Clinical and Pathologic Features and Prognostic Factors for Recurrent Gliomas

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■ OBJECTIVE: **To explore related factors that influence time to recurrence and prognosis of gliomas.**

■ METHODS: **A retrospective analysis of pathologic and clinical data of patients with glioma who underwent surgery for the first time and had a recurrence between 2009 and 2018 in West China Hospital was performed. Clinical characteristics of patients were reviewed, and survival analysis was performed to identify prognostic factors for the recurrent time. Molecules with differential changes in the paired samples were included in the survival analysis.**

■ RESULTS: **A total of 84 patients met our inclusion requirements and were included in the study; other related factors were also considered in detail in the integrated analysis. Significant differences among O^6-methylguanine-DNA methyltransferase (positive/negative), isocitrate dehydrogenase 1 (positive/negative), and Ki-67 were determined by statistical analysis of paired samples ($P = 0.013$, $P = 0.014$, $P = 0.017$). Univariate analysis demonstrated that Ki-67 (low expression, medium expression, high expression), initial World Health Organization grade (low or high), tumor side (left, right, middle), age (≥50 years, <50 years), and extent of resection were significantly correlated with time to recurrence (log-rank $P = 0.008$, $P < 0.001$, $P = 0.015$, $P < 0.001$, $P = 0.001$). Multivariate analysis results showed that Ki-67 lower expression (hazard ratio [HR] = 0.585, 95% confidence interval [CI] = 0.146–2.336, $P = 0.448$), medium expression (HR = 0.256, 95% CI = 0.084–0.784, $P = 0.017$), and high expression (HR = 1 as a reference) together with the initial World Health Organization grade (HR = 0.148, 95% CI = 0.029–0.749, $P = 0.021$) were independent predictive factors for glioma recurrence.**

■ CONCLUSIONS: **This comprehensive analysis revealed that initial World Health Organization grade and Ki-67 proliferative index were independent prognostic factors that predict the time to recurrence of glioma in patients after first surgery.**

INTRODUCTION

Glioma is a common malignant tumor originating from central glial cells and has devastating effects.[1-4] Many treatment interventions have previously been proposed for the management of patients with glioma, such as microsurgery, 5-aminolevulinic acid fluorescence-guided surgery, laser ablation, intraoperative imaging and navigation, chemotherapy, radiotherapy, and other comprehensive interventions meant to improve the prognosis of gliomas.[1,5,6] Although there are many treatment options for glioma, their therapeutic efficacy is still unsatisfactory, as almost all gliomas recur.[7-9] In particular, high-grade gliomas are known to recur more frequently, especially grade III and IV categories according to the World Health Organization (WHO) pathologic grade. According to previous studies, the time to recurrence varies based on the pathologic grade.[10] Numerous factors can affect the prognosis and recurrence. Thus, we conducted this study to explore the factors related to time to recurrence by analyzing the clinical characteristics, molecular difference, and pathologic data of patients.

MATERIALS AND METHODS

Patient Selection

This is a retrospective study of collected data. During the period from June 2009 to January 2018, 1486 patients underwent surgery

Key words
- Glioma
- Ki-67
- Prognostic factors
- Recurrent time

Abbreviations and Acronyms
CI: Confidence interval
EOR: Extent of resection
HR: Hazard ratio
IDH: Isocitrate dehydrogenase
MGMT: O^6-Methylguanine-DNA methyltransferase
WHO: World Health Organization

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Citation: World Neurosurg. (2019) 128:e21-e30.
https://doi.org/10.1016/j.wneu.2019.02.210

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

and had gliomas diagnosed through histopathologic analysis at West China Hospital. All medical data of patients were stored in the computers in our center. A retrospective study was undertaken for 42 paired patients with glioma (initial and recurrent) archived in the Department of Neurosurgery of West China Hospital, Sichuan University. All data were extracted directly from the database (Figure 1). We computerized our data, and 42 paired patients met the following inclusion criteria: 1) The intracranial lesion was first discovered and surgically treated immediately in our hospital, and the postoperative pathologic examination confirmed the presence of glioma; a second operation was performed immediately on finding the recurrence of glioma. 2) The diagnosis of glioma was confirmed by at least 2 pathologists. 3) All data, including clinical characteristics, medical records, pathologic data, postoperative follow-up data, and preoperative and postoperative imaging, were available. 4) The patients were ≥18 years old. The following patients were excluded from the study: patients who underwent biopsy; patients who underwent a second operation due to other intracranial diseases; patients with other organ tumors. These patients were excluded because these factors could affect the survival and time to recurrence. Ultimately, 84 patients divided into 42 pairs were included.

Data Extraction

Patient demographics (sex, age), clinical characteristics (tumor size, tumor side, infiltrated site, initial WHO grade, recurrent time, Ki-67 variation), extent of resection (EOR), treatments after the first surgery (radiotherapy, chemotherapy, radiotherapy and

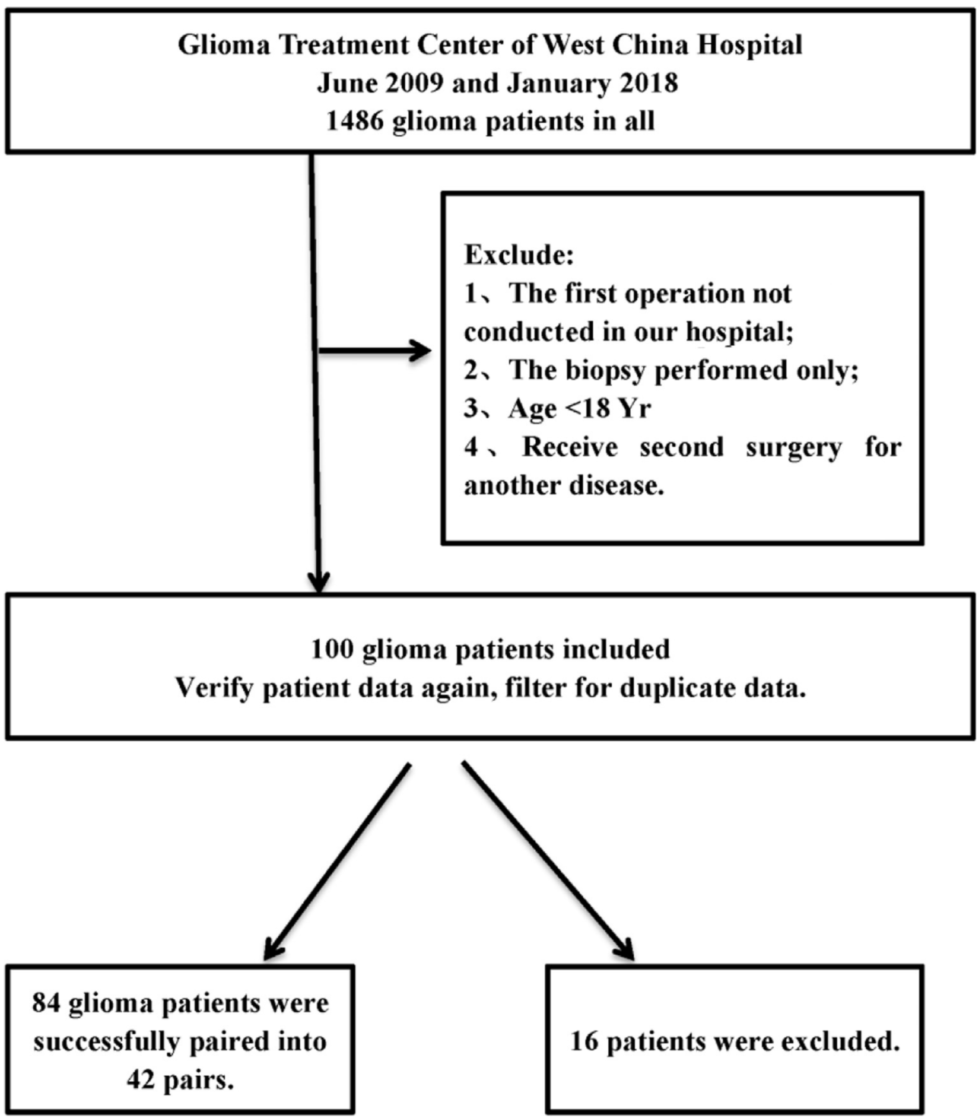

Figure 1. Procedure for selection of the 42 paired samples for this study.

Table 1. Characteristics of Patients

Characteristic	Value	Quantity (%)
Sex		42 (100)
Male	26 (61.9)	
Female	16 (38.1)	
Age, years		42 (100)
Median	37.5	
Range	18–80	
Tumor size		42 (100)
<3.5 cm	11 (26.2)	
≥3.5 cm	31 (73.8)	
EOR		42 (100)
Total resection	31 (73.8)	
Subtotal resection	11 (26.2)	
Tumor side		42 (100)
Right	24 (57.1)	
Left	17 (40.5)	
Midline	1 (2.4)	
Infiltrated part		41 (97.6)
Single	18 (42.9)	
Multiple	23 (54.7)	
Initial WHO grade		41 (97.6)
Low	15 (35.7)	
High	26 (61.9)	
Recurrent time, months		42 (100)
Median	19.35	
Range	3–100	
Treatment after first surgery		42 (100)
RT	2 (4.8)	
Chemo	9 (21.4)	
RT+Chemo	17 (40.5)	
None	14 (33.3)	
Ki-67 variation		24 (57.1)
<0.1	10 (23.8)	
≥0.1	14 (33.3)	

Values are reported as number (%) except for age and time to recurrence, which are reported as median and range.
EOR, extent of resection; WHO, World Health Organization; RT, radiotherapy; Chemo, chemotherapy.

chemotherapy, none), and time to recurrence were extracted for data analysis. During data analysis, the age of the patients was divided into 2 groups: <50 years and ≥50 years. The proliferation of Ki-67 was classified into 3 groups: Ki-67 <0.1, 0.1 ≤ Ki-67 <0.3, and Ki-67 ≥0.3.[11,12] The time to recurrence was calculated as the difference between the 2 operations (first and second). Tumor infiltration sites were obtained from the medical records or magnetic resonance imaging or computed tomography scans, and the EOR was judged from postoperative computed tomography or magnetic resonance imaging. The surgical records were verified by an experienced surgeon as a reconfirmation of the EOR. Pathologic immunohistochemistry data were obtained from the Pathology Information System and interpreted by 2 senior pathologists. Our focus was on the expression of the following biomarkers: Ki-67, O^6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase (IDH) 1, IDH2, P53, ATRX, and glial fibrillary acidic protein. In addition, changes between the paired samples were explored to determine the relationships between the biomarkers, clinical features, and time to postoperative recurrence.

All statistical analyses were performed using IBM SPSS Version 23.0 software (IBM Corporation, Armonk, New York, USA). Kaplan-Meier estimation was performed to identify the prognostic factors for time to recurrence, whereas a log-rank test was conducted to compare the groups. Cox regression analysis was performed to determine the predictive factors for recurrence. Hazard ratios (HRs) with 95% confidence intervals (CIs) were evaluated. The significance level was set at $P < 0.05$.

RESULTS

This study retrospectively evaluated the clinical records of 42 paired patients. Medical records, picture archiving and communication system imaging data, clinical characteristics, and pathologic reports were also evaluated. Median patient age was 37.5 years (range, 18–80 years), female-to-male ratio was 1:1.63 (16:26). The median time to recurrence was 19.35 months (range, 3–100 months) (Table 1). All details of the 42 (100%) patients, including sex, age, tumor size, tumor side, EOR, time to recurrence, and treatment after first surgery, were available. However, details of Ki-67 variation, WHO grade, and infiltrated sites were available only in 24 (57.1%), 41 (97.6%), and 41 (97.6%) patients, respectively (Table 1).

We observed that the expression of Ki-67 was significantly different between the initial operation group and the recurrence group. In addition, we found that the expression of MGMT and IDH1 was increased in the recurrence group compared with the initial group. The proportion of IDH1 and MGMT expression in the paired group varied from 11.9% to 50% and 20.6% to 47.1%, respectively. The difference was statistically significant ($P = 0.014$, $P = 0.013$). We also noted that there is a differential expression of IDH2, ATRX, P53, and glial fibrillary acidic protein between the 2 groups. However, there was no statistical significance (Table 2).

To explore the factors influencing the time to recurrence, the patient's sex, age, molecular expression (Ki-67, IDH1, MGMT), infiltrated site, tumor side, tumor size, treatment after first surgery, initial WHO grade, and EOR were calculated. Univariate analysis performed using Kaplan-Meier survival analysis and log-rank test showed that the tumor side, Ki-67 index, initial WHO grade, age (≥50, <50), and EOR were significantly associated with the time of glioma recurrence ($P < 0.05$) (Tables 3 and 4 and Figures 2–8). The time of glioma recurrence was not associated with sex, MGMT, IDH1, infiltrated part, tumor size, treatment

Table 2. Molecular Data of Paired Samples of Included Gliomas

Molecular Marker	First Surgery	Second Surgery	*P* Value
IDH1			0.014*
+	5 (11.9)	17 (50)	
−	21 (50)	15 (44.1)	
IDH2			0.269
+	1 (2.9)	0	
−	13 (38.2)	18 (52.9)	
ATRX			0.359
+	10 (29.4)	16 (47.1)	
−	2 (5.9)	8 (23.5)	
MGMT			0.013*
+	7 (20.6)	16 (47.1)	
−	11 (32.4)	6 (17.6)	
P53			0.759
+	20 (58.8)	26 (76.5)	
−	2 (5.9)	3 (8.8)	
GFAP			0.351
+	24 (70.6)	34 (100)	
−	10 (29.4)	0	
Ki-67			0.017*
<0.1	10 (29.4)	4 (11.8)	
≥0.1, <0.3	6 (17.6)	11 (32.4)	
≥0.3	7 (20.6)	17 (50)	

All values are reported as number (%).
IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine-DNA methyltransferase; GFAP, glial fibrillary acidic protein.
*$P < 0.05$.

after first surgery, and Ki-67 variation ($P > 0.05$). Multivariate analyses revealed that Ki-67 index and initial WHO grade were independent risk factors for recurrence of gliomas (**Tables 3–5** and **Figure 9**).

DISCUSSION

Glioma is a common malignant tumor of the central nervous system that originates from central glial cells. It accounts for approximately 27% of all central nervous system malignancies and has a poor prognosis with a high recurrence rate.[3] Although several comprehensive therapies are available to combat gliomas, the outcome is dismal.[13,14] Why does glioma recur, and what are the key factors that affect the recurrent time of glioma? These have always been controversial issues associated with glioma. Moreover, how to treat glioma has been a longstanding challenge.[1] To better understand the factors related to the recurrence of glioma, we compared and analyzed the clinical and pathologic data of 42 patients who had 2 operations.

Table 3. Univariate Analysis for Recurrent Time

Variable	Recurrent Time (Months)	χ^2	*P* Value
Sex		0.491	0.483
Male	17.7		
Female	19.6		
Tumor size		1.203	0.273
<3.5 cm	21.3		
≥3.5 cm	17.7		
Tumor side		8.425	0.015*
Right	19.6		
Left	19.1		
Midline	4.7		
Infiltrated part		0.002	0.968
Single	17.4		
Multiple	19.6		
Initial WHO grade		18.476	<0.001*
Low	29.1		
High	14.6		
Treatment after first surgery		2.075	0.557
RT	14.9		
Chemo	22.3		
Both	19.1		
None	15.5		
Ki-67		9.652	0.008*
<0.1	21.9		
≥0.1,<0.3	19.0		
≥0.3	8.6		
Ki-67 variation		1.462	0.227
<0.1	17.4		
≥0.1	12		
MGMT			
+	19.0	1.112	0.292
−	11.1		
IDH1			
+	21.9	1.233	0.267
−	14.6		

WHO, World Health Organization; RT, radiotherapy; Chemo, chemotherapy; MGMT, O^6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase.
*$P < 0.05$.

Age and Sex

In our study, there were significantly more male patients (61.9%) than female patients (38.1%), and male patients were found to have a shorter recurrence time than women (17.7 months vs. 19.6 months). Patients ≥50 years old with the same level of glioma had

Table 4. Univariate Analysis for Recurrent Time

Variable	Recurrent Time (Months) Low Grade	High Grade	χ^2	*P* Value
Age, years			12.555	<0.001*
≥50	22.8	6.8		
<50	29.1	15.5		
EOR			10.224	0.001*
Total resection	34.5	15.5		
Subtotal resection	27	8.6		

EOR, extent of resection.
*$P < 0.05$.

a shorter recurrence time than patients <50 years old (22.8 months vs. 6.8 months, 29.1 months vs. 15.5 months). However, our study found that sex and age were not independent prognostic factors that influenced the time to recurrence after the first operation. This is substantially different from previous studies, which have claimed that age and sex are important factors affecting survival of patients.[4] Younger patients tended to have a better prognosis compared with older patients,[15-18] and women had a better prognosis than men.[16] Similar to the study by Yang et al.,[18] sex was not a significant factor influencing the prognosis of patients. In our study, we found that age was an important factor affecting the recurrence of glioma, and sex was not a main factor affecting the time to recurrence. This is inconsistent with most of the previous studies, which claimed that age is an important factor that affects the prognosis of glioma patients. This may be due to the existence of selection bias in our study and the nature of samples.

Tumor Size and EOR

The extent of tumor resection is partially dependent on the size of the tumor.[19] At the present time, surgery, radiotherapy, and chemotherapy are the mainstream treatments for glioma[19,20] and are significantly associated with prolonged survival and quality of

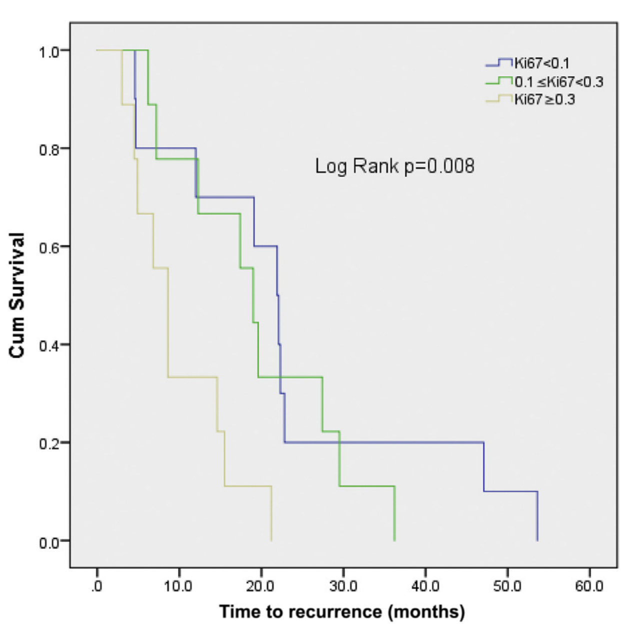

Figure 2. Relationship between Ki-67 expression (Ki-67 <0.1, 0.1 ≤ Ki67 <0.3, and Ki67 ≥0.3) and survival outcome ($P = 0.008$). Cum, cumulative.

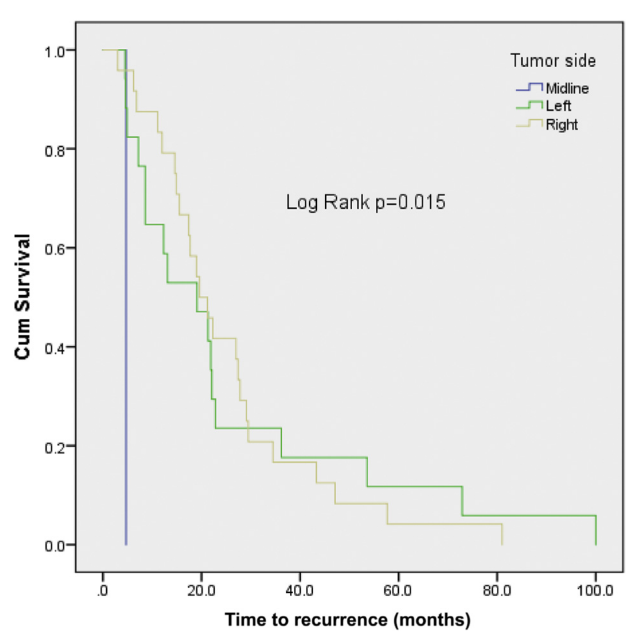

Figure 3. Relationship between tumor side (midline, left, right) and survival outcome ($P = 0.015$). Cum, cumulative.

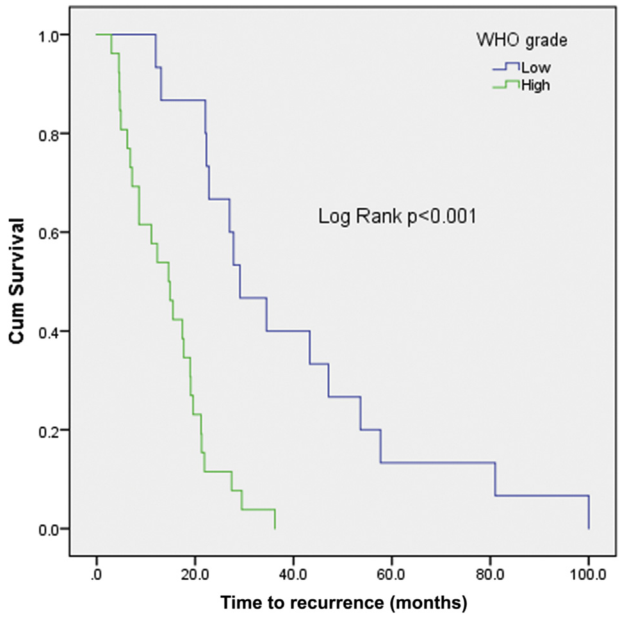

Figure 4. Relationship between initial World Health Organization grade (low, high) and survival outcome ($P < 0.001$). WHO, World Health Organization; Cum, cumulative.

life of patients.[21] In some cases, it is difficult to achieve the desired EOR. For instance, larger tumors require more invasive surgery making removal more difficult. However, when combined with chemotherapy/radiotherapy, greater EOR lowers the tumor burden leading to a better prognosis and longer time to recurrence.[5,10] However, this is inconsistent with the conclusions of our study, as our results show that EOR was a significant, but not an independent, factor affecting recurrence. This may be due to the retrospective nature of this study, which carries

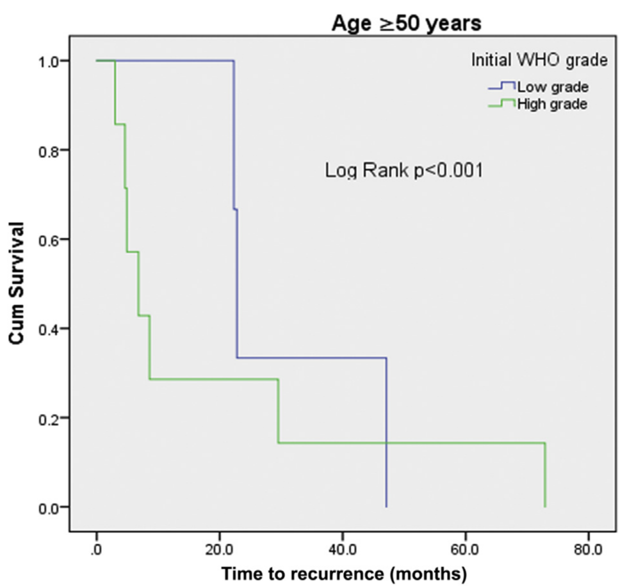

Figure 5. Relationship between age ≥50 years and survival outcome ($P < 0.001$). WHO, World Health Organization; Cum, cumulative.

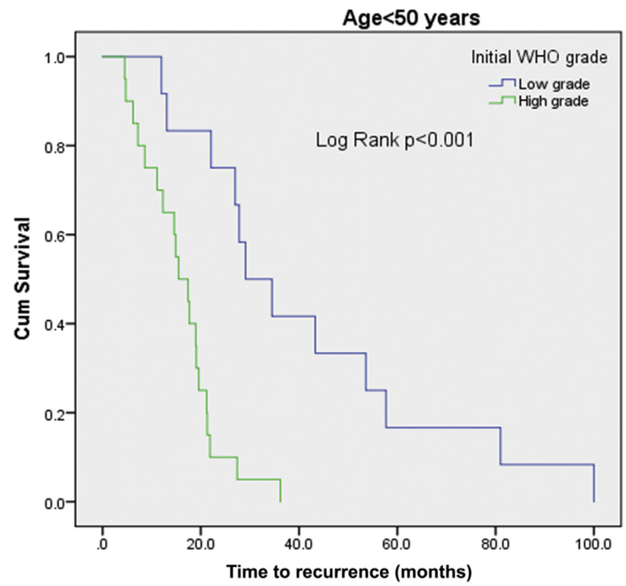

Figure 6. Relationship between age <50 years and survival outcome ($P < 0.001$). WHO, World Health Organization; Cum, cumulative.

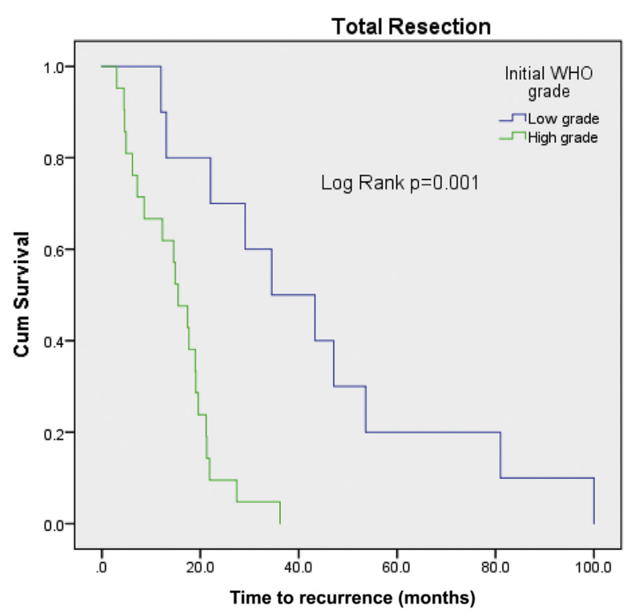

Figure 7. Relationship between total resection and survival outcome ($P = 0.001$). WHO, World Health Organization; Cum, cumulative.

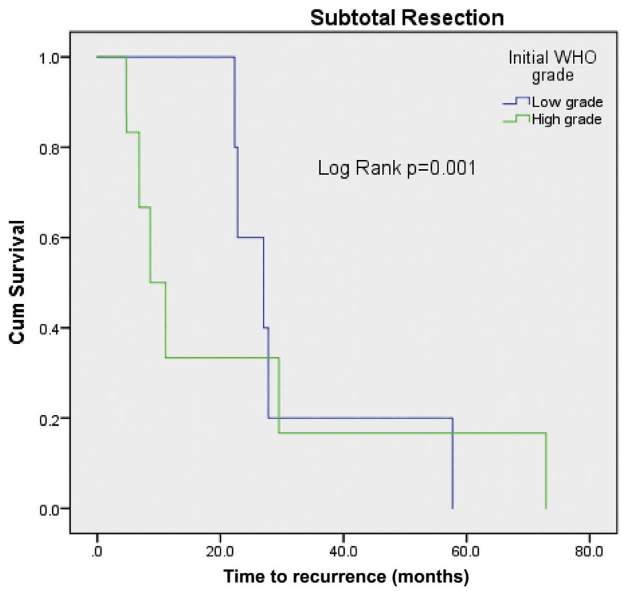

Figure 8. Relationship between subtotal resection and survival outcome ($P = 0.001$). WHO, World Health Organization; Cum, cumulative.

selective bias, or the presence of more invasive sites in the entire group. Moreover, the differences in EOR and recurrent time between different tumor grades may affect the accuracy of the results. As demonstrated by D'Amico et al.,[5] neurosurgeons must consider the balance between EOR and preservation of neurologic function.

Molecular Markers and Pathologic Grade

Based on the studies performed in the last 2 decades, several molecular biomarkers (e.g., IDH1, IDH2, MGMT) have been identified to be significantly associated with the prognosis of patients with glioma.[5] These biomarkers have been incorporated into the field of brain tumors and were used in the WHO 2016 classification of central nervous system tumors.[22] IDH is a key rate-limiting enzyme in the Krebs cycle.[23] IDH mutation is an independent predictor of good prognosis in patients. Indeed, patients with IDH mutation have a longer overall survival and progression-free survival. Moreover, IDH1 has a significant correlation with the glioma grade, whereby the mutation level of IDH1 decreases as the glioma grade increases.[13,23] The expression of IDH1 in the initial and recurrent groups increased notably (11.9% vs. 50%). The secondary gliomas are usually of higher grade and have higher IDH1 mutation, which may be the main cause.

Table 5. Multivariate Analysis for Recurrent Time

Covariates	*P* Value	HR	95% CI
Tumor side	0.621	1.254	0.511–3.074
Ki-67			
<0.1	0.448	0.585	0.146–2.336
≥0.1,<0.3	0.017*	0.256	0.084–0.784
≥0.3	1†		
WHO grade	0.021*	0.148	0.029–0.749
EOR	0.991	1.006	0.322–3.412
Age	0.391	1.590	0.551–4.587

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; EOR, extent of resection.
*$P < 0.05$.
†As reference.

MGMT is a DNA repair enzyme that can methylate the guanine nucleotide onto the DNA sequence. Methylation of MGMT promoter is associated with decreased DNA repair activity. Furthermore, methylation of the promoter decreases the DNA repair caused by chemotherapeutic agent–induced alkylation.[13,24] Therefore, MGMT can be used as a prognostic marker for patients with glioma.[13,24,25] In our study, we found that MGMT methylation status increased with tumor progression. This is inconsistent with a previous study in which the MGMT methylation status was found to be low in the recurrent gliomas.[26] We suspect that the treatment after initial surgery would be the main cause of MGMT methylation. Hence, the relationship between glioma grade and MGMT methylation remains controversial.

Ki-67 regulates the cell cycle and can directly influence cell proliferation and hence tumor progression and metastasis. Ki-67 is not expressed in normal brain tissue, but it is highly expressed in glioma cells. The higher the Ki-67 positive marker index, the higher the degree of malignancy.[27] In this study, we found a significant difference in the expression of IDH1, Ki-67, and MGMT between the recurrent pathologic specimens and the primary pathologic specimens ($P < 0.05$). Specifically, there was a significant difference in the expression of IDH1 and MGMT between the primary and recurrence groups, in which the IDH1 mutation was 11.9% versus 50% ($P = 0.014$) and the methyl ratio of MGMT was 20.6% versus 47.1% ($P = 0.013$). Additionally, there was a difference in the expression of Ki-67 at the 3 expression levels (Ki-67 <0.1, $0.1 \leq$ Ki-67 <0.3, Ki-67 ≥ 0.3). The proportions of Ki-67 in the initial group compared with the recurrence group were 29.4% versus 11.8%, 17.6% versus 32.4%, and 20.6% versus 50% ($P = 0.017$) (Table 2).

Univariate analysis showed that patients with MGMT methylation and the IDH1 mutation had longer time to recurrence, which is consistent with findings from previous studies (Table 3).[13,23] However, there was no significant statistical difference, which may be due to the limited number of pathologic specimens and selection bias. In our paired sample study, the Ki-67 index was significantly different between the 2 groups and was statistically significant. The amount of change in the Ki-67 index is related to the recurrence time of glioma. The greater the changes, the shorter the recurrence time. Multivariate analysis showed that the Ki-67 index was an independent prognostic factor affecting the time to relapse. This is consistent with previous studies, which reported that higher glioma grades are associated with high proliferative activity.[27] Therefore, for patients with higher Ki-67 expression and higher tumor grade, a maximal resection should

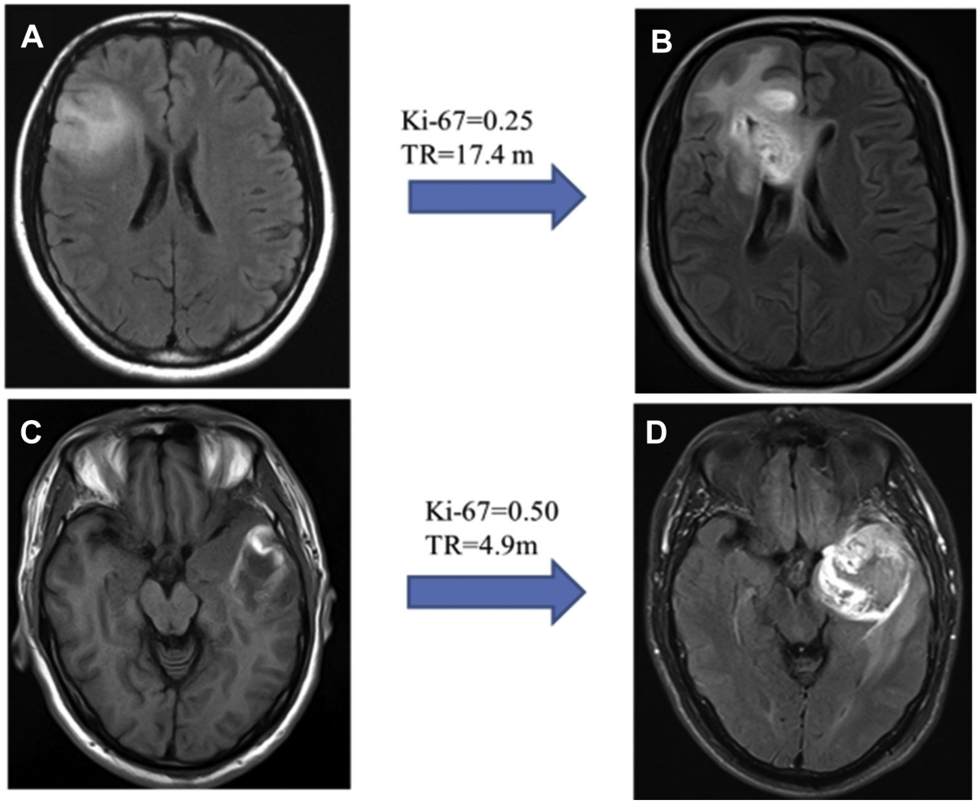

Figure 9. Effects of different Ki67 proliferation on the recurrence time of glioma of the same grade. Preoperative imaging data of 2 patients (**A**–**D**, respectively) diagnosed with the same low-grade glioma. TR, time to recurrence.

be performed to prevent tumor cell proliferation, reduce the tumor burden, and prolong the time to recurrence.[5] The pathologic grade of the tumor is an independent risk factor for tumor recurrence and is determined by the degree of malignancy of the tumor itself. In this study, we observed that the Ki-67 variation and index were associated with the WHO grade of the tumor. We also found that the higher the expression of Ki-67, the faster the recurrence time in the same-grade gliomas (Figure 9). Therefore, we suspect that the enhancement of tumor erosion ability by Ki-67 may explain these observations. Moreover, the therapeutic interventions (including radiotherapy and chemotherapy) and the tumor scavenging effect of the autoimmune system promote tumor cell proliferation to produce therapeutic tolerance. This may lead to recurrence of tumors.

Infiltration Sites and Tumor Side

Our results suggest that the side of tumor is a significant predictor of tumor recurrence. However, previous studies have claimed that there is no correlation between tumor recurrence and tumor side.[4,28,29] Interestingly, we found that the median recurrence time of left and right cerebral gliomas is almost the same (Table 3). We suspect that this may be caused by the inclusion bias in the sample. Moreover, the midline involvement is a predictor of transformation and recurrence, which is the result of difficulty to achieve surgical total resection.[10,30] Generally, the presence of many infiltrating sites translates to a higher degree of tumor malignancy and hence a high probability of malignant transformation. This will indirectly lead to a shorter recurrence time.[31] However, we did not obtain such a conclusion in this study.

Treatment After First Surgery

Currently, surgery is recommended for the treatment of gliomas. In addition, a combination of radiotherapy and chemotherapy after surgery is more effective compared with the single application of either of these therapies or no treatment at all.[6,32,33] In our study, for high-grade glioma, radiotherapy consisted of fractionated focal irradiation at a dose of 1.8–2 Gy per fraction for a total of 54–60 Gy. For low-grade glioma, the radiation dose consisted of fractionated focal irradiation in daily fractions of 1.8–2 Gy per fraction for a total of 45–54 Gy. Chemotherapy consisted of temozolomide at a dose of 150–200 mg/m^2 for 5 days during each 28-day cycle. Chemoradiotherapy consisted of temozolomide at a dose of 75 mg/m^2 per day, given 7 days per week for 6 weeks from the first day of radiotherapy until the last day of radiotherapy. Then the patients received standard chemotherapy up to 6 cycles. In this study, patients treated with radiotherapy alone had a shorter recurrence time than untreated patients, probably because of the increased tumor mutations due to radiotherapy. Moreover, in a subset of patients, chemotherapy and radiotherapy may increase the risk of mutations. This can also explain the fact that some patients have a shorter time to recurrence when undergoing radiotherapy.[31] However, there is no statistical significance between the treatments after first surgery.

Study Strengths and Limitations

The main strength of this study is that we explored the prognostic factors affecting the time to recurrence. In particular, the molecular variation and expression and the clinical characteristics were evaluated. However, the study has some limitations. First, owing to the small sample size, there could be some selection bias, and some data may not reflect the actual situation in the larger population. Second, as an independent risk factor affecting postoperative recurrence, Ki-67 requires further exploration to determine how the expression rate of Ki-67 is related to the pathologic grade of the patient to accurately predict the time to recurrence. Third, further studies are recommended to investigate the relationship among the expression of Ki-67, the expression patterns of biomarkers, and time to relapse after surgery.

CONCLUSIONS

In patients with glioma, the key factors affecting the time to recurrence are the level of Ki-67 expression and the pathologic grade. With respect to treatment of glioma, comprehensive therapy should be given regardless of the tumor level. The maximum degree of safe resection should be performed to reduce the tumor burden to the patient. Additionally, assessment of the pathologic molecular markers of gliomas in postoperative patients should be performed to facilitate individualized comprehensive treatment. In particular, tumor cell proliferation activity should be reduced in postoperative patients to prolong the time to recurrence of glioma.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 29 October 2018; accepted 23 February 2019

Citation: World Neurosurg. (2019) 128:e21-e30.
https://doi.org/10.1016/j.wneu.2019.02.210

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

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