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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prognostic significance of clinical parameters in patients with cerebral low-grade glioma

Miloš Joković, Radovan Mijalčić, Vladimir Baščarević, Nemanja Jovanović
Clinical Center of Serbia, Clinic of Neurosurgery, Belgrade, Serbia

SUMMARY
Introduction/Objective Low-grade gliomas affect younger adults and carry a favorable prognosis. We aim to describe clinical patterns of low-grade gliomas as well as prognosis in different groups of patients. Our intention was to determine clinical parameters that may affect prognosis, and whether a greater extent of resection would increase the long-term progression-free or overall survival of patients with low-grade gliomas.
Methods We analyzed data obtained from the files of the patients with a diagnosis of the World Health Organization classification grade II gliomas. The relationships among categorical variables were analyzed using standard statistical tools and a 95% confidence interval.
Results We analyzed 118 patients with median age of 34 years. Over 57% were male and the primary site location was the cerebrum. All these patients were operated on and some of them received radiation and/or chemotherapy. Median overall survival was 9.6 years and better prognosis is associated with younger age, frontal and noneloquent zone location, seizures as the first symptom of the disease, and gross total resection of the tumor. Indications for early surgery are increased intracranial pressure, preoperative neurologic deficit, tumor size larger than 6 cm with contrast enhancement, and older age.
Conclusion Tumor location, 1p/19q co-deletion, and age were the main determinants of treatment received and overall survival, likely reflecting tumor biology differences. Any form of treatment was preferred over watchful waiting. This study found that a greater extent of resection could significantly increase the overall survival of patients with low-grade gliomas.
Keywords: low-grade glioma; surgery; prognosis; survival

INTRODUCTION

Low-grade gliomas (LGG) are in general relatively slow-growing primary brain tumors, but they have a very heterogenous clinical behavior. They are an extremely important problem for a number of reasons: estimation of the timing of surgery, intraoperative procedure (extent of surgical removal), value of intraoperative mapping, application of radiotherapy and chemotherapy, as well as treatment with recurrent tumor.

The best treatment policy for these tumors is still unclear. Some physicians advocate early and extensive surgery or early radiation therapy, whereas others tend to postpone treatment until functional deficits are present [1, 2]. Several studies have attempted to identify prognostic factors in LGG. However, except for age, the importance of other prognostic factors for survival in LGG remains a matter of debate. A number of patient and tumor characteristics, such as age at diagnosis, performance status, histology subtype, primary tumor classification, tumor site, presence of seizures at diagnosis, and extent of resection, have been proposed as prognostic factors for progression-free or overall survival. In this review, the current approaches to different LGGs presenting with different symptoms in different regions of the brain will be reviewed and the rationale for making decisions discussed.

Gliomas are classified as grades I to IV based on histology and clinical criteria [3]. Under the recent World Health Organization (WHO) classification of primary intracranial tumors, LGGs would encompass grade I and grade II neuro-epithelial tumors. The difference between these two groups is important since the grade I tumors are generally benign and can be cured by surgical excision [4]. Grade II tumors are generally incurable but have median survival times of more than five years [5]. Tumors with oligodendroglial components generally do better than astrocytomas, with prognosis being partially related to gene deletions on chromosome 1p and 19q [6]. Essentially, all grade II lesions eventually progress to high-grade glioma (grade III/IV or HGG). Grade IV tumors (glioblastoma multiforme or GBM) that arise from LGG are termed "secondary GBM" to differentiate them from "primary" or "de-novo" GBM [7]. Even with the best magnetic resonance imaging (MRI, Figure 5), differentiation between grade I and II tumors is very difficult, therefore establishing tissue diagnosis can be important [8].

Most patients initially receive surgical resection/biopsy at time of diagnosis and then radiation therapy (XRT) and/or the single chemotherapeutic agent temozolamide (TMZ) at some point. A surgical gross total resection appears associated with better survival for

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Correspondence to:
Miloš JOKOVIĆ
Clinical Center of Serbia
Dr Koste Todorovića 4
11000 Belgrade, Serbia
severovo@yahoo.com

patients able to undergo such a procedure [9, 10]. Some clinical studies suggest XRT prolongs time to recurrence but not overall survival and may be associated with reduction in the quality of life and cognition [10], while the impact of the primary single TMZ now used to treat LGG has shown benefit primarily in HGG but is not fully assessed in LGG [10, 11]. The goal of this review is to examine population-based survival rates for LGG within Serbia by standard patient demographics.

METHODS

Patients

We performed a retrospective review of 118 patients with LGG, 68 males and 50 females (mean age 34.20 ± 2.23 years). All of these patients had been operated on one or more times over a 10-year period at the Clinic of Neurosurgery, Clinical Center of Serbia, Belgrade. The youngest patient was six years old and the oldest one was 64 years old. Written consents from each subject were obtained before screening according to the Declaration of Helsinki and the local ethics committee of the participating institution approved the study.

Both adult and pediatric patients were eligible for this study. The patients were divided into the following three age categories: (I) the patients younger than 35 years (52.5%), (II) those aged 35–45 years (25.4%), and finally (III) the patients over 45 years (22.1%). The total follow-up period for these subjects was 18 years. In order to describe the characteristics of these patients, we used descriptive statistics methods such as absolute numbers and proportions, but also distribution analysis of a single variable including its central tendency (mean, median, and mode) and dispersion (range, standard deviation).

Clinical evaluation

Clinical evaluation of the performed surgical treatment was done according to data obtained from patients' files and clinical examinations. We have also performed neurological examination both preoperatively and postoperatively in each patient. All patients undergoing biopsy, subtotal resection (STR), and gross total resection (GTR) were compared for the outcome measures of overall survival (OS), postoperative Karnofsky performance status (KPS), progression-free survival, mortality, and morbidity.

Follow-up computed tomography (CT) or magnetic resonance (MR) scans of the brain were done for each patient at regular intervals, paying particular attention to the localization and size of the tumor lesion, its characteristics after contrast administration, the extent of surgery, the appearance of relapse, etc.

Neurologic deficit was defined as absent [Medical Research Council (MRC) neurologic scale 1 or 2, Table 1] or present (MRC grade > 2).

Table 1. Medical Research Council Neurologic Scale

1	No neurologic deficit
2	Some neurologic deficit but function adequate for useful work
3	Neurologic deficit causing moderate functional impairment, e.g., able to move limbs only with difficulty, moderate dysphasia, moderate paresis, some visual disturbances (e.g., field defect)
4	Neurologic deficit causing major functional impairment, e.g., inability to use limbs, gross speech, or visual disturbances
5	No useful function – inability to make conscious responses

Treatment

Tumor characteristics were recorded based on the local interpretation of preoperative CT scans. Predominant site and side were coded as binary factors (fronto-temporal, temporo-parietal, left side, right side, central). Extent of surgical resection, which had been determined intraoperatively and judged by the neurosurgeon, was scored as gross total resection (GTR, 90% to 100% tumor excised), versus less extensive excision (subtotal resection, STR in which 50–89% of tumor volume was removed) or biopsy, partial or minimal tumor removal (less than 50% resection). Histology subtype was grouped as group I and group II according to the official WHO classification.

Prognosis

Survival or death and relapse were taken as outcome variables and monitored dynamically as a function of time.

Survival was calculated as the time from diagnosis until death but provided that the death was due to causes related to the treatment of LGG and not to other associated diseases. Kaplan–Meier estimate is one of the best options to be used to measure the fraction of subjects living for a certain amount of time after treatment. By means of Cox regression, we identified and validated important factors for survival that could be of value for staging patients into low- and high-risk groups. The log-rank test was used to assess whether the difference of survival times between two groups is statistically different or not, and to identify the factors that have an impact on the overall survival or tumor regrowth.

RESULTS

The study was conducted over a period of 10 years. The summarized patient characteristics, sex, age, and associated diseases are shown in Table 2. We report on one-year OS in 112 patients (94.91%), five-year OS in 80 patients (67.80%), 10-year OS in 58 patients (49.15%), and 15-year OS in 29 patients (24.57%). At the end of the 18-year follow-up period, 20 patients (16.94%) survived. Median OS of all patients was 9.6 years ($CI_{95\%}$ = 8–12 years).

At the end of the first year of follow-up, 94.4% patients were without tumor recurrence, after five years the percentage was 71.09%, and after 10 years it was 39.79%. The

Table 2. Sex, age, and associated diseases in our series

Parameters		Absolute frequency (n)	Relative frequency (%)
Sex	Male	68	57.6
	Female	50	42.4
Age	< 35 years	62	52.5
	35–45 years	30	25.4
	> 45 years	26	22.1
Associated diseases	Yes	25	21.2
	No	93	78.8

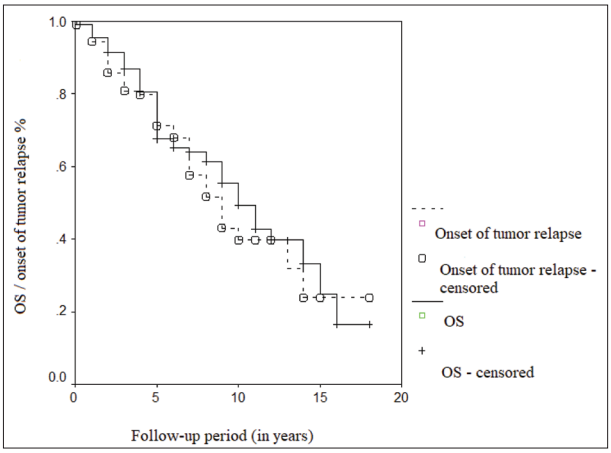

Figure 1. Kaplan–Meier estimate of overall survival (OS) and the onset of tumor relapse for a certain amount of time after initial treatment (follow-up period)

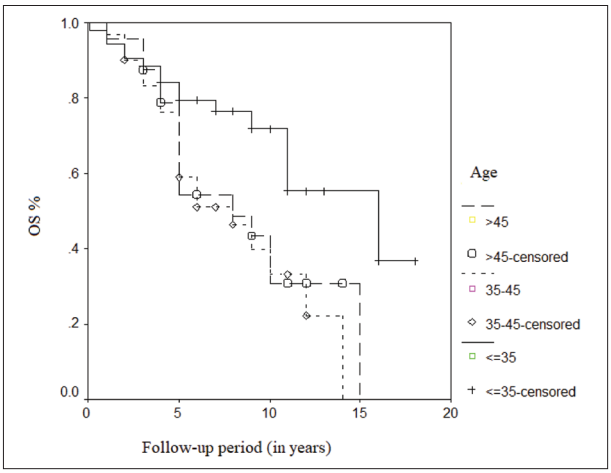

Figure 2. Kaplan–Meier estimate of overall survival (OS) for three different age groups

probability of non-recurrence at the end of the 15-year period was 23.87%. The median onset of relapse was nine years ($CI_{95\%}$ = 7–11 years), Figure 1.

The age of the subjects had a statistically significant effect on OS. Log-rank cross-group analysis showed that patients in the first group (those younger than 35 years) had statistically significantly longer survival than the other subjects in groups II or III. The results obtained indicate a significant predictive value of the patient's age factor and further prognosis of the disease, so that the group of the youngest patients stands out as the group with the best prognosis. The median OS in the first group of patients was 16 years ($CI_{95\%}$ = 7–25 years), Figure 2.

Clinical course, symptoms, and signs are summarized in Table 3. Using log-rank test, we noticed something statistically significant among patients in whom seizures were the principal symptom of the disease – they had longer OS compared to those patients in whom disease started gradually, without epi-manifestations. Patients with seizures also had a better prognosis regarding the occurrence probability of tumor regrowth – median probability of tumor relapse was 14 years ($CI_{95\%}$ = 5-23 years), compared to the group of patients without seizures and gradual onset of symptoms, in which median probability of tumor recurrence was seven years ($CI_{95\%}$ = 6–8 years).

Table 3. Clinical course, symptoms, and signs of disease

Parameters		Absolute frequency (n)	Relative frequency (%)
Onset of disease	Acute (seizures)	64	54.2
	Gradual	54	45.8
Clinical course of disease	Intermittent	79	68.1
	Progressive	37	31.9
Visual test findings	Normal	93	78.8
	Papilledema	17	14.4
	Other abnormalities	8	6.8
Symptoms	Due to increased ICP	20	16.9
	Seizures	47	39.8
	Motor deficits	11	9.3
	Cognitive deficits	11	9.3
	Other abnormalities	29	24.6
Signs	No signs	64	54.2
	Motor signs	30	25.4
	Other signs	14	11.9
	Combination of more signs	10	8.5
Karnofsky performance status	70–80	17	14.4
	90	32	27.1
	100	69	58.5
Neurologic deficit on admission	No	81	68.6
	Yes	37	31.4

ICP – intracranial pressure

We also identified several factors that have negative influence on OS: increased intracranial pressure (ICP), preoperative neurologic deficit, and KPS lower than 70. Median OS in patients with symptoms of increased ICP was not reached, indicating that increased ICP had a big impact on postoperative neurologic findings, final outcome, and overall OS, Figure 3. Median OS in patients with different KPS were as follows: five years for those with KPS 70–80, also five years for those with KPS 90, but 12 years for those with KPS 100, which is statistically significantly longer OS.

Neuroradiological interpretation of CT and MR findings is shown in Table 4. Patients with some foci of hyperdensity on preoperative CT had significantly shorter OS; their median OS was just two years ($CI_{95\%}$ = 0–4 years), Figures 4 and 5A–B. Tumor size also has a statistically significant effect on OS in LGG patients. Based on CT images, the tumors were divided into four groups: up to 2 cm in

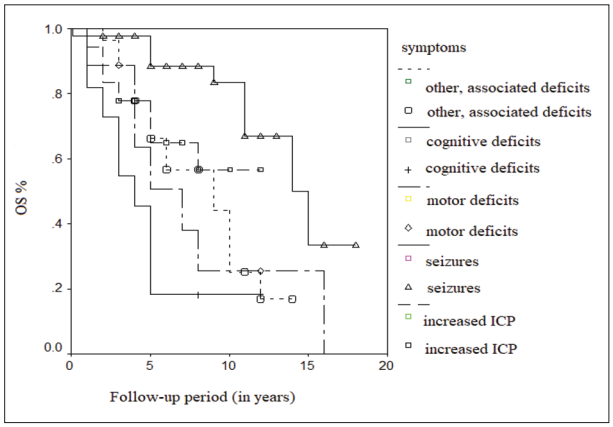

Figure 3. Kaplan–Meier estimate of overall survival (OS) for different symptoms

Table 4. Computed tomography (CT) and magnetic resonance (MR) findings on admission

Parameters		Absolute frequency (n)	Relative frequency (%)
Density on CT	Hypodensity	59	50
	Isodensity	47	39.8
	Hyperdensity	12	10.2
Clear tumor borders on CT	Yes	56	47.5
	No	62	52.5
Size of LGG on CT	Up to 2 cm	11	9.3
	2–4 cm	47	39.8
	4–6 cm	41	34.7
	> 6 cm	19	16.1
Contrast enhancement	No enhancement	78	66.1
	Homogenous	11	9.3
	Marginal enhancement	29	24.6
Intensity on MR	Hypointensity	8	19.5
	Isointensity	27	65.9
	Hyperintensity	6	14.6
Side	Left	47	39.8
	Right	66	55.9
	Bilateral	5	4.2
Cortical presentation	Yes	45	38.1
	No	73	61.9

LGG – low-grade gliomas

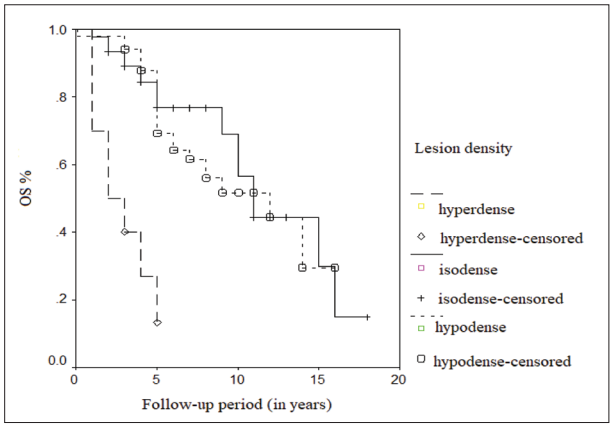

Figure 4. Kaplan–Meier estimate of overall survival (OS) for different density of lesion on preoperative computed tomography

Table 5. Surgical treatment and its complications

Parameters		Absolute frequency (n)	Relative frequency (%)
Principal reason for surgery	Progress of neurologic deficit	28	23.7
	Increased ICP	32	27.1
	Deterioration – seizures	28	23.7
	Others	30	24.4
Extent of tumor resection	Biopsy	5	4.2
	STR	68	57.7
	GTR	45	38.1
Tumor consistency	Firm	38	32.2
	Tough	45	38.1
	Soft	35	29.7
Margins towards brain	Infiltrative	73	61.9
	Clear margins	45	38.1
General complications	None	101	85.6
	Present	17	14.4
Surgical complications	None	73	61.9
	Requiring surgery	8	6.8
	Not requiring surgery	37	31.4

STR – subtotal resection; GTR – gross total resection

diameter, 2–4 cm in diameter, 4–6 cm in diameter, and over 6 cm in diameter. Using the log-rank test, we showed that subjects in the first and second group in whom the tumor was smaller than 4 cm had significantly longer OS than patients in the remaining two groups. However, no statistically significant difference in the likelihood of recurrence was observed among subjects with different tumor sizes. Therefore, we can conclude here that the size of the tumor has nothing to do with the likelihood of recurrence.

All analyzed patients were operated on while some were operated on more than once. In this regard, we considered indications for surgical treatment, extent of surgical resection of the tumor, characteristics of the tumor during surgery, and postoperative complications. These data are summarized in Table 5. Of all these variables, only the extent of tumor resection would be emphasized here. Those patients who underwent GTR had a statistically significantly longer OS than all other groups. The median survival in the GTR group was not even reached, the median survival in the STR group was eight years, while the patients in the biopsy group lived five years on average.

Looking at the literature data, it is possible to conclude that over time, sooner or later, almost all subtotal resected LGGs, and even those tumors in which GTR is achieved, relapse. The most common cause of death in LGG is disease progression, as nearly 50% of these tumors undergo malignant transformation. These data are summarized in Table 6.

DISCUSSION

After analyzing this data, we came to the conclusions that there are good reasons why these tumors are called just that – benign or slow-growing tumors. Although these are primary brain tumors, our results give a lot of optimism as the five-year OS in our series was 67.55% and the 10-year

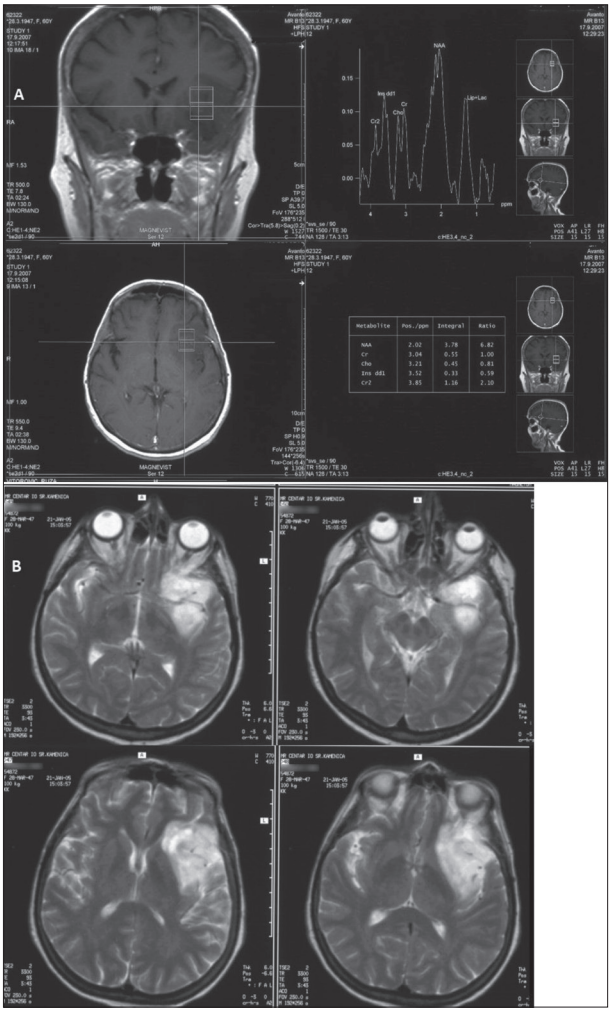

Figure 5. (A) Magnetic resonance (MR) of the brain (T1W sequence) with MR spectroscopy, of a patient from our series, showing intra-axial lesion in the left frontotemporal area; (B) MR of the brain (T2W sequence) of a patient from our series, showing intra-axial lesion in the left frontotemporal area

Table 6. Redo surgery and histopathological finding after redo-surgery

Parameters		Absolute frequency (n)	Relative frequency (%)
One single operation	Yes	73	61.9
	No	45	38.1
Second surgery	Yes	45	38.1
	No	73	61.9
Third surgery	Yes	9	7.6
	No	109	92.4
HP after redo-surgery	Same finding (LGG)	26	48.1
	Progression to astrocytoma gr. III	19	35.2
	Progression to GBM	9	16.7

HP – histopathological finding; LGG – low-grade gliomas; GBM – glioblastoma

OS was 49.22%, which is very similar to the data from other authors.

This study highlights the predictive factors for good prognosis in patients with LGG and emphasizes different variables that may have some influence on OS. Results of the present study also show the importance of regular follow-up after initial surgery, because we know that nearly half of these patients with LGG have a chance of developing a malignant alteration to anaplastic astrocytoma gr. III or GBM.

It should be acknowledged that some LGGs are not eligible for a meaningful extent of resection with an acceptable risk. We have demonstrated that early resection is associated with a clinically relevant survival benefit when compared with watchful waiting in LGGs. However, an overall treatment strategy in favor of watchful waiting cannot be recommended in patients eligible for resection. Finally, malignant transformation usually occurs with time but extensive surgical resection may delay this process [12].

High-risk features for mortality in patients with a diagnosis of LGGs include age older than 45 years, tumor diameter greater than 6 cm, midline crossing, presence of neurological deficit, and astrocytic histology [13]. Duffau and Taillandier [13] determined that patients defined as low-risk after gross total resection have a 50% risk of tumor progression at five years [14, 15]. However, due to the overlapping molecular prognostic factors, heterogeneity of these tumors, and challenges of completing clinical trials in a rarer and long-surviving cancer, treatment recommendations remain unestablished.

With the updated WHO classification of the nervous system in 2016, molecular profiling is required for proper LGG classification. Risk assessment is based on three groups: IDH mutant tumors with 1p/19q co-deletion (predominantly oligodendroglial), IDH mutant without 1p/19q co-deletion (predominantly astrocytic), and IDH wild-type tumors.

In surgical treatment, the technique of classical craniotomy was applied, after which, depending on the localization of the tumor, the most commonly used microsurgical extirpation of tumors of different extent was applied. In our conditions, stereotaxic biopsy was not performed due to technical impossibilities, but only open biopsy in small tumors that were localized in the motor cortex. One of the major dilemmas in the treatment of slow-growing astrocytomas is the degree of surgical resection. Many patient series show quite opposite results: in some we find that the degree of resection is proportional to the length of survival, while in other series they do not find this correlation at all. The strongest argument against GTR is the evidence that there are tumor cells at sites that are substantially distant from the tumor itself. Other arguments that support the inability of GTR are invasive and infiltrative tumor growth, multifocal lesion, and the possibility of an additional neurological deficit. The proponents of GTR, on the other hand, point out their arguments: cytoreduction that allows for reduction of ICP, improvement of neurological deficit, reduction or even elimination of epi-attacks; maximal tumor reduction enables the immune response to better effect to smaller number of cells; the potential error in HP tumor verification is reduced; by reducing the total number of tumor cells, the possibility of malignant transformation of tumors is also reduced. In our study, GTR was achieved in about 40% of cases, but more importantly, we observed that

there was a statistically significant interdependence between the degree of tumor resection and the length of survival.

The same conclusion was reached by Thon et al. [16] in their series of 86 patients as well as by Xia et al. [17], who published the results of 77 patients with LGG. By a retrospective analysis of 132 patients, Sanai et al. [18] found that the five-year survival in those who achieved GTR was about 80% and in those operated on in terms of STR, the overall five-year survival was 52%. However, in some other series, no correlation was found between the survival rate and the extent of surgical tumor resection. This again opens the dilemma of significance, usefulness, and harm of radical surgical resection.

Our results reflect the benefits of surgery with maximal safe resection. We have done surgery as the first treatment step in over 70% of our patients and this strategy has clearly shown usefulness, as surgical resection and its extent both have a significant survival benefit [18, 19].

CONCLUSION

A typical patient with LGG is a person in the second half of the fourth decade of life, with near-normal neurological findings and epilepsy as the first symptom of the disease. For definitive diagnosis, mandatory MR examination with paramagnetic contrast application is also required. Longer OS was statistically significant in patients in the first group (younger than 35 years), whose symptoms lasted longer in the preoperative period and in which the GTR procedure was performed. Factors that have a statistically significant negative effect on OS are increased ICP, pronounced preoperative neurological deficit, and KPS below 70. Sex, associated diseases, and, interestingly, postoperative XRT have no impact on OS.

Time interval between the first surgery and the second one because of the occurrence of tumor regrowth is statistically shorter in patients with progressive course of the disease and preoperative neurologic deficit, in those with signs and symptoms of increased ICP, if there is a contrast enhancement of tumor on preoperative CT, and if there is a larger volume of residual tumor following initial surgery. Malignant transformation of LGG into anaplastic astrocytoma or GBM occurred in 51% of patients who relapsed. This transformation is particularly rapid in elderly patients. Immediate perioperative mortality was 4.2%.

Conflict of interest: None declared.

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Прогностички значај клиничких параметара код болесника са нискоградусним глиомом мозга

Милош Јоковић, Радован Мијалчић, Владимир Башчаревић, Немања Јовановић

Клинички центар Србије, Клиника за неурохирургију, Београд, Србија

САЖЕТАК

Увод/Циљ Нискоградусни глиоми су тумори мозга који углавном погађају младе одрасле особе.

Циљ овог рада је одређивање клиничких параметара као могућих прогностичких фактора у лечењу нискоградусних супратенторијалних глиома. Наша намера је и уочавање корелације између обима хируршке интервенције и дужине преживљавања.

Методе Користили смо податке из историја болести болесника са нискоградусним глиомом по класификацији Светске здравствене организације, градуса 2. Однос између варијабли анализиран је уз помоћ стандардних статистичких тестова уз интервал поверења од 95%.

Резултати Анализирали смо 118 болесника, просечне старости 34 године. Око 57% њих су мушког пола уз предоминантну супратенторијалну локализацију тумора. Сви ови болесници су оперисани, али је код неких спроведен и постоперативни зрачни третман са хемотерапијом или без ње. Средње време преживљавања је било 9,6 година. Фактори боље прогнозе су нађени код млађих болесника, код локализације тумора фронтално и у неелоквентним зонама, у случају да су епи-напади први симптом болести и код оних болесника код којих је постигнута потпуна екстирпација тумора. Индикације за рану операцију биле су постојање повишеног интракранијалног притиска, преоперативног неуролошког дефицита и тумор већи од 6 *cm*.

Закључак Локализација тумора, 1*p*/19*q* коделеција и узраст болесника су биле главне детерминанте у лечењу и укупном преживљавању. Било која врста третмана боља је од праћења болесника у дужем периоду. Овај рад потврђује примарни значај хируршког лечења болесника са нискоградусним глиомима мозга – што је обимнија ресекција туморске масе, то је преживљавање дуже.

Кључне речи: нискоградусни глиоми; операција; прогноза; преживљавање