Turkish Neurosurgery 2008, Vol: 18, No: 4, 336-344

Efficacy of Prognostic Factors on Survival in Patients with Low Grade Glioma

Düşük Evreli Gliomlarda Prognostik Faktörlerin Sağ Kalıma Etkisi

Ramazan DURMAZ[1]
Murat VURAL[2]
Ersin IŞILDI[3]
Erhan COŞAN[4]
Emre ÖZKARA[5]
Cengiz BAL[6]
Evrim ÇİFTÇİ[7]
Ali ARSLANTAŞ[8]
Metin And ATASOY[9]

[1,2,4,5,8,9] Eskişehir Osmangazi University School of Medicine, Deparment of Neurosurgery, Eskisehir, Turkey
[3] Ministry of Health, Ağrı Government Hospital, Neurosurgery Clinic, Ağrı, Turkey
[6] Eskişehir Osmangazi University School of Medicine, Department of Biostatistics, Eskisehir, Turkey
[7] Eskişehir Osmangazi University School of Medicine, Department of Pathology, Eskisehir, Turkey

Received : 20.04.2008
Accepted : 04.06.2008

Correspondence address:
Ramazan DURMAZ
Associated professor of Neurosurgery
Deparment of Neurosurgery,
Eskişehir Osmangazi University
School of Medicine,
26480 Eskişehir, Turkey
Phone : +90-222-239 29 79
Fax : +90-222-239 22 20
E-mail : rdurmaz@ogu.edu.tr

ABSTRACT

AIM: In this report, we aim to determine the prognostic factors influencing the length of survival in patients with low-grade gliomas.

MATERIAL and METHODS: In a retrospective evaluation, we have reviewed fifty-three patients who had been operated between the years of 1980 and 2006. The diagnoses of the patients were histopathologically verified as low-grade glioma(LGG). The medical records of the patients were reviewed for age, gender, tumor locations, extent of resection, and presence of seizure, the neurological status as defined by the Karnofsky Performance Scale (KPS) and radiotherapy treatment after surgery as possible prognostic factors.

RESULTS: Median cumulative survival time for all the patients with LGG was 141+/-14.83 months. Median survival time was 216+/-78.52 months for astrocytoma Grade I; 115+/-8.22 months for astrocytoma Grade II, and 242+/-76.36 months for oligodendroglioma. Young age, histology subtype (oligodendroglioma) and preoperative KPS were determined to have positive influence on survival according to Log Rank Test. In contrast, age, histology type and the extent of resection remained independent prognostic factors upon survival when Cox Regression Backward Stepwise (Wald) method was performed.

CONCLUSION: It can be concluded that surgery seems to be an appropriate first step option in the treatment of LGG.

KEY WORDS: Low grade glioma, Prognostic factors, Survival

ÖZ

AMAÇ: Bu çalışmada, amacımız, düşük dereceli gliomu (DDG) olan ve opere edilen hastalarda sağ kalım üzerine etki eden prognostik faktörleri tespit etmektir.

YÖNTEM ve GEREÇ: Bu çalışmada 1980-2006 yılları arasında ameliyat edilen elli üç hasta retrospektif olarak incelenmiştir. Hastaların yaş, cinsiyet, tümör lokalizasyonu, tümörün rezeksion genişliği, nöbet varlığı, Karnofsky Performans Skalası (KPS) ve cerrahiden sonra radyoterapi tedavisi gibi faktörlerin sağ kalım üzerine olan etkisi araştırılmıştır.

BULGULAR: Tüm DDG'lu hastalarda ortalama yaşam süresi 141+/-14.83 ay olarak tespit edilmiştir. Tümör alt tiplerinde bu yaşam süresi; evre I astriositoma için 216+/-78.52 ay, evre I I astriositoma için 115+/-8.22 ay, oligodentrioglioma için 242+/-76.36 aydır. Log Rank Testine göre genç yaş, tümörün histolojik alt tipi (Oligodendrogliom) ve preoperatif KPS sağ kalım üzerinde olumlu etkide bulunmuştur. Buna karşın, "Cox regression Backward Stepwise (Wald) method uygulandığında, genç yaş, tümörün histolojik alt tipi ve rezeksiyon genişliği sağ kalım üzerinde etkili bağımsız prognostik faktörler olarak belirlenmiştir.

SONUÇ: Bu sonuç, DDG'ların tedavisinde ilk adım tedavi seçeneği olarak cerrahi yaklaşım önerebilir.

ANAHTAR SÖZCÜKLER: Düşük evreli gliom, Astrositom, Oligodentrogliom, Prognostik faktörler, Sağ kalım süresi

INTRODUCTION

Glioma is the most common type of primary intracerebral neoplasm. The most frequent gliomas are astrocytomas. Diffusely infiltrating astrocytomas account for more than 60% of all primary brain tumors (17). Several variables affect prognosis and therapy options of patients with glioma; favorable clinical parameters are young age, good performance status and gross-total resection. In addition, histological type and tumor grade are the main histopathological parameters of survival (7,11,16,17,19). Low-grade gliomas are classified into astrocytomas, oligodendrogliomas, oligoastrocytomas and ependymomas based on the presumed cell of origin. They have a tendency to progress to higher-grade gliomas. High-grade gliomas can develop from previous verified low-grade tumors or manifest de novo. Low-grade diffuse astrocytomas (WHO grade II) are well-differentiated, slow growing tumors, which develop principally in young adults with a relatively long survival. These tumors may display an intrinsic tendency to progress to a more malignant phenotype, like anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV). Such malignant transformation is responsible for the majority of the patient mortality (24,38,39). Certain clinical parameters such as age, tumor site, performance status, duration of symptoms, and seizure as a presenting symptom have been reported as significant prognostic factors (12,23,39).

This retrospective analysis was undertaken to evaluate the efficacy of the prognostic factors such as tumor histopathology, the extent of resection, age, gender, preoperative Karnofsky Performance Scale, the presence of seizure and radiotherapy on the length of survival in 53 patients with low grade glioma treated in our clinic between the years of 1980 and 2006.

MATERIALS and METHODS

The clinical records of sixty-three patients who were operated for intracranial low-grade glioma (LGG) at the Neurosurgery Department of Eskisehir Osmangazi University Hospital between the years of 1980 and 2006 were retrospectively evaluated. Nine of these 63 patients were excluded from the analysis due to lack of follow-up data and one patient with oligoastrocytoma was also omitted from the study. The records of the remaining 53 were retrospectively evaluated. The diagnoses of the patients were histopathologically verified as low-grade glioma; of these, 13 were grade I astrocytoma (24.5%); 26 grade II astrocytoma (49.1%), 14 oligodendroglioma (26.4%) and 1 oligoastrocytoma should be omitted. The medical reports of the patients were reviewed for age, gender, tumor locations, the extent of resection, presence of seizure, the neurological status as defined by the Karnofsky Performance Scale (KPS) at the time of admission and radiotherapy following operation in order to determine their prognostic effects on the length of survival.

The patients ranged in age from 4 to 76 years and the mean age was 36.68+/-16.39 years. Of the 53 patients, 17 (32.1%) were female and 36 (67.9%) were male.

Computerized tomography (CT) scan has been used regularly for diagnosis; with the addition of magnetic resonance imaging (MRI) for more recent tumors (28 patients had CT scans; 16, MRI and 8, both CT and MRI). After initial diagnosis, all the patients received follow-up examinations and imaging studies according to their clinical needs.

The extent of tumor removal was based on operative record and postoperative CT and/or MRI findings. Gross total removal was defined if the mass was removed totally in the operation and no residual tumor enhancement was seen on CT or MRI image. However, a subtotal resection was defined if tumor mass was removed by 50% to 99%. In order to protect the patients from elevated intracranial hypertension that may be associated with such operative complications as edema or hematoma, replacement of the bone flap was delayed until the patients became stable.

Preoperative functional status was evaluated according to KPS scale.

The majority of the patients (66%) received whole brain radiotherapy postoperatively.

The date of death or last examination of the patient was used to establish endpoints. The entire study population was evaluated for histology of recurrence/progression and survival, starting from the time of diagnosis.

The survival data were analyzed using the Kaplan-Meier method (13). Differences in survival between the groups were tested for statistical significance by the log–rank test (26). After analyzing with a multivariate test (Multiple Cox Regression), Cox Regression Backward Stepwise (Wald) method

was performed to identify independent prognostic factors (6). Data were expressed as median +/- standard error (SEM). P-value <0.05 was considered statistically significant.

RESULTS

Postoperative mortality and morbidity:

Of 53 patients with surgically-proven LGG, 3 patients died within the postoperative 4 weeks (5.6%) and 5 patients developed morbidity (9.4%). Of these 5 patients, postoperatively, 2 had mild hemiparesis, one patient developed hemiplegia, and 2 patients developed hematoma in the tumor bed and were re-operated for the evacuation of the hematoma. There were no cases of infection secondary to operation and no cerebrospinal fluid (CSF) leak.

Survival:

Median cumulative survival time for all the patients with LGG was 141+/-14.83 months (Figure 1). The efficacies of prognostic factors upon survival are summarized in Table I and Table II. The overall five-year survival was 57.4%, and ten-year survival was 31.5%.

Tumor type:

Of the 54 patients with surgically-proven low-grade gliomas, 17 tumors (32.1%) occurred in the frontal lobe (grade I astrocytoma, 3; grade II astrocytoma, 9; oligodendroglioma, 5; oligoastrocytoma, 1), 9 (17%) in posterior fossa (grade I, 6; grade II, 3), and the remaining 27 tumors (50.9%) were localized in temporoparietal region. Median survival time was 216+/-78.52 months for astrocytoma Grade I; 115+/-8.22 months for astrocytoma Grade II, and 242+/-76.36 months for oligodendroglioma (Figure 2). No significant differences were determined between astrocytoma Gr I and astrocytoma Gr II or between astrocytoma Gr I and oligodendroglioma. However, a significant difference was found between astrocytoma Gr II and oligodendroglioma according to Log Rank test and Multiple Cox Regression Analysis ($p<0.05$) (Figure 3 and Table I). In addition, according to Cox Regression Backward Stepwise (Wald) method, tumor histopathology was also a significant independent prognostic factor on survival ($p<0.05$, Table II).

Extent of resection:

Gross-total resection was succeeded in 24 patients (45.3%), whereas a subtotal resection was achieved in 29 patients (54.7%). The patients who had a total resection survived longer than the patients who had subtotal removal (141+/-16.62 months versus 107+/-75.76). Although the difference between these groups was not statistically significant according to Log Rank test and also multiple Cox regression analyses ($p>0.05$, Table I), the extent of resection was a significant independent prognostic factor when the Cox Regression Backward Stepwise (Wald) method was performed ($p<0.05$, Table II).

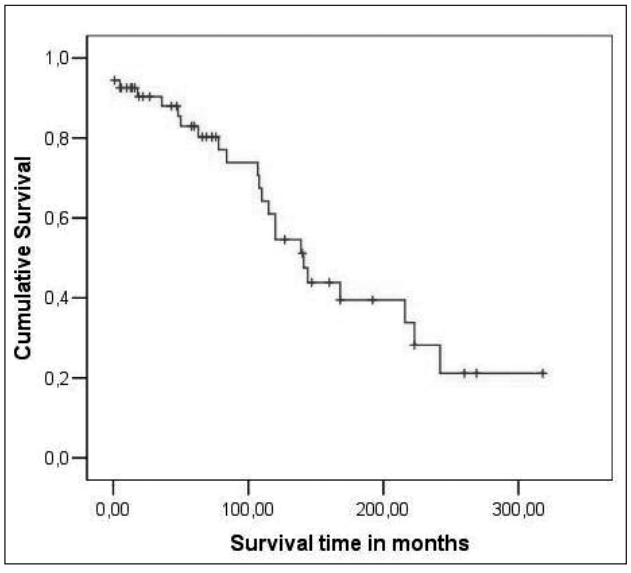

Figure 1: *Kaplan-Meier cumulative survival curve for 53 patients with low grade glioma.*

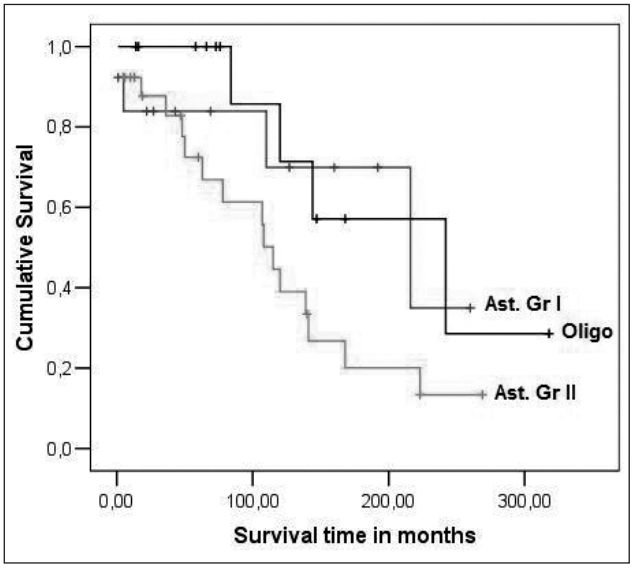

Figure 2: *Overall survival curve according to tumors histopatholgy. (Grade I astrocytoma, Grade II astrocytoma and oligodendroglioma). Ast: Astrocytoma, Gr: Grade, Oligo: Oligodendroglioma.*

Table I. Efficacies of prognostic factors on survival time according to Log Rank test and Multiple Cox Regression analysis (Multivariate test).

Factors	No of patients (%)	Median Survival time (months)	Log Rank Test-*P* value	Multiple Cox Regression Analysis – *P* value
Tumor type	13 (24.5)	216		
Astrocytoma Gr I	26 (49.1)	115		
Astrocytoma Gr II	14 (26.4)	242		
Oligodendroglioma				
Ast. Gr I vs Ast. Gr II			0.15	0.13
Ast. Gr I vs Oligo			0.78	0.38
Ast. Gr II vs Oligo			0.042*	0.045*
Tumors localizations				
Frontal	17 (32.1)	168	0.65	0.395
Temporoparietal	27 (50.9)	120		0.195
Posterior fossa	9 (17)	223		0.094
Extend of resection Total	24 (45.3)	141	0.36	0.09
Subtotal	30 (54.7)	107		
Gender				
Male	36 (67.9)	120	0.198	0.54
Female	17 (32.1)	216		
Age				
≤40	29 (54.7)	168	0.026*	0.006*
>40	24 (45.3)	108		
Karnofsky score				
80-100	34 (64.1)	144	0.029*	0.024*
≤70	19 (35.9)	107		
Radiotherapy				
Radiotherapy (+)	35 (66)	139	0.39	0.87
Radiotherapy (-)	18 (34)	216		
Seizure				
Seizure (+)	31 (58.4)	120	0.96	0.69
Seizure (-)	22 (41.6)	168		

* denotes *p*-values less than <0.05. **Ast**.: Astrocytoma, **Gr**: Grade, **vs**: versus, **Oligo**: Oligodendroglioma.

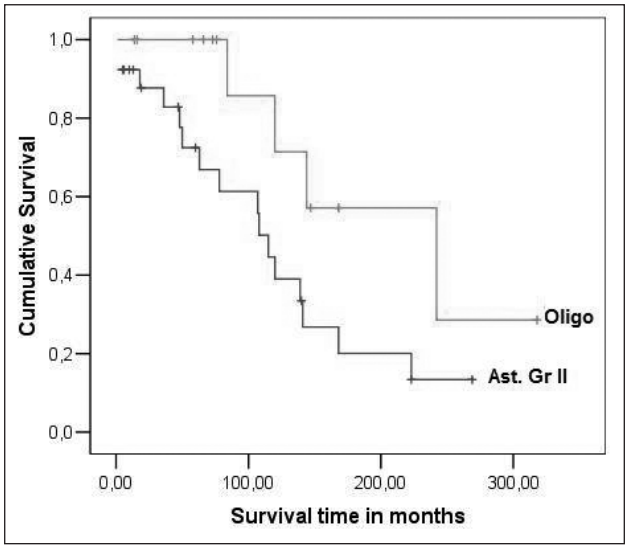

Figure 3: *Kaplan–Meier survival curves demonstrating Grade II astrocytoma versus oligodendroglioma. Ast.: Astrocytoma,Gr: Grade, Oligo: Oligodendroglioma. There was a significant difference between the survival times of patients with astrocytoma Gr II and Oligodendroglioma.*

Table II. Independent prognostic factors are shown analyzed by Cox Regression Backward Stepwise (Wald) method.

	B	P value	O.R.	95.0 % CI for OR	
Age	.047	.002*	1.049	1.018	1.080
Tumor histology type	-	.036*	-	-	-
Ast. GI vs Oligo.	-.228	.776	.796	.165	3.827
Ast. GII vs Oligo.	1.125	.064†	3.081	.937	10.126
Extent of resection	1.032	.031*	2.808	1.101	7.159

(**B:** Beta, **Sig:** Significance, **O.R:** Odds ratio, **CI:** Confidance interval). **Ast.**: Astrocytoma, **Gr:** Grade, **vs:** Versus,
Oligo: Oligodendroglioma.* denotes *p*-values less than <0.05. † denotes borderline significance.

Age and gender:

Twenty nine patients were under the age of 40, while 24 were over 40 years of age. The median survival time for the patients who were under the age of 40 was significantly higher (168+/-20.42 months) than that of the patients over the age of 40 (108+/-32.47 months) according to Log Rank test, Multiple Cox Regression and Cox Regression Backward Stepwise (Wald) analyses (p<0,05, Table I, Table II). Young age at the time of diagnosis showed a significant influence upon survival. Gender was not a prognostic factor correlating with long survival.

Preoperative Karnofsky score:

Thirty-four patients (64.1%) scored 80-100, while 19 (35.9%) scored 70 or less. Karnofsky performance status (KPS) seemed to be an important factor on the survival time according Log Rank test and multiple Cox regression analysis (p>0.05). On the other hand, KPS was eliminated in the Cox regression Backward Stepwise (Wald) method. The median survival time for the patients whose KPS scores were over 80 was significantly higher (144+/-37.75 months) than that of the patients whose scores were below 80 (107+/-38.54 months) (p<0.05). The Patients with KPS scores of 80 or higher survived longer than the patients with KPS scores below 80.

Radiotherapy:

Thirty-five patients (66.0%) received whole brain radiotherapy at a dose of 4500-6000 cGy, over a period of six weeks. The majority of these patients were in a good postoperative neurological and mental condition. In the present study, the influence of radiotherapy on survival time was not statistically significant. Median survival time for patients receiving radiotherapy was 139+/-18.71 months, while it was 216+/-70.87 months in the patients receiving no radiotherapy. The survival time of the groups that received radiotherapy and no-radiotherapy did not significantly differ based on the results of Log Rank test and Multiple Cox Regression analysis (p>0,05).

The presence of seizure:

The majority of the patients (31 patients, 58.4%) had seizures as the presenting symptom. The remaining 22 patients (41.6%) had variable symptoms like headache, ataxia, difficulty in walking, nausea, vomiting, blurred vision, changes in mental stage and hemiparesia/hemiplegia. The patients with seizure presented shorter survival time than the patients who had no seizure (120+/-6.7 versus 168+/-20.94 months respectively). However, no significant differences were detected for the presence of seizure between the two groups according to the results of Log Rank test and Multiple Cox Regression analysis (p>0,05).

Reoperation:

Forty-three patients (81.1%) did not develop recurrence or show progression. Tumor recurrence/progression was documented in 11 patients (20.7%), of whom ten patients were operated twice and only one patient was operated three times. Tumor recurrence was seen in 6 patients. Recurrences occurred at the site of the initial tumor in all the patients. Malignant transformation was seen in 5 patients (9.4%). Three patients with grade II astrocytoma developed GBM and anaplastic astrocytoma, while one patient with oligodendroglioma developed malignant oligodendroglioma. In addition, one patient with astrocytoma Gr II developed GBM in a different region from that of the original site due to low dose of adjuvant radiotherapy. Among the initial 6 tumor recurrences, all the recurrences remained low-grade tumors as confirmed histopathologically. Second recurrence was documented in only one patient at a median of 4 years after initial surgery.

DISCUSSION

Low-grade glial tumors constitute approximately 40% of all glial neoplasms, and occur in patients with a median age of 40 years (29). Management of these tumors is still controversial because of lack of evidence to prove that aggressive treatment with either surgery or radiotherapy improves overall survival (1,35). In our study, the results of such an aggressive treatment modality involving surgery followed by radiotherapy were evaluated to determine the prognostic factors associated with tumor histopathology, the degree of tumor removal, age, preoperative KPS and the presence of seizure as an initial symptom on survival.

Overall survival:

The median survival time for all the patients with LGG after surgical intervention was 141 months in our study. In addition, the overall 5-year survival rate was 57.4%, while for 10-year survival, it was 31.5%. Leibel et al found a 46% 5-year survival rate in adult patients after subtotal resection with

radiotherapy and 19% for those without radiotherapy (21). Laws et al and Uihlein et al found no differences between the survival rates of radiated and non-radiated groups (20,36). In the report of Arienti et al, among 49 patients with low-grade astrocytoma, values of overall survival were 65.3% for 2-year survival, 46.9% for 5-years survival and 24.5% for 10-year survival. The median survival time was 51 months in their study (2). Because oligodendroglial tumors are more responsive to treatment than astrocytomas are, they are associated with a better prognosis (5). In our patients, median survival time was 216 months for astrocytoma Grade I; 115 months for astrocytoma Grade II and 242 months for oligodendroglioma. There were no significant differences for median survival time between astrocytoma Gr I and astrocytoma Gr II or between astrocytoma Gr I and oligodendroglioma. However, a significant difference was found between astrocytoma Gr II and oligodendroglioma according to the results of Log Rank test and multiple Cox Regression analysis and also the Cox Regression Backward Stepwise (Wald) method ($p<0,05$).

Extent of surgery:

Because of the infiltrative growth pattern of these tumors, complete surgical removal could be rarely achieved. There are inconsistent reports regarding the extent of surgery on survival. Some authors have reported that the extent of surgical removal did not correlate with the survival rates, while some reports have indicated that the extent of surgery is an important prognostic factor for survival (3,4,22,27,34). In the present study, the median survival time (141 months) in patients undergoing total tumor removal did not differ from that of patients with subtotal tumor resection (107 months) based on the results of Log Rank test, but it became significant when Backward Stepwise (Wald) Cox regression model was taken into consideration.

Recurrence and progression:

The cause of death in the majority of patients with LGG is progression to higher-grade tumors, which occurs more rapidly in older patients (27, 31, 38). In our study, 10 deaths occurred among 24 patients who underwent gross-total tumor resection. Four of those 10 patients were lost within the postoperative first 5 years. (Two of these deaths were at the very early postoperative period due to lung and cardiac complications). Two of the remaining 6 patients who survived more than five years were lost due to progression to higher grade. In 30 patients with subtotal tumor removal, there were 14 deaths. Six deaths were the result of recurrence; three deaths, due to progression to malignant gliomas, and one, due to early postoperative pulmonary and cardiac complications.

Location:

LGG are most common among men and white people and typically affect patients at a younger age than high-grade gliomas (fourth versus sixth decade of life) do. LGG most commonly involve the cerebral hemispheres, and are typically located in the frontal, parietal, or temporal lobes (5,8). In our study, the number of the tumors located in the frontal lobe was 17 (32.1%). The remaining 27 (50.9%) were in temporoparietal region, and 9 (17%) were in the posterior fossa. Although the patients with tumor in the posterior fossa had a longer survival time than those with tumors in other regions, the difference was not significant according to the results of Log Rank test and Multiple Cox Regression analysis ($p<0,05$).

Age and sex:

Some authors have observed the importance of age as a determinant of prognosis; the younger the patient, the better the prognosis (10). In our study, the overall survival rate of the patients with younger age (age under 40) was significantly better. The multivariate analysis also showed a clear correlation between increasing age and decreasing overall survival. Age-associated physiological and pathological changes and comorbidities may also predispose to adverse outcomes (5). Gender was not determined as a prognostic factor among our patients although there are various reports of its positive effect on the overall survival (20,25).

Radiotherapy:

Shaw and Wisoff made an evidence-based conclusion in the light of the results of 5 prospective clinical trials on intracranial low-grade glioma (LGG) including more than 1600 patients. In adults with LGG, there is no difference in survival whether RT is given postoperatively or delayed to the time of recurrence. However, about half of adults with LGG will develop tumor progression by 5 years despite surgery with or without postoperative RT. (9,14,15, 30,32,33). Thirty five of our patients received

radiotherapy while the remaining 18 did not receive radiotherapy. None of the patients received any additional therapies like chemotherapy, brachytherapy, or radiosurgery. Our study was unable to show any statistically significant differences in the survival time of the groups of the patients that received radiotherapy or did not receive radiotherapy.

Presenting symptoms:

Seizures as an initial symptom are well documented in literature and associated with longer survival due to earlier presentation and diagnosis (20,25,37). Pignatti et al found the presence of epilepsy associated with longer survival in univariate analysis, but noted that the presence of neurological deficits superseded its prognostic importance in multivariate analysis. They attributed this result to the negative association between the presence of seizures and the presence of other concomitant symptoms and suggested that once other symptoms were present, seizures were no longer of good prognostic significance (28). In our study, the presence of seizure was found to be associated with shorter survival. The location of the tumor influences the risk of seizure. Tumors located cortically are chiefly the main reason of seizures. According to our evaluation, the patients harboring cortical tumors were not operated. Instead, a 'wait and see' policy was adopted to prevent any possible morbidity that could be a consequence of operating these eloquent regions. In our opinion, because of this reason, our results do not support the positive influence of seizure on survival time.

Preoperative neurological status:

Karnofsky performance status seemed to be an important factor on the survival time in the present report. In our study, KPS had a significant influence on survival according to the results of Log Rank test and multiple Cox Regression analysis. On the other hand, it showed no positive effect on survival when it was evaluated by Cox regression Backward Stepwise (Wald) method. Arienti et al. found the positive influence of KPS statistically significant on survival among 49 low-grade astrocytoma patients (2). Kreth et al reported that age over 50 years, a tumor volume more than 20 mL, and/or Karnofsky score <80 were associated with decreased survival or progression-free survival in low-grade glioma patients undergoing interstitial 125I radiosurgery as primary treatment. Based on univariate analysis of their study, 5-year survival rate was 67%, and 10-year survival rate was 44% among 239 patients whose KPS score was over 90. In addition, 5-year survival rate was 43%, and 10-year survival rate was 26% in the group who scored below 90 (18).

There are various reports on the prognostic factors for LGG in the literature. Gross total surgical removal, lack of preoperative neurological deficit, long duration of symptoms prior to surgery, seizures as a presenting symptom and younger age have been declared as important factors to prolonged survival (4,10,20,22,38). In our study; according to the results of Log Rank test; the factors of gender, type of symptoms, tumor location, extent of resection, and receiving radiation therapy failed to reach significance for length of survival. In addition, young age, histologic type of the tumor (oligodendroglioma versus Gr II astrocytoma), and KPS were found to have statistically significant effects. Based on the results of Cox Regression Backward Stepwise (Wald) method; while young age, histological type of the tumor, and the degree of resection showed a positive prognostic influence on survival, transformation of the tumor to a higher grade showed a negative influence (Table II).

CONCLUSION

Although some reports show the extent of resection or radiotherapy as a factor that affects the outcome in low-grade gliomas, there is still no general consensus on optimal treatment of these tumors. Regarding our results, young age, the tumor type (astrocytoma Gr II vs oligodendroglioma) and preoperative Karnosfsky score between 80-100 are the only statistically significant factors according to the findings obtained through both Log Rank and multiple Cox regression tests. However, the extent of tumor removal was become a significant prognostic factors when all variable were taken into consideration. This may suggest that surgery may be an appropriate first step option in the treatment of LGG.

REFERENCES

1. Abeloos L, Brotchi J, De Witte O: Management of low-grade glioma: a retrospective study concerning 201 patients. Neurochirurgie 53: 277-283, 2007
2. Arienti VM, Botturi A, Boiardi A, Broggi G, Collice M, Fariselli L, Zanni D, Botturi M: Adult brain low-grade astrocytomas: survival after surgery and radiotherapy. Neurol Sci 22: 233-238, 2001

3. Bauman G, Lote K, Larson D, Stalpers L, Leighton C, Fisher B, Wara W, MacDonald D, Stitt L, Cairncross JG: Pretreatment factors predict overall survival for patients with low-grade glioma: A recursive partitioning analysis. Int J Radiat Oncol Biol Phys 45: 923–929, 1999
4. Berger M, Deliganis A, Dobbins J, Keles GE: The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer 74: 1784–1791, 1994
5. Cavaliere R, Lopes MB, Schiff D: Low-grade gliomas: an update on pathology and therapy. Lancet Neurol 4: 760-770, 2005
6. Cox DR: Regression models and life tables. J Roy Stat Soc 34: 187–220, 1972
7. Devaux BC, O'Fallon JR, Kelly PJ: A retrospective study of clinical parameters, therapy, and outcome. J Neurosurg 78: 767-775, 1993
8. Duffau H, Capelle L: Preferential brain locations of low-grade gliomas. Cancer 100: 2622–2626, 2004
9. Eyre HJ, Crowley JJ, Townsend JJ, Eltringham JR, Morantz RA, Schulman SF, Quagliana JM, al-Sarraf M: A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: A Southwest Oncology Group study. J Neurosurg 78: 909–914, 1993
10. Ganju V, Jenkins RB, O'Fallon JR, Scheithauer BW, Ransom DT, Katzmann JA, Kimmel DW: Prognostic factors in gliomas: A multivariate analysis of clinical, pathologic, flow cytometric, cytogenetic, and molecular markers. Cancer 74: 920–927, 1994
11. Gudinaviciene I, Pranys D, Juozaityte E: Impact of morphology and biology on the prognosis of patients with gliomas. Medicina (Kaunas) 40:112-120, 2004
12. Kandil A, Khafaga Y, ElHusseiny G, Allam A, Jamshed A, Schultz H: Low-grade astrocytoma a retrospective analysis of 102 patients. Acta Oncol 38: 1051-1056, 1999
13. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481, 1958
14. Karim AB, Afra D, Cornu P, Bleehan N, Schraub S, De Witte O, Darcel F, Stenning S, Pierart M, Van Glabbeke M: Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council Study BR04: An interim analysis. Int J Radiat Oncol Biol Phys 52: 316–324, 2002
15. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, Mascarenhas F, Horiot JC, Parvinen LM, van Reijn M, Jager JJ, Fabrini MG, van Alphen AM, Hamers HP, Gaspar L, Noordman E, Pierart M, van Glabbeke M: A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer Study (EORTC) Study 22844. Int. J Radiat Oncol Biol Phys 36: 549–556, 1996
16. Keles GE, Lamborn KR, Berger MS: Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 95: 735-745, 2001
17. Kleihues P, Burger PC, Collins VP, Newcomb EW, Ohgaki H, Cavenee WK: Pathology and Genetics of Tumours of the Central Nervous System. In: Kleihues P, Cavenee WK, editors. World Health Organization Classification of Tumours. Lyon: IARC Press, 2000: 6-69.
18. Kreth FW, Faist M, Grau S, Ostertag CB: Interstitial 125I radiosurgery of supratentorial de novo WHO Grade 2 astrocytoma and oligoastrocytoma in adults: long-term results and prognostic factors. Cancer 106: 1372-1381, 2006
19. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95: 190-198, 2001
20. Laws ER Jr, Taylor WF, Clifton MB, Okazaki H: Neurosurgical management of low-grade astrocytomas of the cerebral hemispheres. J Neurosurg 61: 665-673, 1984
21. Leibel SA, Sheline GE, Wara WM, Boldrey EB, Nielsen SL: The role of radiation therapy in the treatment of astrocytomas. Cancer 35: 1551-1557, 1975
22. Leighton C, Fisher B, Bauman G, Depiero S, Stitt L, MacDonald D, Cairncross G: Supratentorial lowgrade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol 15: 1294–1301, 1997
23. Lote K, Egeland T, Hager B, Stenwig B, Skullerud K, Berg-Johnsen J, Storm-Mathisen I, Hirschberg H: Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. J Clin Oncol 15: 3129–3140, 1997
24. McCormack BM, Miller DC, Budzilovich GN, Voorhees G, Ransohoff J: Treatment and survival of low-grade astrocytoma in adults – 1977–1988. Neurosurgery 31: 636–642, 1992
25. North CA, North RB, Epstein JA, Piantadosi S, Wharam MD: Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. Cancer 66: 6-14, 1990
26. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 35: 1–39, 1977
27. Piepmeier J, Christopher S, Spencer D, Byrne T, Kim J, Knisel JP, Lacy J, Tsukerman L, Makuch R: Variations in the natural history and survival of patients with supratentorial lowgrade astrocytomas. Neurosurgery 38: 872–878, 1996
28. Pignatti F, van den Bent M, Curran D, et al: European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group; European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20: 2076-2084, 2002
29. Rosenfeld MR: Should radiotherapy for low-grade glioma be given immediately after surgery or at the time of progression? Nat Clin Pract Neurol 2: 128-129, 2006
30. Sanford A, Kun L, Sposto R, Holmes E, Wisoff JH, Heier L, McGuire-Cullen P: Low-grade gliomas of childhood: Impact of surgical resection. A report from the Children's Oncology Group. J Neurosurg 96: 427–428, 2002
31. Shafqat S, Hedley-Whyte ET, Henson JW: Age-dependent rate of anaplastic transformation in low-grade astrocytoma. Neurology 52: 867–869, 1999
32. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, Nelson D, Earle J, Jones C, Cascino T, Nichols D, Ivnik R, Hellman R, Curran W, Abrams R: Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 20: 2267–2276, 2002

33. Shaw EG, Wisoff JH: Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro Oncol 5: 153-160, 2003

34. Soffietti R, Chio A, Giordana MT, Vasario E, Schiffer D: Prognostic factors in well-differentiated cerebral astrocytomas in the adult. Neurosurgery 24: 686–692, 1989

35. Szeifert GT, Prasad D, Kamyrio T, Steiner M, Steiner LE: The role of the Gamma Knife in the management of cerebral astrocytomas. Prog Neurol Surg 20:150-163, 2007

36. Uihlein A, Colby MY Jr, Layton DD, Parsons WR, Carter TL: Comparison of surgery and surgery plus irradiation in the treatment of supratentorial gliomas. Acta Radiol 5: 67-78, 1966

37. van Veelen ML, Avezaat CJ, Kros JM, van Putten W, Vecht C: Supratentorial low grade astrocytoma: Prognostic factors, dedifferentiation, and the issue of early versus late surgery. J Neurol Neurosurg Psych 64: 581-587, 1998

38. Walker DG, Kaye AH: Diagnosis and management of astrocytomas, oligodendrogliomas and mixed gliomas: a review. Austral Radiol 45: 472-482, 2001

39. Watanabe T, Katayama Y, Yoshino A, Komine C, Yokoyama T, Fukushima T: Treatment of low-grade diffuse astrocytomas by surgery and human fibroblast interferon without radiation therapy. J Neurooncol 61: 171-176, 2003