72	27	56	
Histopathology					
Grade II astrositoma	53	70	34	7	
Grade II oligodendroglioma	15	20	10	21	0.7
Grade II oligoastrositoma	8	10	4	8	
Neurologic deficit existence at diagnosis					
No	42	55	31	65	0.3
Yes	34	45	17	35	
Tumor crossing the midline at diagnosis					
No	51	67	31	65	0.7
Yes	25	33	17	35	
Seizures at diagnosis					
No	44	58	22	46	0.1
Yes	32	42	26	54	
Pignatti risk scale					
Low risk	47	62	32	67	0.5
High risk	29	38	16	33	
Radiation dose (Gy)					
Median	54		54		0.5
Range	50-64		50-66		
Recurrens or progression					
No	47	62	16	33	0.002*
Yes	29	38	32	67	
Malignant transformation					
No	61	80	41	85	0.4
Yes	13	17	6	12	
Unknown	2	3	1	3	

Abbreviations: Early –RT= RT within 4 months from the diagnosis; Delayed- RT= RT at progression or recurrence. *Statistically significant

Survival Analysis

At a mean 46 months follow-up (range; 6-132 months), 30 patients (24%) died, 94 patients (76%) were alive and 23 of them were alive with disease.

The average OS for the all patients was 7.8 years. 2-, 5- and 10- year OS ratios were 91%, 73% and 55%, respectively. Pignatti risk score, seizure, extent of resection, GTR, biopsy, biopsy or partial resection, residue, recurrence or progression, malignant transformation, new pathological subtype after second surgery were the significant prognostic factors for OS according to the Kaplan Meier analysis. Patients with low pignatti risk score had a longer OS (p=0.01). Biopsy or partial resection of tumor had a poorer OS than GTR or subtotal resection (p=0.02). Patients with seizure had a longer OS (p=0.03). Patients with residue after initial surgery had a worse OS (p=0.01). If the disease had recurrence or progression, the patients had a worse OS (p=0.01). Patients with malignant transformation had worse OS (p=0.01) and glioblastoma subtype after second surgery had a poorer OS (p=0.003). Table 3 shows the results of univariate analysis for OS.

Table 3. Univariate cox proportional hazard regression analysis related with OS

Variables	HR	95% CI	P- value
Pignatti risk scale			
Low risk	1		
High risk	2.37	1.14-4.93	0.02*
Seizures at diagnosis			
Yes	1		
No	2.14	1.02-4.48	0.04*
Extent of removal			
GTR	1		
STR	2.49	0.90-6.86	0.07
PR+BX	4.30	1.45-12.67	0.008*
Gross total resection			
Yes	1		
No	2.45	1.18-5.07	0.01*
Biopsy or partial resection			
No	1		
Yes	2.36	1.45-12.67	0.02*
Biopsy			
No	1		
Yes	2.36	1.09-5.08	0.02*
Recurrence or progression			
No	1		
Yes	3.49	1.20-10.09	0.02*
New pathological subtype after second surgery			
The others	1		
Glioblastoma	4.49	1.93-10.44	<0.001*
Malignant transformation			
No	1		
Yes	2.53	1.15-5.57	0.02*

Abbreviations: BX=biopsy, GTR= gross total resection, HR=hazard ratio, OS= overall survival, PR=partial resection, STR= Subtotal resection
***Statistically significant**

According to multivariate analysis; recurrence or progression (HR=4.21, 95% CI, 1.15-15.37, p=0.02) and extent of surgery (HR=2.17, 95% CI, 1.13-4.15, p=0.02) were the poor prognostic factors for OS. The mean OS were 61, 87, and 113 months for the patients with PR+BX, STR and GTR, respectively (Figure 1a). Similarly, the mean OS was 121 months for the patients with no recurrence or progression vs 85 months for the patients with recurrence or progression (Figure 1a-b).

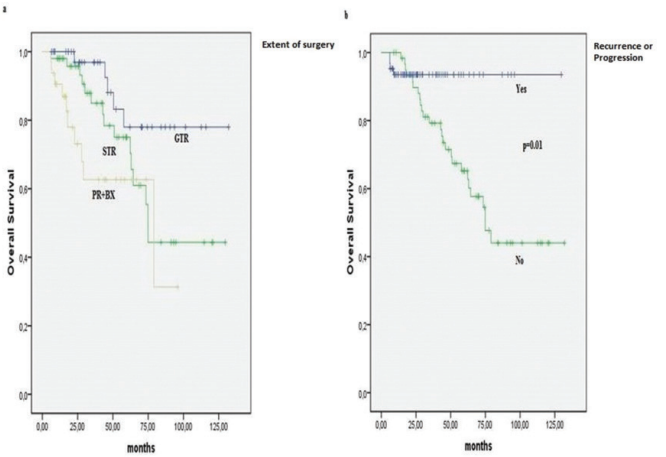

Figure 1. (a) Overall survival according to extent of surgery **(b)** Overall survival according to recurrence or progression.

The average PFS for the all patients was 5.7 years. 2-, 5- and 10-year PFS ratios were 91%, 58% and 10%, respectively. Kaplan Meier analysis revealed that seizure (p=0.04) was the only prognostic factor that affect PFS. Table 4 shows the results of univariate analysis for PFS. According to multivariate analysis; to have high pignatti risk score (HR=1.73, 95% CI, 1.00- 3.03, p=0.05) and not to have seizure (HR=2.02, 95% CI, 1.17- 3.49, p=0.01) were the poor prognostic factors for PFS. The mean PFS was 75 months for the patients with high pignatti risk score vs 61 months for the patients with low pignatti risk score (Fig 2a). Also, the mean PFS was 77 months for the patients with seizure vs 61 months for the patients with not seizure (Figure 2 a-b).

Table 4. Univariate cox proportional hazard regression analysis related with PFS

Variables	HR	95% CI	P- value
Seizures at diagnosis			
Yes	1		
No	1.76	1.04-2.96	0.03*
Pignatti risk scale			
Low risk	1		
High risk	1.54	0.95-2.56	0.09
Extent of Surgery			
GTR	1		0.4
STR	1.42	0.80-2.52	0.2
PR+BX	1.38	0.61-3.08	0.4

Abbreviations: BX= biopsy, GTR= gross total resection, HR=hazard ratio, PFS=progression free survival, PR= partial resection.
***Statistically significant**

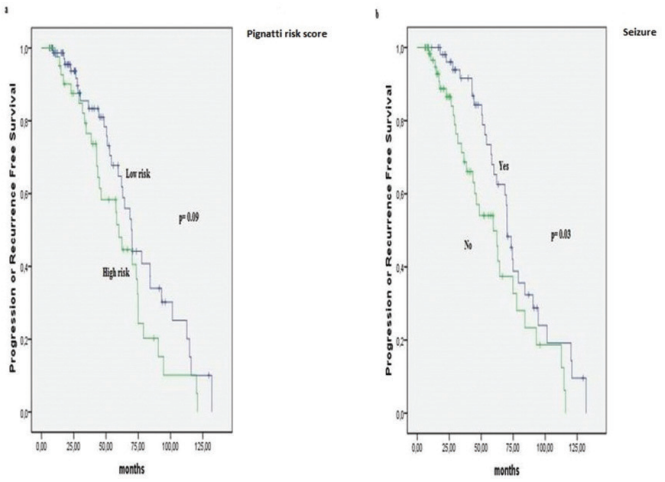

Figure 2. (a) Progression free survival according to Pignatti risk score **(b)** Progression free survival according to seizure.

DISCUSSION

LGGs are primer brain tumors which are slow growing and heterogeneous clinical behaviour (3). When compared to high grade glial tumors, patients with LGGs have longer survival (6,7) but 50-75% of cases ultimately die because of either the malignant transformation of tumor or its progression (11). To know prognostic factors is very substantial for the decision of treatment modality and for the prediction of survival outcomes. Our study gives useful information about the survival outcomes of patients with Grade II glioma and predictive role of clinical prognostic factors on survival in despite of the potential unpredictable disadvadvantages of any retrospective research. In univariate analysis, pignatti risk score, seizure, extent of resection, GTR, biopsy or partial resection, residue, recurrence or progression, malignant transformation, new pathological subtype after second surgery were the significant prognostic factors for OS in the current study. Among these factors, the extent of surgical resection and recurrence or progression were the other independent prognostic factors in this research. Despite executed numerous studies (1-11), there are some questions about the extent of resection, thus determination of prognostic factors is important for selecting appropriate treatment approaches. In general, a more aggressive initial surgery of LGGs is estimated remarkable improvement in PFS and OS when compared with simple debulking but no randomised controlled researchs have been done yet (4,6,9,12). Maximum safe resection is also associated with a delay in malign transformation (4,9) but complete removal of extended tumors is usually not feasible as these tumors frequently diffuse into eloquent regions (13,14). In current study, 34% of patients had GTR, 40% of patients had STR and 26% of patients had BX or PR at the time of diagnosis and the extent of surgery was found one of the independent prognostic factor for OS. The hazard ratio for BX+PR was found 2.17, it means that the mortality rate of patients with BX+PR was 2.17 times higher than patients who had GTR or STR. According to results of EFNS-EANO (European Federation of Neurological Societies-European Association for Neuro-Oncology) Task Force study, complete or near complete resection may improve OS and PFS while minimising the risk of degeneration into high grade glioma (12). In current study, malignant transformation was pathologically proven in 20 patients and malignant transformation was much lower in patients with GTR than patients with not-GTR, the results were not statistically significant but reach nearly significant (p=0.06). Similarly to our results, Smith et al. revealed in their study included in 216 cases with LGGs that extent of surgery was significantly related with improved survival outcomes. In their study, the 5-year survival rate was 97% in cases with minumum 90% resection while this rate was 76% in cases who had less than 90% resection (15). In current study, the 5- year OS in patients with minumum 90% resection was 78% whereas this rate was 67% in patients who had less than 90% resection. Sanai et al. showed in their study that a more aggressive removal was associated with a longer survival time from 61 months to 90 months (16). Similarly to this results, in the current study, the mean OS was 61, 87 and 113 months for the patients with BX/, STR, and GTR, respectively.

According to present study, recurrence or progression was the other independent prognostic factor that affect OS. The occurrence of local recurrence or progression after initial surgery was associated with increased mortality rates. To our knowledge, the present study could be the first in literature which demonstrated the association between local recurrence or progression of Grade II glioma and OS. This association most particularly has been showed in researchs related with breast cancer, soft tissue sarcoma and rectal cancer (17-19). Local recurrence or progression of tumor after resection can be included as a potential risk factor predicting decreased OS for Grade II glioma. There is a need for prospective studies for the clarification of this issue.

The other remarkable issue in current study was the PFS of Grade II glioma. According to univariate analysis, seizure was the only significant prognostic factor for PFS. But according to mutivariate analysis Pignatti risk score and seizure were the independent prognostic factors for PFS. Pignatti risk score is one of the prognostic index which was constructed utilizing the prospectively collected data on European Organization for Research on Treatment of Cancer (EORTC) trial 22844 and then validated with patients from EORTC trial 22845 (20). According to these studies, tumor diameter ≥6 cm, age ≥40, astrocytoma histology, tumor crossing midline, and presence of neurologic deficit before surgery were defined as adverse prognostic factors. High-risk patients identified as the presence of three or more of these factors and low-risk patients identified as the presence of two or less of these prognostic factors. To have high Pignatti risk score was one of the independent prognostic factor for PFS although none of these five EORTC prognostic factors were not independent prognostic factors in current analyses. The progression or recurrence rate of patients with high Pignatti risk score was 1.73 times that of patients with

low Pignatti risk score in this study. Similar to present study, Daniel et al. showed that patients with low-risk had significantly improved median PFS than the patients with high risk (7). The median PFS was 6.2 years for low-risk group whereas 1.9 years for high risk group in their study. The other significant prognostic factor for PFS was seizure in the current study. Patients with seizure had improved PFS compared with no-seizure. The mean PFS was 77 months for the patients with seizure vs 61 months for the patients with not seizure The presence of seizure might be an early sign for recurrence or progression of disease. Similarly, Rudoler et al. showed that seizure correlated with improved relapse- free survival (64% vs 21%)(21).

The timing of RT of LGGs remains a controversial topic. There were two large study investigated the timing of radiotherapy and radiation dose in LGGs (22,23). In EORTC 22845 study, 314 patients with LGG randomised 2 groups. The first group received RT postoperatively and the second group received RT at progression. There was not any difference between the groups in terms of OS whereas the patients which received RT postoperatively had a significantly better PFS (23). In our study, OS and PFS were similar in an early-RT group and a delated-RT group although to evaluate the affect of timing of RT on survival is very difficult in retrospective studies. Similarly, Van den et al. reported in their research that OS was similar in an irradiation group and a control group. Hanzely et al. reported in their study that early-RT didn't effect the PFS in patients who had totally resected tumor (24).

To assess the OS and PFS was the other aim of this study. According to our results, the mean OS and PFS were 7.8 and 5.7 years, respectively. 2-, 5- and 10- year OS and PFS rates were 91%, 73% and 55% and 91%, 58% and 10%, respectively. Claus et al. revealed in their study that the cumulative 5- and 10- year survival rates were 59.9% and 42.6%, respectively (25). Jung et al. showed that the 5-year OS and PFS were 81% and 57%, respectively (6). The 5-year OS was 91% and the 5-year PFS was 68% in Majchrzak et al.'s prospective study (26). These differences can be associated with heterogeneous clinical behavior of LGGs and retrospective design of the studies.

World Health Organization (WHO) classification of central nervous system tumors updated in 2016, which consist of phenotypic and genotypic parameters. The lack of re-classification of tumors according to new version of WHO staging and the retrospective nature of the study were the limitations of study.

CONCLUSION

LGGs have a heterogeneous clinical behavior and to know the prognostic factors for the decision of treatment is important. According to present study, the extent of resection and recurrence or progression were the independent prognostic factors for OS and Pignatti risk score and the seizure were the independent prognostic factors for PFS.

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