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Clinical outcome of surgically treated low-grade gliomas: A retrospective analysis of a single institute

Erhan Turkoglu*, Bora Gurer, Ahmet M. Sanli, Habibullah Dolgun, Levent Gurses, Nezih A. Oral, Teoman Donmez, Zeki Sekerci

Neurosurgery Clinic, Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, 06100 Ankara, Turkey

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ABSTRACT

Objective: Low grade gliomas (LGGs) are slow-growing primary brain tumors with heterogeneous clinical behaviors. The aim of our study is to review the treatment outcome of 63 patients with LGGs focusing on surgical outcome and the current therapeutic strategy.
Methods: We retrospectively enrolled 63 patients surgically treated for LGGs. The gross total resection (GTR) was performed in 35 patients (60.3%), subtotal resection (STR) was performed in 19 patients (31.7%) and partial resection (PR) or biopsy was performed in 9 patients (14.3%). We analyzed their progression-free survival (PFS), overall survival (OS), and malignant transformation with regard to age, gender, Karnofsky performance score (KPS), clinical presentation, tumor location, radiologic pattern, contrast enhancement, extent of removal, pathologic subtype, chemotherapy (CT) and radiotherapy (RT) treatment.
Results: Among all LGGs, the 3-year OS rate was 80% and the 5-year OS was 76%. The 3-year PFS rate was 83.6% and the 5-year PFS was 25%. The non-eloquent area location showed a longer PFS than the eloquent area location ($p = 0.05$). Oligodendroglial pathology showed a longer PFS compared to oligoastrocytomas and astrocytomas ($p = 0.02$). Patients older than 60 years had poorer OS than younger patients ($p < 0.05$). Female gender had a shorter OS than male gender ($p < 0.05$), and a KPS of 90 or 100 had a longer OS than a KPS of 80 ($p < 0.05$). Oligodendroglial pathology statistically correlated with a longer OS ($p < 0.05$).
Conclusion: The findings from our study, which were confirmed by uni- and multivariate analyses, demonstrated that radical tumor resection was associated with better long-term outcomes and tumor progression for patients with LGG.

1. Introduction

LGGs are grade 2 tumors and account for approximately 11% of all primary brain tumors [3]. LGGs are infiltrative tumors that are characterized by a more favorable prognosis and slower progression than high grade gliomas [1,2]. The median survival rate for patients is between 5 and 10 years [3,4]. Despite the long-term survival rate for most LGG patients, there is risk of anaplastic transformation, which can eventually cause neurological decline and death [5–8]. Therefore, the management of LGG remains one of the major controversies in current neurosurgical practice. Identifying prognostic factors can help to create therapeutic strategies related to better quality of life and prolonged survival. These prognostic factors include the patient age at diagnosis, gender, initial presentation, duration of symptoms, degree of disability, KPS, radiologic parameters, extent of resection (EOR) and pathologic subtype [9–12]. It is believed that a greater EOR significantly influences the rate of OS and PFS. Postoperative RT is an advisable option for patients after subtotal resection, and it correlates with improved OS and PFS [2].

The objective of this study is to retrospectively analyze the outcomes of low-grade gliomas focusing on surgical treatment and the current therapeutic strategy.

2. Materials and methods

2.1. Clinical and tumor characteristics of the patients

We retrospectively analyzed patients who underwent surgery for LGGs during January 1999 and December 2011 at the Neurosurgery Clinic, Diskapi Yildirim Beyazit Education and Research Hospital. A total of 63 surgically treated LGG patients were included in the study. All the surgical procedures were performed by senior authors (AMS, TD, LG and ZS). Table 1 shows the clinical and tumor characteristics. The patients who were not treated surgically

* Corresponding author at: Cukurambar Mah. Ogretmenler Cad. No. 5/6, Ankara, Turkey. Tel.: +90 5056260200; fax: +90 3124359506.
E-mail address: drmet122@yahoo.com (E. Turkoglu).

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Table 1
Clinical and tumor characteristics of 63 patients with low-grade gliomas.

Clinical factors		No. of patients (63)	%
Sex	Male/female	36/2736	57/43
Age	<18/18–60/>60	6/50/7	9.5/79.5/11
Presentation	Seizure/HA/other	22/27/14	35/43/22
KPS	80/90/100	8/25/30	12.8/39.6/47.6
Side of tumors	Left/right	27/36	42.8/57.2
Main location	Frontal/temporal/parietal/occipital	37/16/16/2	58.7/25.4/12.7/3.2
Tumor location	Eloquent/non-eloquent	29/34	46/54
Radiologic pattern	Localized/diffuse	23/40	46/54
Contrast	Intense/moderate/none	5/20/38	7.9/31.7/60.3
Extent of removal	GTR/STR/PR or biopsy	35/19/9	55.6/30.2/14.3
Tumor subtype	Astrocytoma	28	44.4
	Oligodendroglioma	27	42.9
	Oligoastrocytoma	8	12.7
Radiotherapy	+	22	34.9
	–	41	65.1
Chemotherapy	+	17	27.0
	–	46	73.0
Malignant transformation	+	13	20.6
	AA	8	12.7
	AO	1	1.6
	GBM	4	6.3

AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; GBM, glioblastoma multiforme; GTR, gross total resection; KPS, Karnosfsky performance score; STR, subtotal resection; PR, partial resection; +, yes; –, no.

excluded from the study. The median follow-up for the patients was 4.9 years (range, 1,1–11 years). The male:female ratio was 36:27. The median patient age was 38 (range, 15–68 years). We divided the patients into 3 age groups according to Jung et al.: <18 years (n = 6, 9.5%), 18–60 years (n = 50, 79.5%) and >60 years (n = 7, 11%) [2]. The initial symptoms were seizure in 22 patients (35%), headache in 26 (41%), other neurological presentation, such as hemiparesis or aphasia in 15 patients (22%) and incidental in 2 (2%). The patients' functional statuses were evaluated using the KPS. Thirty patients scored 100 (47.6%), 25 scored 90 (39.6%), and 8 scored 80 (12.8%). The tumors were diagnosed as follows: oligodendrogliomas (n = 27, 41.8%), astrocytomas (n = 30, 46.6%) and oligoastrocytomas (n = 8, 11.6%).

We defined an "eloquent" area as any tumor involving one or more of the following: internal capsule, basal ganglia, language cortex, sensory cortex, motor cortex, thalamus and hypothalamus. A diffuse pattern signified an infiltrating tumor, involving more than two lobes and/or having contralateral involvement. The tumors were located in the left hemisphere in 27 patients (43%) and in the right hemisphere in 36 patients (57%). The tumors were mainly located in the frontal lobe in 37 patients (58.7%), in the temporal lobe in 16 patients (25.3%), in the parietal lobe in 8 patients (12.7%) and in the occipital lobe in 2 patients (3.3%). The tumors occurred in eloquent areas for 29 patients (46%) and in near or non-eloquent areas for the remaining patients (54%). The tumors were localized in 23 patients (36.5%) and diffuse in 40 patients (63.5%). We grouped the enhancement pattern as none, patchy or moderate and intense. Based on the enhancement patterns, none, moderate and intense enhancements were observed in 38 patients (60.3%), 20 patients (31.7%) and 5 patients (8%), respectively.

3. Surgical treatment

Based on preoperative neurological and advanced radiological examination (functional MRI, MR spectroscopy) eloquent localization was found. Twenty nine patients located adjacent to an involving cortical and subcortical eloquent areas underwent tumor resection with aid of intraoperative physiological mapping techniques in the Diskapi Yildirim Beyazit Education and Research Hospital. It was performed prior to resection and was repeated intraoperatively after resection was complete. The methods of direct cortical and subcortical stimulation, in addition to electrocorticography, enabled us to maximize tumor resection, minimize morbidity.

The gross total resection (GTR) was performed in 35 patients (60.3%), subtotal resection (STR) was performed in 19 patients (31.7%) and partial resection (PR) or biopsy was performed in 9 patients (14.3%). The postoperative fluid-attenuated inversion recovery (FLAIR) signal abnormality was used to determine the extent of the resection, we obtained postoperative MRI and FLAIR sequences within 24 h after surgery in all the cases. On postoperative MRI, increased signal observed within the cavity (postresection products) or within the brain extending into areas that were null of preoperative FLAIR images was not likely indicative of residual tumor.

4. Adjuvant treatment

Postoperatively, 22 patients (34.9%) who had incomplete resection, because of recurrence or malignant degeneration of the tumor, received adjuvant RT (180 cGy/day, 5 days/week, total dose 5400–5800 cGy) following 4 weeks later after initial surgery. RT reserved for possible tumor progression in ordinary LGGs such as pilocytic astrocytoma or cystic cerebellar astrocytoma. 13 (20.6%) patients underwent adjuvant temozolomide therapy (150 mg/m^2/5 days for 4 weeks) because of tumor progression. We started chemotherapy as soon as tumor progression was diagnosed. If there was tumor on the post-op MRI with contrast which obtained within 24 h after surgery was defined residual tumor left behind by the surgeon. Tumor recurrence was defined as the appearance of residual tumor growth or the development of new lesions on MR images. If the recurrent tumors were suitable for surgical removal, we re-operated and those patients then received RT (180 cGy/day, 5 days/week, total dose 5400–5800 cGy) or temozolomide chemotherapy (200 mg/m^2/5 days for 4 weeks) until the tumor progressed.

4.1. Follow-up

OS, PFS and malignant degeneration-free survival (MFS) were used to assess outcomes. OS was defined as the time from surgery to death. PFS was defined as the time from surgery to increase in tumor

Table 2
Univariate analysis related with PFS and OS in LGGs.

Clinical variables		PFS	OS
Sex	Male/female	$p = 0.01$	$p = 0.01$
Age	<18/18–60/>60	$p = 0.03$	$p = 0.04$
Presentation	Seizure/headache/other	$p = 0.63$	$p = 0.67$
KPS	80/90/100	$p = 0.04$	$p = 0.02$
Side of tumors	Left/right	$p = 0.32$	$p = 0.78$
Main location	Frontal/temporal/parietal/occipital	$p = 0.21$	$p = 0.67$
Tumor location	Eloquent/non-eloquent	$p = 0.05$	$p = 0.19$
Radiologic pattern	Localized/diffuse	$p = 0.14$	$p = 0.01$
Contrast enhancement	Strong/moderate/none	$p = 0.004$	$p = 0.89$
EOR	GTR/STR/PR or biopsy	$p = 0.03$	$p = 0.04$
Tumor subtype	Astrocytoma/oligodendroglioma/o.astrocytoma	$p = 0.02$	$p = 0.01$
RT	−/+	$p = 0.01$	$p = 0.001$
CT	−/+	$p = 0.06$	$p = 0.001$

CT, chemotherapy; EOR, extent of removal; GTR, gross total resection; KPS, Karnofsky performance score; LGGs, low grade gliomas; OS, overall survival; PR, partial resection; STR, subtotal resection; −, no; +, yes.

size on follow-up imaging or malignant degeneration. Malignant transformation was defined as the time from surgery to the demonstration of gadolinium enhancement on follow-up imaging and/or WHO Grade III or IV tumor on subsequent biopsy. If the patients had received RT after initial surgery, we performed MR spectroscopy in distinguishing tumor from radiation necrosis. If imaging did not reliably differentiate, we performed biopsy to clarify this suspicion.

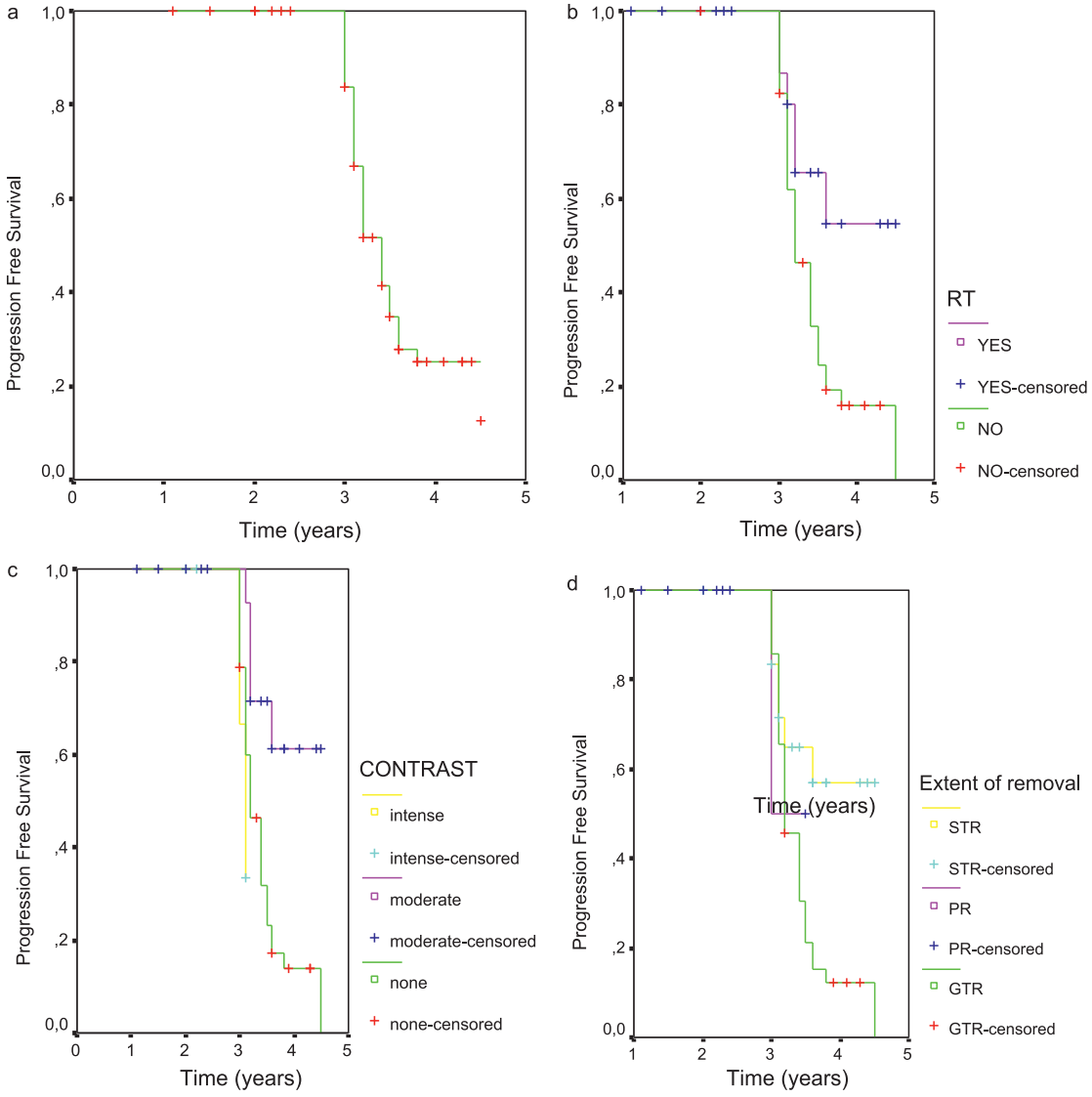

Fig. 1. (a) Progression-free survival curve (Kaplan–Meier method) in low-grade gliomas. (b) No-radiotherapy group showed improved PFS compared to the radiotherapy group ($p = 0.01$). (c) The no-contrast enhancement group showed improved PFS compared to moderate or intense enhancement ($p = 0.004$). (d) Gross total removal showed improved PFS ($p = 0.03$).

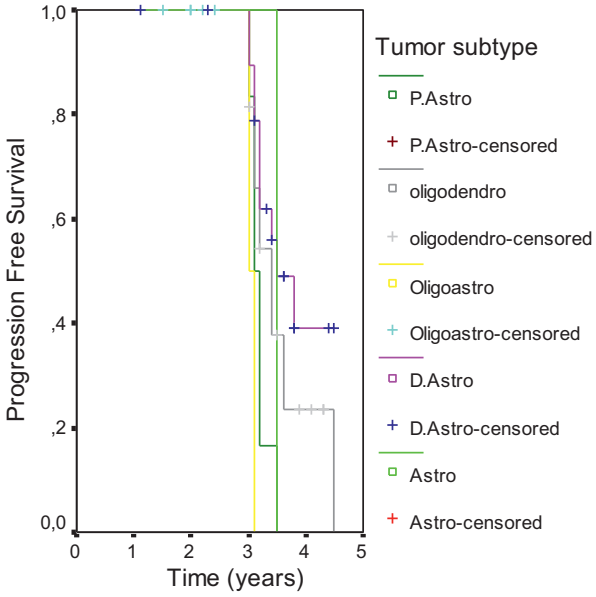

Fig. 2. Oligodendroglioma has longer PFS more than the other pathologies ($p = 0.02$).

4.2. Statistical analysis

Descriptive statistics (mean, median, standard deviation of mean, minimum, maximum, percentage range) of all variables in the study were calculated. The likelihood-ratio Chi-squared test was used for statistical comparisons of the categorical variables. Probability survival (OS, PFS, and MFS) was calculated using the Kaplan–Meier method. Differences regarding the survival curves of the analyzed variables of particular survival times were compared using the log-rank test for variables with many categories, and $p < 0.05$ was considered statistically significant.

5. Results

5.1. Progression-free survival

Among all LGGs, the 3-year PFS was 83.6% and the 5-year PFS was 25%. Depending on the pathology, oligodendrogliomas showed an 81.5% 3-year PFS and a 46% 5-year PFS, oligoastrocytomas showed a 65% 3-year PFS and a 40% 5-year PFS and astrocytomas had a 57% 3-year PFS and a 48% 5-year PFS. For the univariate analysis, we used the Kaplan–Meier method with the log-rank test for comparisons (Table 2). The clinical variables from the no-radiotherapy group ($p = 0.001$), no-contrast enhancement ($p = 0.001$) and GTR ($p < 0.05$) correlated with a longer PFS (Fig. 1). The non-eloquent area location showed a longer PFS than the eloquent area location ($p = 0.05$). Oligodendroglial pathology showed a longer PFS compared with oligoastrocytomas and astrocytomas ($p < 0.05$, Fig. 2). The Cox regression analysis revealed that astrocytoma pathology had a poor PFS (hazard ratio = 2.305, 95% CI, 0.687–7.729, $p = 0.05$) compared to that of oligodendroglial pathology (Table 3).

5.2. Overall survival

Among all LGGs, the 3-year OS was 80% and the 5-year OS was 76%. Depending on the pathology, oligodendrogliomas showed a 93.8% 3-year OS, oligoastrocytomas showed an 83% 3-year OS and astrocytomas had a 71% 3-year OS.

In the univariate analysis, we found that the clinical variables of age, gender, diffuse pattern and tumor location, EOR, and tumor subtype correlated statistically with overall survival (Table 2). Patients older than 60 years had poorer OS than young patients ($p < 0.05$). Female gender had a shorter OS than male gender ($p = 0.05$), and a KPS of 90 or 100 had a longer OS than a KPS of 80 ($p < 0.05$). The initial symptom of headache had a poorer OS than seizure or other neurological symptom but without statistical significance ($p > 0.05$). The clinical variables of local radiologic pattern ($p < 0.05$), GTR ($p < 0.05$) and oligodendroglial pathology ($p < 0.05$) correlated statistically with a longer OS. The overall survival curve (Kaplan–Meier method) in LGGs showed a diffuse radiologic pattern, radiotherapy and chemotherapy treatment had poorer OS (Fig. 3). Regarding the radiologic parameters, no-contrast enhancement had a longer OS ($p > 0.05$) but without statistical significance. The Cox regression model revealed that a patient age of 18–60 years was associated with longer OS (hazard ratio = 1.046, 95% CI, 0.992–1.102, $p = 0.09$) compared with a patient age of 60 years. A location in an eloquent area (hazard ratio = 2.681, 95% CI, 0.601–11.963, $p = 0.19$) and diffuse radiologic pattern (hazard ratio = 1.946, 95% CI, 0.740–5.119, $p = 0.17$) both had poor OS (Table 4).

5.3. Malignant transformation

Malignant transformation was pathologically diagnosed in 13 patients (20.6%, 1 anaplastic oligodendroglioma of 27 oligodendrogliomas, 8 anaplastic astrocytomas and 4 glioblastoma multiformes of 29 oligoastrocytomas and diffuse astrocytomas). In the logistic regression model, diffuse radiologic pattern correlated with malignant transformation but without statistical significance ($p > 0.05$).

6. Discussion

The optimal strategy regarding the surgical treatment of LGG is still a matter of debate. In general, the current literature supports the theory that radical tumor resection is preferable in terms

Table 3
Multivariant analysis related with progression free survival in LGGs.

Clinical variables		Hazard ratio	*p* value	95% CI
Sex	Male	1.689	0.178	0.788–3.620
Tumor location	Non-eloquent	0.760	0.623	0.254–2.271
Radiologic pattern	Local	0.809	0.639	0.333–1.964
EOR	GTR	0.652	0.625	0.275–7.857
	PR	1.515	0.757	0.109–21.105
Contrast enhancement	Moderate	0.313	0.167	0.060–1.625
	Intense	7.173	0.159	0.462–111.482
Tumor subtype	Oligodendroglioma	1.551	0.395	0.564–4.267
	Others	2.305	0.176	0.687–7.729
RT	–	0.604	0.632	0.076–4.765
CT	–	4.870	0.395	0.393–60.378

CT, chemotherapy; EOR, extent of removal; GTR, gross total resection; LGGs, low grade gliomas; PR, partial resection; –, no.

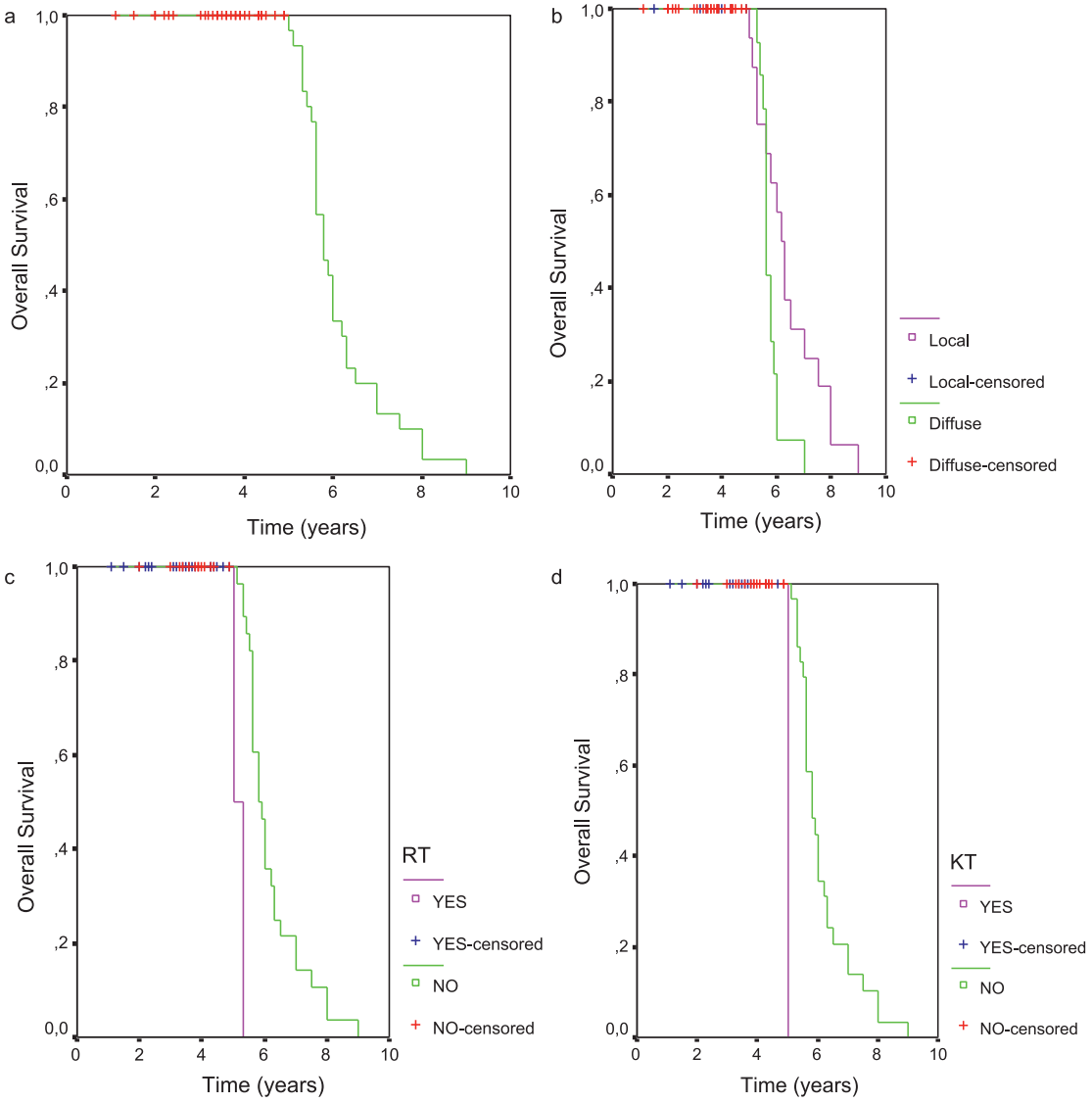

Fig. 3. (a) The overall survival curve (Kaplan–Meier method) for the low-grade gliomas. (b) Localized masses showed better PFS than diffuse masses ($p = 0.17$). (c) Radiotherapy correlated with poorer OS ($p = 0.001$). (d) Chemotherapy correlated with poorer OS ($p = 0.001$).

of yielding better OS and PFS compared to STR, PR and biopsy [13,14]. Extensive surgical resection is associated with delayed malignant transformation [2,4,15,16]. Gross-total resection may prove difficult if it involves eloquent brain lesions [14]. Jung et al. performed a retrospective analysis of LGGs in 86 patients and found that GTR statistically correlated with improved PFS and OS in the univariate analysis and was independently associated with longer PFS [2]. Smith et al. reported that patients with over 90% resection showed 5- and 8-year OS of 97% and 91%, respectively; whereas patients with less than 90% resection showed 5- and 8-year OS rates of 76% and 60%, respectively [17]. Mariani et al. reported that they were only able to achieve >90% resection in 10% of treated patients and furthermore noted that smaller postoperative tumor volume was associated with longer OS [14]. Thus, it is recommendable to perform surgical resection before the tumor volume increases, as this predicts a worsened outcome. In our study, gross total resection was performed in 60.3% of the cases due to small volume of the tumor and correlated statistically with improved PFS and OS in the univariate analysis and associated independently with longer PFS. Aggressive resections are more likely to be performed in patients with more favorable tumor characteristics, such as localized mass or location in a non-eloquent area. In our study, 46% of the masses were in eloquent areas, and 40% showed a diffuse pattern. The delineation of functional areas by intraoperative mapping with electrocortical stimulation can maximize tumor resection and improve long-term survival rates [18]. Thus, in order to maximize the extent of tumor removal and minimize morbidity, the neurosurgeon can use intraoperative methods to identify critical physiological areas and underlying pathways before and during resection.

Table 4
Multivariate analysis related with overall survival in LGGs.

Clinical variables		Hazard ratio	*p* value	95% CI
Age	>60 years-old	1.046	0.094	0.992–1.102
Sex	Female	1.798	0.173	0.773–4.184
Tumor location	Eloquent	2.681	0.196	0.601–11.963
Radiologic pattern	Diffuse	1.946	0.177	0.740–5.119
RT	+	29.131	0.001	3.986–212.890

LGGs, low grade gliomas; +, yes.

We analyzed the data from three radiological findings: the main tumor location, its laterality, and the enhancement pattern of each tumor, whether it was in an eloquent or non-eloquent area and whether it was a localized or diffuse mass. Radiologically, the masses were mainly located in the right hemisphere (57%) and the frontal lobe (59%). The contrast enhancement observed on CT scans and MRI frequently associated with a high-grade glioma, but it can occur in 15–40% of patients with LGGs [18]. LGGs with contrast enhancement have an independent 2.6-fold increased risk of recurrence [19]. In our study, 60.3% of the cases showed non-enhancement, and 39.7% of the patients showed contrast enhancement (31.8% moderate and 7.9% intense). In the univariate analyses, non-eloquent location and localized mass were associated with longer PFS and OS. Tumor enhancement did not correlate with prognosis.

EORTC study revealed that astrocytoma pathology and large tumor size was strongly associated with the poor prognosis of LGGs [20]. Astrocytomas were correlated with recurrence and malignant progression and had a worse prognosis than oligoastrocytomas or oligodendrogliomas [20–23]. Some studies have reported preoperative contrast enhancement, tumor size, and subtotal resection to be other prognostic factors associated with malignant degeneration [24,25]. The malignant transformation could occur toward the end of the natural evolution of LGGs. In this study, oligodendroglioma subtype had more favorable OS and PFS, while diffuse astrocytoma was an independent factor for malignant transformation ($p < 0.05$).

Retrospective studies are inconsistent whether RT is effective after surgery or at the time of progression [26,27]. Van den et al. have reported similar OS in an irradiated group and a control group [26]. Early RT did not influence the PFS in patients with radically resected tumors [27]. Jung et al. reported that the no-RT group showed longer PFS than the RT group; the authors explained this finding resulted from the indications for postoperative RT. The patients receiving postoperative RT had undergone limited resections [2]. In our study, which is similar to Jung et al., the RT group showed poorer PFS and OS because we could only partially resect the tumors.

Research into the chemosensitivity of LGG has increased interest in CT, both for newly diagnosed and recurrent LGG. Temozolomide (TMZ), procarbazine, lomustine and vincristine in combination (PCV) form a chemotherapeutic agent that is currently used to treat LGG [28]. In our study, the no-CT group showed longer PFS and OS. Note that the patients receiving postoperative CT underwent limited resection. Therefore, we could not obtain statistically meaningful data regarding chemotherapy.

Majchrzak et al. have reported that the overall 5-year survival rate for all patients was 91%, progression free 5-year survival was 68%, and malignant degeneration was 16% [10]. Jung et al. have reported that the 5-year OS was 81%, the 5-year PFS was 57%, and the MTF rate was 15% [2]. In the current study, the 3-year OS was 80%; the 5-year OS was 76%; the 3-year PFS was 83.6%; the 5-year PFS was 25%; and the MTF rate was 20.6%. These different results can be explained by the retrospective designs of the studies, which could not provide direct causal relationships between the observations and results. A prospective study would ideally provide more accurate data on the survival and malignant transformation rates.

In conclusion, the findings from our study, which were confirmed by uni- and multivariate analyses, demonstrated that radical tumor resection as associated with better long-term outcomes and tumor progression for patients with LGG. However, radical resection is not always possible because of the infiltration of eloquent areas. Intraoperative brain mapping techniques may be used to all patients with superficial and deep supratentorial LGGs to enhance to extent of resection and minimize the operative morbidity. Thus future studies with larger samples are necessary to confirm this finding.

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