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Overall survival in adult patients with low-grade, supratentorial glioma: Ten years' follow up at a single institution

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Abstract

Background: Low-grade gliomas (LGGs) are the second most prevalent type of primary brain tumors in adults. The prognosis for LGGs can differ according to the clinical-pathological prognostic factors determined during diagnosis and treatment. The purpose of this study was to identify 10-year, disease-free survival (DFS), 10-year overall survival (OS), and related clinical-pathological prognostic factors of adult patients with supratentorial, low-grade gliomas who were treated with or without surgery and radiation therapy.

Methods: The study included 110 patients who were confirmed to have low-grade, supratentorial gliomas and who had received surgery and adjuvant radiation therapy or salvage radiotherapy as part of their treatment. These patients were followed by the radiation-oncology ward at Shohada-e-Tajrish Hospital in Tehran, Iran, between 2002 and 2012. The log-rank test (univariate) and the Cox proportional hazards model (multivariate) were used to examine the 10-year DFS and OS and to assess the strengths of various histo-clinical factors relative to 10-year DFS and OS.

Results: The study included 110 patients for whom 10-year DFS and OS were found to be 23 and 28%, respectively. Favorable prognostic factors in the univariate analysis using the Kaplan-Meier 10-year OS analysis were the following: age below 40, karnofsky performance status (KPS) more than 70, the presence of oligodendroglioma, tumor size of < 5 cm, and gross-total resection (p=0.02, p=0.01, p=0.03, p=0.01, p=0.02, respectively). Good prognostic factors in multivariate analysis using the Cox regression model were as follows: age below 40, the presence of oligodendroglioma, tumor size< 5 cm, and gross total resection in10-year OS (p=0.01, p=0.03, p=0.00, p=0.02, respectively).

Conclusions: Gross-total resection, tumor size < 5 cm, age below 40, and the presence of oligodendroglioma had better 10-year DFS and OS rates. We recommend that all patients with LGG tumors be referred to neuro-oncology centers that have sufficient experience to achieve the best results of treatment.

Keywords: low-grade glioma, overall survival, disease-free survival, prognostic factors, radiotherapy

1. Introduction

Low-grade gliomas (LGGs) are the second most prevalent type of primary brain tumors in adults. LGGs occur more frequently in young adults and more frequently in males than females (1). The most common histology subtypes of LGGs in adults are astrocytomas, oligodendrogliomas, and mixed oligostrocytomas. They may arise from astrocytic, oligodendrocytic, or mixed lineage. Non-pilocytic or diffusely-infiltrating, low-grade gliomas are classified by the World Health Organization (WHO) as grade II tumors. Most non-pilocytic astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are classified as diffuse tumors in final pathology reports (2). These patients may have various symptoms, such as headache (especially in the morning); vomiting; nausea; seizures; cerebral palsy; and motor, sensory, visual, hearing, and speech disorders (3).

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The unfavorable prognostic factors include poor Karnofsky Performance Status (KPS), age over 40, diffuse astrocytomas histology, subtotal resection, no resection, tumors' crossing the midline, the greatest dimension of the tumor≥ 6 cm, and the existence of motor or sensory deficits at the time of surgery (4). Unfortunately, there are still significant disagreements between neurooncologists concerning the optimal surgery for LGGs and the appropriate amount of radiotherapy (adjuvant radiotherapy or radiation therapy at progression) with or without concomitant chemotherapy or adjuvant chemotherapy. In general, treatment is reserved for patients with symptomatic residual disease despite optimal surgical resection or for patients who are suspected to have high-risk features (5). The prognosis of LGG can differ depending on the clinical-pathological prognostic factors determined during diagnosis and treatment (6). The purpose of this study was to identify 10-year, disease-free survival (10-year DFS), 10-year overall survival (10-year OS) and related clinical-pathological prognostic factors of adult patients with low-grade, supratentorial gliomas who were treated with and without surgery and radiation therapy.

2. Materials and methods

2.1 Research Design and Setting

This was a cross sectional, analytical study. The patients in the study consisted of patients who were diagnosed with histopathologically-confirmed LGGs and were followed by the radiation-oncology ward at Shohada-e-Tajrish Hospital in Tehran, Iran, between 2002 and 2012. The medical records of the patients were investigated for pertinent information, such as gender, KPS, age, histopathology subtype, existence of motor or sensory deficits at the time of surgery, complete or incomplete resection of the tumor, existence of headaches or seizures at diagnosis, 10-year disease free survival (DFS), 10-year overall survival (OS), and adjuvant radiation therapy.

The patients who were excluded from the study were patients who met the following exclusion criteria: 1) patients without histopathology diagnosis or with high-grade gliomas, 2) patients with pilocytic or astrocytomas grade I, infra-tentorial tumors, 3) patients who were less than 16 years old, and 4) patients who adjuvant treatments, such as radiation therapy or Gamma Knife treatment, at another radiation oncology center. The 10-year DFS rates were calculated from the date of surgery until the date of the first recurrence or progression, and the 10-year OS rates were calculated from the date of surgery until the date of death.

2.2. Sampling

The sample size of 110 patients was calculated using the formula "$n= Z^2p\ (1-p)/d^2$"; where: Z=the appropriate value from the normal distribution for 95% confidence (1.96), P=the anticipated prevalence, d=the confidence interval.

2.3. Data collection

All of the patients were treated with 50.4-54 Gy in 28-30 fractions radiation therapy with Compact 6 MV or Co60 without concomitant chemotherapy as adjuvant radiotherapy or salvage radiotherapy. As the clinical target volume, the radiation fields included the volume of the pre-operative tumor as defined by a pre-operative MRI in the T2 phase. We used 50.4-54 Gy in 28-30 fractions to the primary tumor plus a safe margin of 2 cm in the two lateral fields or the anterior or posterior field with two lateral fields (three fields). Radiation therapy was used five days per week, from Saturday to Wednesday (with the exception public holidays) with 1.8 Gy per fraction with two-dimensional (2D) or three-dimensional (3D) treatment. All patients were followed by standard guidelines. Ten-year DFS rates were calculated from the date of surgery until the date of the first recurrence or progression, and 10-year OS rates were calculated from the date of surgery until the date of death.

2.4. Ethical consideration

The ethical regulations dictated in the act provided by Shohada-e-Tajrish Hospital at Shahid Beheshti University of Medical Sciences (reference number of research ethics committee: 2589) were strictly observed. The data were preserved without using the patient`s names. All patients were treated and followed by standard guidelines.

2.5. Statistical analyses

We used the Kaplan–Meier method and compared the use of one- or two-sided log rank tests for univariate analysis. Ten-year DFS and 10-year OS were calculated by using the Kaplan-Meier method based on disease-free and survival analyses. The examination of the 10-year DFS and 10-year OS by univariate analyses was performed using the log-rank test. For the multivariate analysis, the Cox proportional hazards model was used to assess the strengths of the various histo-clinical factors associated with 10-year DFS and OS rates. Statistical analyses were performed using SPSS software, version 21 (SPSS IBM).

3. Results

The study included 110 patients, 71 of whom were males (64.5 %) and 39 of whom were females (35.5 %). The mean age of the patients was 39.7±13.2, and the age range was from 18 to 72. Seventy-three patients (66.4 %) were less than 40 years old, and 37 of the patients (33.6 %) were 40 or older. Sicty-four patients (58.2 %) had histories of epileptic seizures during diagnosis, and 44 patients (40%) had headaches when they were diagnosed. The KPS score was > 70 for 84 of the patients (76.4%) before radiation therapy (RT) (Table 1).

Table 1. Baseline characteristics and the clinical-pathological features of 110 adult patients with low-grade, supratentorial gliomas (LGG patients)

Characteristics		Value (%)
Gender	Male	71 (64.5)
	Female	39 (35.5)
Age (years)	<40	73 (66.4)
	≥40	37 (33.6)
Tumor size	≥5 cm	73 (66.4)
	<5 cm	37 (33.6)
Histology	Astrocytoma	70 (63.6)
	Oligodendroglioma	33 (30)
	Mixed oligoastrocytoma	7 (6.4)
Headache at diagnosis	Yes	44 (40)
	No	66 (60)
Seizures at diagnosis	Yes	64 (58.2)
	No	46 (41.8)
Motor or sensory deficit at diagnosis	Yes	35 (31.9)
	No	75 (68.1)
Karnofsky performance status	50-70	26 (23.6)
	Greater than 70	84 (76.4)
Type of surgery	Gross-total resection	18 (16.4)
	Subtotal resection	26 (23.6)
	Biopsy (no surgery)	66 (60)
Setting of radiotherapy	Adjuvant radiotherapy	99 (90)
	Radiation therapy at progression	11 (10)
Total patients		100 (100)

Diagnoses of the patients were performed through biopsy in 66 patients (60%), subtotal resection in 26 patients (23.6%), and total/gross total resection in 18 patients (16.4%). The histopathology types of patients during diagnosis were grade II astrocytoma for 70 patients (63.6 %), oligodendroglioma for 33 patients (30%), and mixed oligoastrocytoma in seven patients (6.4 %). Seventy-three patients (66.4%) had tumor sizes ≥5 cm before surgery. Ninety-nine patients (90%) received adjuvant post-operative RT after the initial diagnosis, whereas 11 patients (10%) received RT at progression (Table 1). All 110 patients completed the scheduled radiation therapy program. The mean follow-up period was determined as 50±47 months (minimum: 6.3 months; maximum: 122.2 months). Ten-year DFS and OS were 23% and 28%, respectively. The median 10-year DFS was 38 months with 95% CI (25-51). The median 10-year OS was 57 months with 95% CI (45-71).

According to the Kaplan-Meier 10-year DFS analysis and the log-rank test, eight factors had a statistically significant relationship with the 10-year DFS. These eight factors, determined by univariate analysis (Table 2) are listed here: 1) Age≥40 (p=0.04), hazard ratio (HR)=2.84, 95% CI=1.50 -4.34, 2) Tumor size ≥5 cm (p=0.01, HR=1.83, 95% CI=0.36-3.33), 3) Presence of oligodendroglioma (p=0.04, HR=0.62, 95% CI=0.30 -1.07), 4) Motor or sensory deficit at diagnosis (p=0.05, HR=1.45, 95% CI=0.30-2.39), 5) KPS greater than 70 (p=0.01, HR=0.52, 95% CI=0.28-1.01), 6) Subtotal resection (p=0.04, HR=1.32, 95% CI=0.22-2.43), Biopsy (p=0.01, HR=2.51, 95% CI=0.18-4.88), and 7) Radiation therapy at progression (p=0.04, HR=2.37, 95% CI=0.57-3.72). Then the favorable prognostic factors in our study based on univariate analysis, using the Kaplan-Meier 10-year DFS analysis and log-rank test, were as follows (Table 2): 1) Age below 40, 2) KPS greater than 70, 3) Presence of oligodendroglioma, 4)

Tumor size <5cm, 5) Absence of motor or sensory deficit at diagnosis, 6) Gross-total resection and adjuvant radiotherapy.

Based on the univariate analysis, there was no statistically significant relationships between 10-year DFS and gender, headache, seizures at diagnosis, of the presence of mixed oligoastrocytoma (Table 2). The univariate analysis indicated that six factors had a statistically significant relationship with 10-year DFS (Table 2), i.e.: 1) Age≥40 (p=0.02, HR=0.48, 95% CI=0.13-0.73), 2) Tumor size≥5 cm (p=0.00, HR=2.04, 95% CI=0.23-4.98), 3) Presence of oligodendroglioma (p=0.04, HR=1.88, 95% CI=0.34-5.78), 4) Subtotal resection (p=0.02), 5) HR=1.67, 95% CI=0.34-2.83), 6) Biopsy (p=0.00, HR=1.34, 95% CI=1.33-2.44), and 7) Radiation therapy at progression (p=0.02, HR=3.16, 95% CI=0.66-5.78). Then, prognostic factors were studied in the multivariate analysis by using the Cox regression model. As a result, the following favorable prognostic factors for 10-year DFS were identified: age less than 40, the presence of oligodendroglioma, tumor size<5 cm, gross-total resection, and adjuvant radiotherapy (Table 2). Based on the multivariate analysis, there were no statistically significant relationships between 10-year DFS and gender, headache, seizures at diagnosis, presence of mixed oligoastrocytoma, KPS greater than 70, and motor or sensory deficit at diagnosis (Table 2).

Table 2. Ten-year, disease-free survival rate according to univariate and multivariate analysis

Factor	Univariate analysis		Multivariate analysis	
	HR[a] (95% CI[b])	p-value	HR (95% CI)	p-value
Gender	1.28 (0.38-2.44)	0.76	1.32 (0.54-3.23)	0.51
Age ≥ 40	2.84 (1.50 -4.34)	0.04	0.48 (0.13-0.73)	0.02
Oligodendroglioma/Astrocytoma	0.62 (0.30 -1.07)	0.04	1.88 (0.34-5.78)	0.04
Mixed oligoastrocytoma/Astrocytoma	0.86 (0.36-1.52)	0.08	2.78 (1.08-4.06)	0.07
Tumor size ≥ 5 cm	1.83 (0.36-3.33)	0.01	2.04 (0.23-4.98)	0.00
Headache at diagnosis	1.06 (0.55-1.52)	0.28	1.98 (1.48-2.56)	0.46
Seizure at diagnosis	1.28 (0.52-1.80)	0.08	1.06 (0.40-1.44)	0.16
Motor or sensory deficit at diagnosis	1.45 (0.30-2.39)	0.05	1.88 (0.56-3.34)	0.06
KPS greater than 70	0.52 (0.28-1.01)	0.01	1.68 (0.56-2.86)	0.66
Subtotal resection/Gross-total resection	1.32 (0.22-2.43)	0.04	1.67 (0.34-2.83)	0.02
Biopsy (no surgery)/Gross-total resection	2.51 (0.18-4.88)	0.01	1.34 (1.33-2.44)	0.00
Radiation therapy at progression/Adjuvant radiotherapy	2.37 (0.57-3.72)	0.04	3.16 (0.66-5.79)	0.02

[a] HR: hazard ratio; [b] CI: confidence interval

According to Kaplan-Meier 10-year OS analysis and Log-rank test, six factors were statistically significant relation between 10-year OS and age≥40 years (p=0.02, HR=3.33, 95% CI=1.52-5.01), tumor size≥5 cm (p=0.01, HR=2.02, 95% CI=0.47-3.69), presence of oligodendroglioma (p=0.03, HR=0.52, 95% CI=0.18-1.14), subtotal resection (p=0.02, HR=1.87, 95% CI=0.82-2.87), Biopsy (p=0.01, HR=3.16, 95% CI=0.12-5.88) and KPS more than 70 (p=0.01, HR=0.38, 95% CI=0.16-0.61), by univariate analysis (Table 3). Then the favorable prognostic factors in our study in univariate analysis using Kaplan-Meier 10-year OS analysis and Log-rank test, were: age below 40, KPS more than 70, presence of oligodendroglioma, tumor size<5 cm and gross-total resection (Table 3). There was no statistically significant relationship between 10-year OS and gender, headache or seizures at diagnosis, presence of mixed oligoastrocytoma, motor or sensory deficit at diagnosis and radiation therapy at progression by univariate analysis (Table 3).

Five factors were statistically significant relation between 10-year OS and age ≥40 (p=0.01, HR=0.55, 95% CI=0.31-0.80), tumor size≥5 cm (p=0.00, HR=2.09, 95% CI=1.23-3.98), presence of oligodendroglioma (p=0.03, HR=2.21, 95% CI=0.54-4.12), subtotal resection (p=0.02, HR=1.20, 95% CI=1.59-2.57) and Biopsy (p=0.00, HR=2.88, 95% CI=0.93-5.44) by multivariate analysis (Table 3). Then prognostic factors were studied in multivariate analysis using by Cox regression model, age below 40, presence of oligodendroglioma, tumor size<5 cm and gross-total resection were determined as favorable prognostic factors in10-year OS (Table 3). There was no statistically significant relationship between 10-year OS and gender, headache or seizures at diagnosis, presence of mixed oligoastrocytoma, motor or sensory deficit at diagnosis, KPS more than 70 and radiation therapy at progression by multivariate analysis (Table 3).

Table 3. Ten-year overall survival rate according to univariate and multivariate analysis

Factor	Univariate analysis		Multivariate analysis	
	HR[a] (95% CI[b])	p-value	HR (95% CI)	p-value
Gender	1.14 (0.35-1.82)	0.83	1.80 (0.72-2.90)	0.74
Age ≥ 40	3.33 (1.52-5.01)	0.02	0.55 (0.31-0.80)	0.01
Oligodendroglioma/Astrocytoma	0.52 (0.18-1.14)	0.03	2.21 (0.54-4.12)	0.03
Mixed oligoastrocytoma/ Astrocytoma	0.79 (0.42-1.21)	0.11	1.26 (0.58-2.06)	0.10
Tumor size ≥ 5 cm	2.02 (0.47-3.69)	0.01	2.09 (1.23 -3.98)	0.00
Headache at diagnosis	1.08 (0.62-1.47)	0.45	1.14 (0.58 -1.46)	0.50
Seizure at diagnosis	1.31 (0.71-1.92)	0.10	1.13 (0.36-1.77)	0.26
Motor or sensory deficit at diagnosis	1.32 (0.22-2.41)	0.05	1.47 (0.93 -2.30)	0.08
KPS greater than 70	0.38 (0.16-0.61)	0.01	1.34 (0.70-2.00)	0.33
Subtotal resection/Gross-total resection	1.87 (0.82-2.87)	0.02	1.20 (1.59 -2.57)	0.02
Biopsy (no surgery)/Gross-total resection	3.16 (0.12-5.88)	0.01	2.88 (0.93-5.44)	0.00
Radiation therapy at progression/Adjuvant radiotherapy	1.17 (0.57-1.52)	0.09	1.20 (0.42-1.90)	0.08

[a] HR: hazard ratio; [b] CI: confidence interval

4. Discussion

In our study, patients whose ages were less than 40, had tumors< 5 cm in size, and had oligodendroglioma tumors and gross resection were determined as having independent good prognostic factors, both in the univariate analyses and the multivariate analyses. Pignatti et al. showed that patients older than 40 who had astrocytoma histology, tumors larger with diameters of ≥ 6 cm, and had motor or sensory deficits at diagnosis had the worse prognosis (4). We determined a borderline significant relationship between 10-year DFS and the absence of motor or sensory deficit at diagnosis in univariate analysis (p=0.05), but such a relationship was found in the multivariate analyses. There was no significant relationship between 10-year OS and the absence of motor or sensory deficits at diagnosis in both the univariate and multivariate analyses. One potential explanation for these differences could be the low number of patients.

For LGG, the oligodendroglial component was found to be associated with a better prognosis (7, 8). In our study, we determined that there was a significant relationship between both 10-year DFS and 10-year OS and the oligodendroglial sub-type compared to astrocytomas with significant p value in both the univariate and multivariate analyses. We did not find a significant relationship between either the 10-year DFS of the 10-year OS and the mixed oligoastrocytoma sub-type compared to astrocytomas. The low number of patients with mixed oligoastrocytoma sub-type (seven patients) could explain this finding. Seizure was the most frequent symptom observed in 81% of LGG, and it frequently is associated with oligodendrogliomas. Patients presenting with seizure seem to have better DFS and OS. This perhaps was due to the fact that seizures were observed more frequently in patients with oligodendrogliomas, and such patients have a better prognosis (9). We determined that seizure only occurred in 58.2% of the patients. We could not determine a significant relationship between 10-year DFS and10-year OS and seizure. The reason for this probably was the low percentage of the patients who had seizures. The best treatment for LGG is still controversial. However, surgery is the best treatment modality. There are studies demonstrating that maximum safe surgical resection provides a better 10-year DFS and10-year OS and can reduce malignant progression and recurrence. However, some studies have suggested that it provides an advantage for 10-year DFS but not for 10-year OS (10-11). Both the single-variable and multivariate analyses in our study demonstrated that gross-total resection had a better 10-year DFS and10-year OS than subtotal resection, gross-total resection, or no surgery. The exact role of adjuvant radiation therapy in LGG is not clear.

There are two important questions about optimal radiation dose and immediate or delayed radiation therapy. There have been two randomized clinical trials to answer these questions. The first trial was performed by the European Organisation for Research and Treatment of Cancer (EORTC)-22844 to determine the optimal radiation dose in LGG. In that study, 379 LGG patients were randomized to receive either adjuvant radiation therapy with 45 Gy in 25 fractions (low dose group) or 59.4 Gy in 33 fractions (high dose group). The five-year OS rates were 58% for low-dose and 59% for high-dose radiation therapy. There was not any significant difference between the two groups, but neurotoxicity was greater in the high-dose group (12). The currently-accepted treatment for radiation therapy is a

total dose of 50-54 Gy in 1.8 Gy per fraction to the tumor bed with a 1- to 2-cm safe margin in LGG patients. In our study, all 110 patients were treated with a total dose of 54 Gy in 1.8 Gy per fraction to the tumor bed with 1- to 2-cm safe margins. The second randomized clinical trial to determine the timing of the optimal radiation therapy in LGG was the EORTC-22845 trial. LGG patients were randomized to adjuvant radiation therapy or delayed radiation therapy groups. Based on the results of this study, a better 10-year DFS was observed in the adjuvant radiotherapy group, this group did not have a better 10-year OS in the multivariate analyses (13).

In our study, 99 patients (90%) received immediate, post-operative radiation therapy, whereas 11 patients (10%) received radiation therapy at progression. Likewise, in our study, adjuvant radiotherapy had a better 10-year DFS than radiation therapy at progression in both the univariate and multivariate analyses, but it did not have a better 10-year OS in either analysis. Vildan Kaya and colleagues investigated 55 LGG patients and demonstrated that patient who were younger than 40 and had aggressive surgical resection had a better 10-year OS advantage both in single-variable analyses and multivariate analyses (14). The findings of our study were consistent with their findings in that our study also showed that age less than 40 and aggressive surgical resection had a better 10-year OS advantage both in univariate analyses and multivariate analyses. In addition, we demonstrated that gross-total resection, tumor size< 5cm, age below 40, and the presence of oligodendroglioma resulted in a better 10-year DFS both in univariate analyses and multivariate analyses. Bauman and colleagues showed that nonastrocytoma subtype, tumor size, and younger age were associated with a better 10-year OS in multivariate analysis (15). Likewise, our study showed that age below 40, tumor size <5 cm, oligodendroglioma histology (nonastrocytoma histology), and gross-total excision were favorable prognostic factors. Youland and colleagues investigated 852 LGG patients during the past 50 years and showed that younger age, oligodendroglioma histology (nonastrocytoma histology), small tumor size, and gross total resection resulted in improved 10-year OS in multivariate analysis (16). In that study, the 10-year OS rate was between 33 and 47%. Our study showed that the 10-year OS rate was 28% in LGG patients. The lower percentage of LGG patients (16.4%) who received gross total resection can explain the worse 10-year OS rate in our study. We also showed that 10-year DFS rate was 23%, but Youland et al. did not report a value for 10-year DFS rate. We considered that gross-total resection, tumor size<5 cm, age below 40, and the presence of oligodendroglioma were the most important clinical-pathological prognostic factors in low-grade glial tumors.

5. Conclusions

We concluded that gross-total resection, tumor size<5 cm, age below 40, and the presence of oligodendroglioma provided better 10-year DFS and 10-year OS rates, both in univariate analyses and multivariate analyses. We also proved that a KPS value greater than 70 indicated better 10-year DFS and 10-year OS rates in univariate analyses, but this value did not provide any advantage in the multivariate analyses. We demonstrated that adjuvant radiotherapy had a better 10-year DFS rate both in univariate and multivariate analyses, but it did not have a better 10-year OS rate in either the univariate analyses or the multivariate analyses. It seems that to achieve the maximum benefit of the treatment for patients with LGG, we should refer these patients, especially the younger patients, to experienced neuro-oncology centers because these centers can achieve the maximal safe resection of the tumor and then apply adjuvant 3D radiation therapy instead of just doing a biopsy.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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