European Review for Medical and Pharmacological Sciences 2023; 27: 10481-10498

Clinical characteristics and prognostic factors of solitary and multiple adult gliomas: a retrospective study based on propensity score matching

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Abstract. – OBJECTIVE: This study aims to compare the survival and prognostic factors in patients with solitary gliomas to those with multiple to improve the understanding of multiple gliomas and investigate their heterogeneous dissemination pathways.

PATIENTS AND METHODS: Data on 358 patients diagnosed with adult gliomas confirmed by postoperative pathology were retrospectively collected and analyzed. The clinical characteristics, survival rates and prognosis of patients were analyzed by propensity score matching (PSM).

RESULTS: Between the two groups, statistically significant differences were identified in multiple general clinical characteristics, including age, pathological grade, lesion location, *1p19q* co-deletion, *IDH1* mutation, *MGMT* promoter methylation expression rate, *p53* mutation and *NF1* mutation ($p<0.05$). Before PSM, the mOS for patients with multiple gliomas was shorter than that for those with solitary ($p=0.0045$). Multivariate Cox regression analysis revealed that age, pathological grade IV, and absence of concurrent chemotherapy were significant risk factors affecting OS. Pathological grade IV, ki-67 expression range of 25-50%, and absence of concurrent chemotherapy were identified as risk factors for PFS. After PSM, the prognostic factors associated with OS were age and concurrent chemotherapy, while those associated with PFS were ki-67 expression range of 50-75% and lesion located in the right frontal lobe ($p<0.05$).

CONCLUSIONS: The prognosis for multiple gliomas is extremely poor, which is related to the fact that the most common pathological types are glioblastomas and the surgical procedure is challenging. Concurrent chemotherapy and radiotherapy are the strongest protective prognostic factors, and the differences in their molecular pathology expression compared to solitary gliomas remain for further investigation.

Key Words:
Multicentric gliomas, Multifocal gliomas, Gliomas, Prognostic analysis, Propensity score matching.

Introduction

Gliomas are the most common primary brain tumors, with multiple gliomas accounting for about 0.5-20% of all cases[1]. According to their imaging aspects, multiple gliomas are subdivided into multifocal gliomas and multicentric gliomas. Multicentric gliomas were first reported by Bradley in 1880[2]. The diagnostic criteria for multicentric gliomas were proposed by Batzdorf and Malamud in 1963[3], thus distinguishing between multifocal and multicentric gliomas. At present, it is generally held that multifocal gliomas can be explained by development or dissemination through well-defined structural pathways (e.g., corpus callosum, dissemination along the cerebrospinal fluid, metastasis along the subependymal spaces, formation of satellite lesions near tumors). Multicentric gliomas have widely separated lesions, such as in both cerebral hemispheres, or cannot be explained by dissemination through the above-described structural pathways, usually defined as more than one lesion with significant enhancement on T1-weighted sequences in the brain on MRI, more than one lesion without contiguous signal changes in T2-weighted sequences and a minimum distance of 10 mm between isolated lesions[4]. The pathogenesis of multiple gliomas remains unclear. Existing studies do not suggest the diversity of lesions as an independent, influential factor for their poor prognosis. Studies on the prognosis of patients with multiple gliomas are rare, especially when survival differences consider histopathology or molecular pathology[5]. This study attempts to explore the differences between patients with multiple and solitary gliomas in terms of general information, histopathology, and molecular pathology results.

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Patients and Methods

Clinical Data

The data of 596 patients diagnosed with adult gliomas in January 2017-December 2021 at Henan Cancer Hospital were retrospectively reviewed. Among them, 358 cases using preoperative magnetic resonance imaging (MRI) and confirmed by postoperative pathology or biopsy pathology included complete molecular pathology reports (pathological classification is based on the 2016 WHO Central Nervous System Tumor Classification), and all patients underwent treatments including surgery and postoperative radiotherapy and chemotherapy. Finally, all 358 cases were enrolled. There were 264 cases with solitary gliomas, of which 94 cases with multiple gliomas were selected based on MRI results. Among the 94 cases of multiple gliomas, the incidence rate for multiple gliomas as well as the general demographic information (age and gender), molecular pathological results, and Ki67 and NF1 expression in multiple gliomas compared to those in solitary gliomas were observed, and statistically analyzed.

MRI Examination

A GE (General Electric Company, Boston, MA, USA) HD-X 3.0T MRI scan was performed with the following parameters: Repetition time (TR) = 2,000-6,000 ms, echo time (TE) = 9-99 ms, layer thickness = 5 mm, layer spacing = 0.5 mm, matrix = 320×320, field-of-view (FOV) = 240×240. The MRI contrast agent was gadoterate meglumine (Jiangsu Hengrui Pharmaceuticals Co., Ltd, Jiangsu, China) at a dose of 0.2 ml/kg with an injection flow rate of 2-4 ml/s. The images were analyzed and reported by senior radiologists and intermediate radiologists with extensive experience in diagnostic radiology.

Histopathology and Molecular Pathology Results

The expression levels of Ki67, *p53*, *NF1,* and *ATRX* were detected by immunohistochemistry, and methylation of the *MGMT* gene was detected by pyrosequencing. The detection of *IDH* and *TERT* genes was performed by DNA Sanger sequencing, and the *1p19q* deletion status was determined by the FISH method.

Treatments

A total of 318 patients received standard radiotherapy and chemotherapy regimens after surgery, while 44 patients did not receive treatment other than radiotherapy due to their physical health status. The total dose of standard radiotherapy was 60 Gy, and the dose of temozolomide (Jiangsu Tianshili Diyi Pharmaceutical Co., Ltd, Jiangsu, China) was 75 mg/m^2 orally once per day during the radiotherapy period. Chemotherapy was applied until the end of radiotherapy. Among the patients, 23 were treated with bevacizumab (Jiangsu Hengrui Pharmaceuticals Co., Ltd, Jiangsu, China) in combination with temozolomide.

Follow-up Visits

All patients were followed up after the completion of radiotherapy through the outpatient or inpatient medical record review systems or by telephone. Telephone follow-up was only conducted if the patient did not return to the hospital for the regular review. The last follow-up was in August 2022, with a total follow-up time of 5-60 months (2017.7-2022.08) and a median follow-up time of 16.6 months. Patients' overall survival (OS) was defined as the time period from diagnosis to the patient's death by any cause or to the last follow-up, while overall progression-free survival (PFS) was defined as the time interval from diagnosis to either the first radiographic progression or death. Situations such as loss to follow-up and no death by the follow-up cut-off time were defined as censoring.

Statistical Analysis

All statistical analyses in this study were performed using R.2.1 software. The measurement data were described by medians (quartiles), and the enumeration data were expressed as percentages. The *t*-test was used when the variances of continuous variables were homogeneous; otherwise, the nonparametric rank sum test was used. Categorical data were tested by the χ^2 test or Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. Univariate analysis was performed using the Cox regression model, and factors that showed differences in the univariate analysis were included in the multivariate Cox regression model. $p < 0.05$ was considered statistically significant.

Results

Comparison of General Clinical Data for Solitary and Multiple Glioma Patients

Statistically significant differences ($p < 0.05$) were identified for general clinical data, including age, pathological grade, lesion location (frontal lobe, parietal lobe or left thalamus and basal gan-

Table I. The active compounds and their properties.

Factor	[All] (N = 358)	Solitary (N = 264)	Multiple (N = 94)	*p*-overall
Gender:				1.00
Male	200 (55.9%)	148 (56.1%)	52 (55.3%)	
Female	158 (44.1%)	116 (43.9%)	42 (44.7%)	
Age	53.0 [45.0; 63.0]	51.0 [44.0;61.2]	56.0 [48.2; 63.8]	0.01
Pathological grade:				0.01
III	96 (26.8%)	60 (22.7%)	36 (38.3%)	
IV	262 (73.2%)	204 (77.3%)	58 (61.7%)	
ECOG:				0.38
1	269 (75.1%)	202 (76.5%)	67 (71.3%)	
2	89 (24.9%)	62 (23.5%)	27 (28.7%)	
Lesion location:				
Left frontal lobe	93 (26.0%)	56 (21.2%)	37 (39.4%)	<0.01
Right frontal lobe	109 (30.4%)	62 (23.5%)	47 (50.0%)	<0.01
Left parietal lobe	42 (11.7%)	14 (5.30%)	28 (29.8%)	<0.01
Right parietal lobe	40 (11.2%)	15 (5.68%)	25 (26.6%)	<0.01
Left temporal lobe	55 (15.4%)	47 (17.8%)	8 (8.51%)	0.45
Right temporal lobe	54 (15.1%)	31 (11.7%)	23 (24.5%)	0.61
Left occipital lobe	13 (3.63%)	6 (2.27%)	7 (7.45%)	0.51
Right occipital lobe	8 (2.23%)	6 (2.27%)	2 (2.13%)	1.00
Left thalamus and basal ganglia	17 (4.75%)	7 (2.65%)	10 (10.6%)	<0.001
Right thalamus and basal ganglia	17 (4.75%)	11 (4.17%)	6 (6.38%)	0.40
Corpus callosum	14 (3.91%)	9 (3.41%)	5 (5.32%)	0.53
1p19q co-deletion				0.01
Yes	48 (13.4%)	43 (16.3%)	5 (5.32%)	
No	310 (86.6%)	221 (83.7%)	89 (94.7%)	
IDH1:				<0.001
R132 mutation	74(20.7%)	54(20.5%)	20 (21.3%)	
Wild type	284 (79.3%)	210 (79.5%)	74 (78.7%)	
IDH2:				1.00
R172 mutation	2 (0.56%)	2 (0.76%)	0 (0.00%)	
Wild type	356 (99.4%)	262 (99.2%)	94 (100%)	
TERT:				<0.001
C228T mutation	45 (12.57%)	34 (12.9%)	11 (11.7%)	
C250T mutation	42 (11.73%)	30 (11.4%)	12 (12.8%)	
Wild type	271 (75.7%)	200 (75.7%)	71 (75.5%)	
ATRX:				0.04
Mutation	65 (18.2%)	55 (20.8%)	10 (10.6%)	
Wild type	293 (81.8%)	209 (79.2%)	84 (89.4%)	
MGMT:				<0.001
[0.8%]	293 (81.8%)	240 (90.9%)	53 (56.4%)	
(8%, 30%)	34 (9.50%)	10 (3.79%)	24 (25.5%)	
(30%, 60%)	24 (6.70%)	12 (4.55%)	12 (12.8%)	
(60%, 100%)	7 (1.96%)	2 (0.76%)	5 (5.32%)	
p53:				<0.001
Mutation	50 (14.0%)	50 (18.9%)	0 (0.00%)	
Wild type	308 (86.0%)	214 (81.1%)	94 (100%)	
Ki67:				0.65
[0.5%]	42 (11.7%)	30 (11.4%)	12 (12.8%)	
(5%, 25%)	124 (34.6%)	96 (36.4%)	28 (29.8%)	
(25%, 50%)	109 (30.4%)	78 (29.5%)	31 (33.0%)	
(50%, 75%)	73 (20.4%)	54 (20.5%)	19 (20.2%)	
(75%, 100%)	10 (2.79%)	6 (2.27%)	4 (4.26%)	
NF1:				<0.001
Positive	10 (2.79%)	1 (0.38%)	9 (9.57%)	
Negative	348 (97.2%)	263 (99.6%)	85 (90.4%)	

glia), *1p19q* co-deletion, *IDH1* mutation, *TERT* mutation, *ATRX* mutation, *MGMT* expression, p53 mutation and *NF1* mutation, between the two groups. Table I presents the results.

Table II. Comparison of general clinical data of multifocal and multicentric glioma patients before PSM.

Factor	[All] (N=94)	Multifocal (N=82)	Multicentric (N=12)	*p*-overall
Gender:				0.479
Male	52 (55.3%)	47 (57.3%)	5 (41.7%)	
Female	42 (44.7%)	35 (42.7%)	7 (58.3%)	
Age	56.0 [48.2; 63.8]	54.5 [47.2; 63.8]	59.5 [55.8; 64.0]	0.125
Pathological grade:				1.000
III	36 (38.3%)	31 (37.8%)	5 (41.7%)	
IV	58 (61.7%)	51 (62.2%)	7 (58.3%)	
ECOG:				1.000
1	67 (71.3%)	58 (70.7%)	9 (75.0%)	
2	27 (28.7%)	24 (29.3%)	3 (25.0%)	
1p19q co-deletion:				1.000
Yes	5 (5.32%)	5 (6.10%)	0 (0.00%)	
No	89 (94.7%)	77 (93.9%)	12 (100%)	
IDH1:				0.064
R132 mutation	20 (21.3%)	20 (24.4%)	0 (0.00%)	
Wild type	74 (78.7%)	62 (75.6%)	12 (100%)	
IDH2: Wild type	94 (100%)	82 (100%)	12 (100%)	.
TERT:				0.023
C228T mutation	11 (11.7%)	7 (8.54%)	4 (33.3%)	
C250T mutation	12 (12.8%)	10 (12.2%)	2 (16.7%)	
Wild type	71 (75.5%)	65 (79.3%)	6 (50.0%)	
MGMT:				0.912
[0.8%]	53 (56.4%)	46 (56.1%)	7 (58.3%)	
(8%, 30%)	24 (25.5%)	20 (24.4%)	4 (33.3%)	
(30%, 60%)	12 (12.8%)	11 (13.4%)	1 (8.33%)	
(60%, 100%)	5 (5.32%)	5 (6.10%)	0 (0.00%)	
Ki67:				0.888
[0.5%]	12 (12.8%)	11 (13.4%)	1 (8.33%)	
(5%, 25%)	28 (29.8%)	24 (29.3%)	4 (33.3%)	
(25%, 50%)	31 (33.0%)	27 (32.9%)	4 (33.3%)	
(50%, 75%)	19 (20.2%)	17 (20.7%)	2 (16.7%)	
(75%, 100%)	4 (4.26%)	3 (3.66%)	1 (8.33%)	
NF1:				0.014
Positive	9 (9.57%)	5 (6.10%)	4 (33.3%)	
Negative	85 (90.4%)	77 (93.9%)	8 (66.7%)	
ATRX:				0.611
Mutation	10 (10.6%)	8 (9.76%)	2 (16.7%)	
Wild type	84 (89.4%)	74 (90.2%)	10 (83.3%)	
Radiotherapy:	94 (100%)	82 (100%)	12 (100%)	
Chemotherapy:				0.590
No	8 (8.51%)	8 (9.76%)	0 (0.00%)	
Yes	86 (91.5%)	74 (90.2%)	12 (100%)	
Bevaczumab:				1.000
No	91 (96.8%)	79 (96.3%)	12 (100%)	
Yes	3 (3.19%)	3 (3.66%)	0 (0.00%)	

Among the 94 cases with multiple gliomas, there were 12 cases of multicentric gliomas and 82 cases of multifocal gliomas. Meanwhile, 14 cases involved more than two lobes, and 20 cases had lesions located in both cerebral hemispheres. As presented in Figure 1, the relationships between multiple lesions included: (1) dissemination along the white-matter tracts in 62 cases, (2) dissemination and metastasis along membranous structures such as the subependymal and small vascular spaces in 14 cases and (3) dissemination along the subarachnoid space of the meninges in 6 cases.

Comparison of General Clinical Data of Multifocal and Multicentric Glioma Patients Before Propensity Score Matching (PSM)

The factors with statistically significant differences between the two groups were TERT mutation and NF1 mutation, as shown in Table II.

After PSM

The MatchIt package in R was used to match unbalanced factors (i.e., factors with differ-

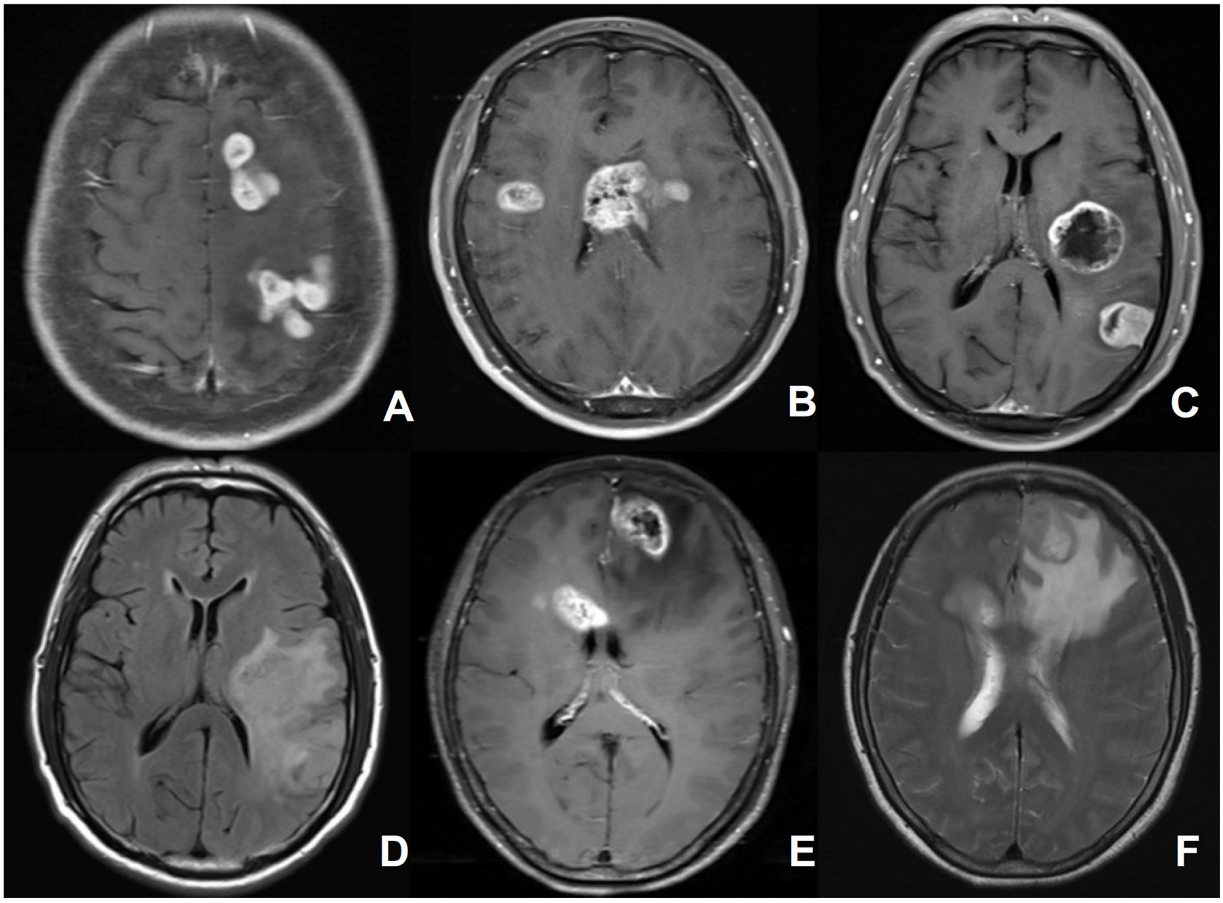

Figure 1. Possible dissemination pathways of multicentric and multifocal gliomas. **A-B**, Multicentric dissemination pathways (**C-F**), multifocal dissemination pathways.

ences) between the two groups at a 1:1 ratio. The differences between the two groups were not statistically significant after matching, as shown in Table III.

Comparison of Survival Rates for Solitary and Multiple Glioma Patients Before PSM

The median overall survival (mOS) rates for solitary and multiple glioma patients were 21.6 and 21 months, respectively, with a statistically significant difference identified by the log-rank test (p= 0.0045). The median overall progression-free survival (mPFS) rates for solitary and multiple glioma patients were 14.6 and 18 months, respectively, and the difference was not statistically significant, as determined by the log-rank test (p= 0.95). Figure 2 displays the results.

After PSM

The mOS rates for solitary and multiple glioma patients were 31.6 and 27 months, respectively, and the log-rank test suggested no statistically significant difference (p= 0.12). The mPFS rates for solitary and multiple glioma patients were 26.2 and 27 months, respectively, with no statistically significant difference identified by the log-rank test (p= 0.69). Figure 3 presents the results.

Comparison of Survival Rates for Multifocal and Multicentric Glioma Patients

The mOS rates for multifocal and multicentric glioma patients were 21 and 18 months, respectively, with no statistically significant difference identified by the log-rank test (p= 0.73). The mPFS rates for multifocal and multicentric glioma patients were 18 and 14 months, respectively, and the difference between the two groups was not statistically significant according to the log-rank test (p= 0.43). Figure 4 presents the results. PSM analysis could not be performed due to the absence of unbalanced factors between the two groups.

Table III. Comparison of general clinical data of multifocal and multicentric glioma patients after PSM.

Factor	[All] (N=6)	Multifocal (N=3)	Multicentric (N=3)	*p*-overall
Gender:				1.000
Male	3 (50.0%)	2 (66.7%)	1 (33.3%)	
Female	3 (50.0%)	1 (33.3%)	2 (66.7%)	
Age	63.8 (14.3)	62.7 (20.5)	65.0 (9.17)	0.870
Pathological grade:				0.100
III	3 (50.0%)	0 (0.00%)	3 (100%)	
IV	3 (50.0%)	3 (100%)	0 (0.00%)	
ECOG:				1.000
1	3 (50.0%)	1 (33.3%)	2 (66.7%)	
2	3 (50.0%)	2 (66.7%)	1 (33.3%)	
No 1p19q co-deletion	6 (100%)	3 (100%)	3 (100%)	
IDH1: Wild type	6 (100%)	3 (100%)	3 (100%)	
IDH2: Wild type	6 (100%)	3 (100%)	3 (100%)	
TERT: Wild type	6 (100%)	3 (100%)	3 (100%)	
MGMT:				0.400
[0.8%]	4 (66.7%)	3 (100%)	1 (33.3%)	
(8%, 30%)	2 (33.3%)	0 (0.00%)	2 (66.7%)	
p53 mutation	6 (100%)	3 (100%)	3 (100%)	
Ki67:				1.000
(5%, 25%)	3 (50.0%)	1 (33.3%)	2 (66.7%)	
(25%, 50%)	2 (33.3%)	1 (33.3%)	1 (33.3%)	
(50%, 75%)	1 (16.7%)	1 (33.3%)	0 (0.00%)	

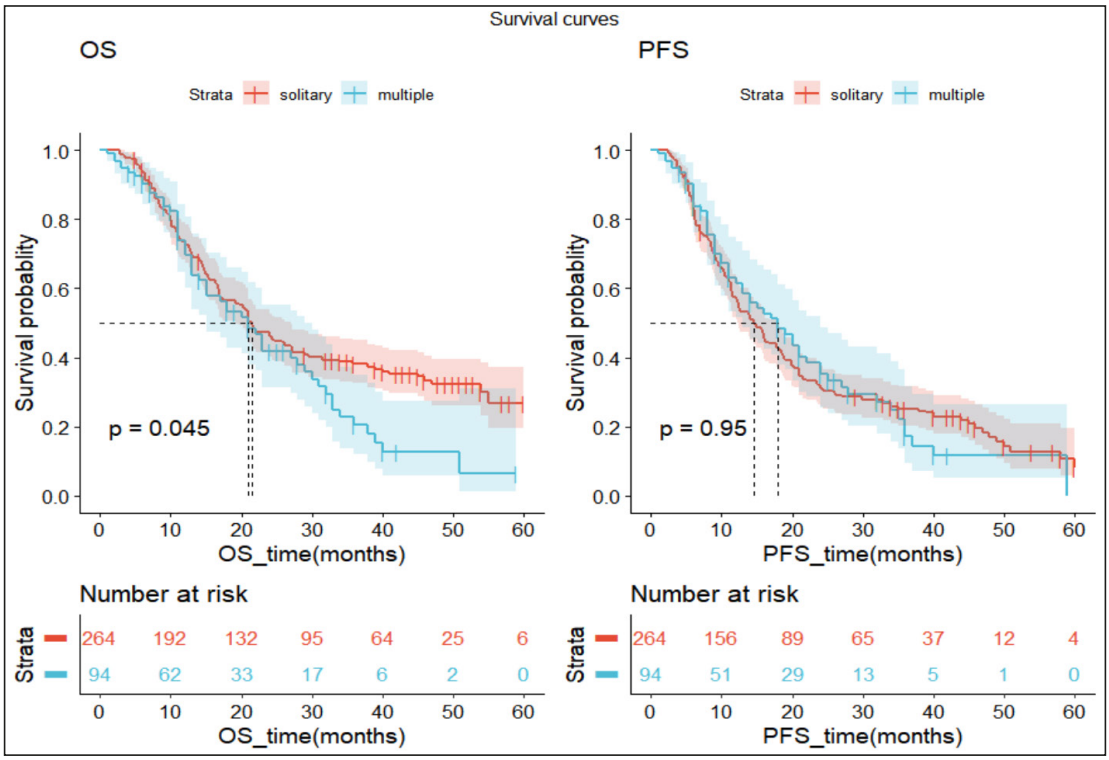

Figure 2. Comparison of survival rates of solitary and multiple glioma patients before PSM.

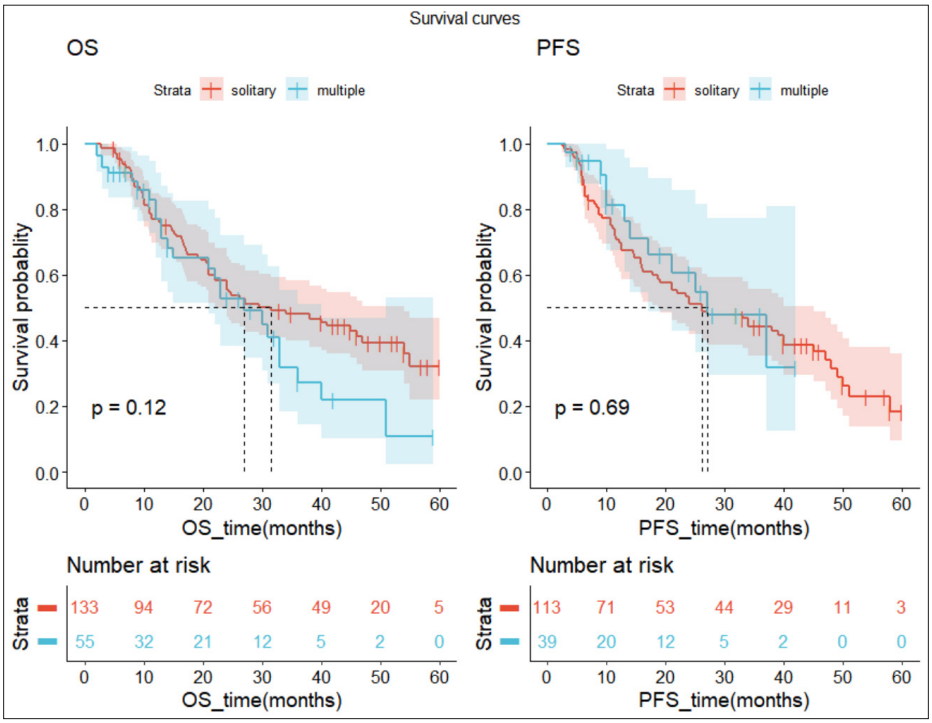

Figure 3. Comparison of survival rates for solitary and multiple glioma patients after PSM.

Cox Regression Analysis of Factors Affecting OS and PFS in Patients with Solitary Gliomas Cox Regression Analysis of Factors Affecting OS in Patients with Solitary Gliomas

Before PSM: Through univariate Cox analysis, age (HR 1.01,95% CI: 1.00-1.03), pathological grade IV (HR 5.14,95% CI: 3.05-8.65), *1p19q* co-deletion (HR 0.32, 95% CI: 0.19-0.56), Ki67 expression range of (25%, 50%] (HR 2.12, 95% CI 1.17-3.84), Ki67 expression range of (50%, 75%] (HR 2.15, 95% CI 1.15-4.03), and concurrent chemotherapy (HR 0.08 95% CI 0.05-0.13) were found to be prognostic factors influencing patients' OS. The inclusion of factors with differences identified by univariate Cox analysis for multivariate Cox regression analysis revealed that age (HR 1.02, 95% CI: 1.00-1.02) and pathological grade IV (HR 3.58, 95% CI 1.76-7.28) were risk factors for OS. Meanwhile, concurrent chemotherapy reduced the risk of death by 91% compared to scenarios without chemotherapy.

After PSM: Univariate analysis indicated that the prognostic factors associated with OS were age (HR1.03, 95 CI: 1.01-1.05) and concurrent chemotherapy (HR0.13, 95 CI: 0.05-0.32) and that the application of concurrent chemotherapy reduced the risk of death by 87%. Incorporating factors with differences in the univariate Cox analysis, a multivariate Cox regression analysis identified age (HR 1.03, 95CI: 1.01-1.05) as the prognostic risk factor associated with OS. In addition, applying concurrent chemotherapy reduced the risk of death by 83% (HR0.17, 95CI:0.07-0.42) (Table IV).

Cox Regression Analysis of Factors Affecting PFS in Patients with Solitary Gliomas

Before PSM: Pathological grade IV (HR 5.2 95% CI 3.38-7.99), *1p19q* co-deletion (HR 0.39, 95% CI 0.25-0.61), *IDH1* mutation (HR 0.26, 95% CI 0.16-0.43), *TERT* mutation (HR 2.11, 95% CI 1.41-3.15), Ki67 expression range of (25, 50%) (HR 2.39, 95% CI 1.43-4.02), and concurrent chemotherapy (HR 0.13, 95% CI 0.01-0.21) were found to be prognostic factors affecting patients' PFS by univariate Cox analysis. Multivariate Cox regression analysis, including factors with differences in the univariate Cox analysis, revealed pathological grade IV (HR 4.14, 95% CI 2.17-7.89) and Ki67 expression in the range (25, 50%) (HR 2.23, 95% CI 1.27-3.92) as

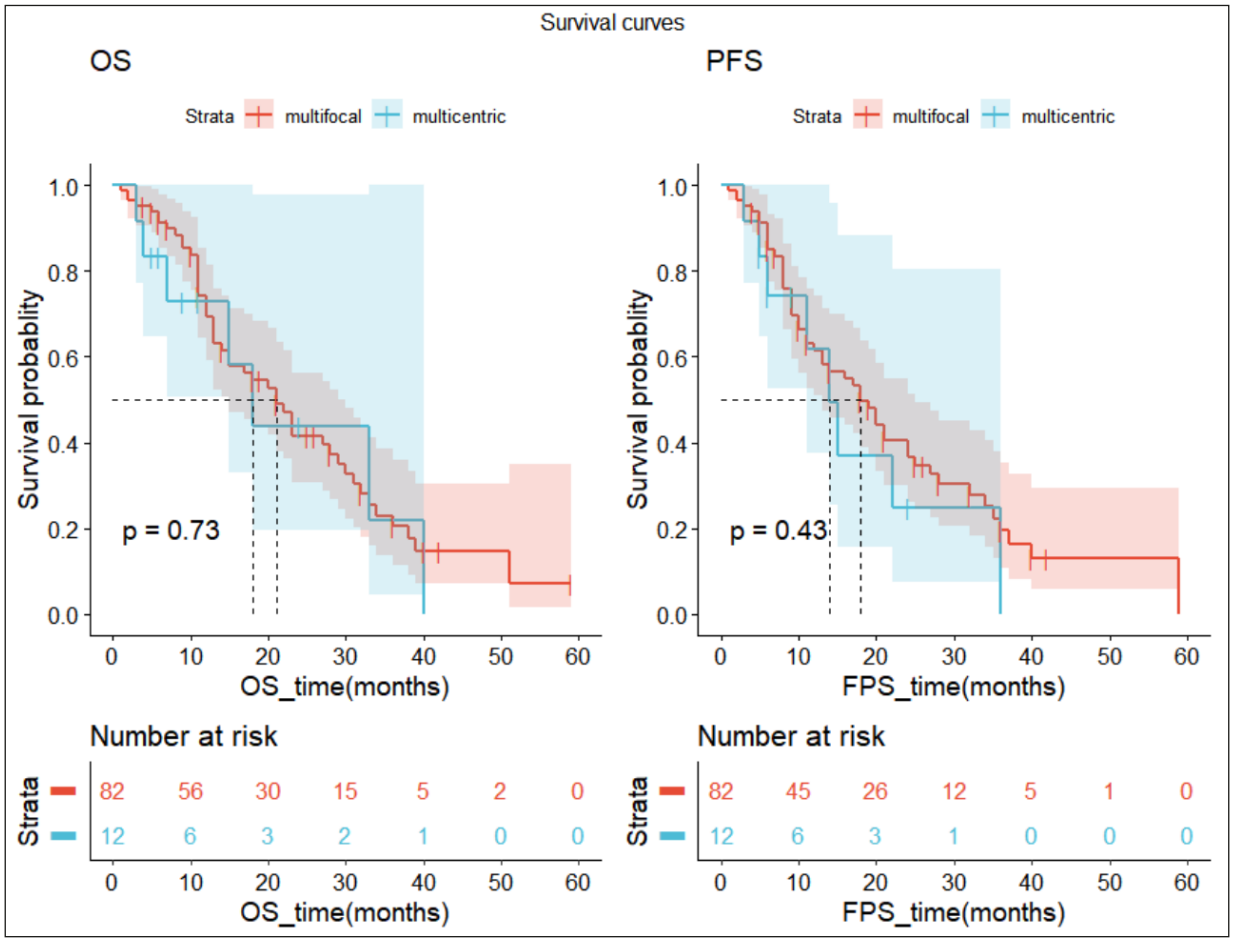

Figure 4. Comparison of survival rates of multifocal and multicentric glioma patients.

risk factors affecting PFS. Meanwhile, concurrent chemotherapy reduced the risk of death by 83% compared to cases without chemotherapy (HR0.17, 95% CI 0.10-0.27).

After PSM: The prognostic factors associated with PFS were identified to be pathological grade IV (HR 1.94, 95% CI 1.06-3.52), lesion located in the right frontal lobe (HR 1.91, 95% CI 1.06-3.42), TERT mutation (HR 3.27, 95% CI 1.35-7.93), and Ki67 expression in the range (50, 75%) (HR 3.44, 95% CI 1.26-9.38) by univariate Cox analysis. Incorporating factors with differences identified by the univariate Cox analysis in the multivariate Cox regression analysis revealed that Ki67 expression range of (50, 75%) (HR 3.98, 95% CI 1.40-11.3) and lesion location in the right frontal lobe (HR 1.86, 95% CI 1.00-3.45) were risk factors for PFS (Table V).

Cox Regression Analysis of Factors Affecting OS and PFS in Patients with Multiple Gliomas Cox Regression Analysis of Factors Affecting OS in Patients with Multiple Gliomas

Before PSM: Applying univariate Cox analysis, pathological grade IV (HR 3.38, 95% CI 1.90-6.03), *IDH1* mutation (HR 0.44, 95% CI 0.23-0.83), *TERT*c250T mutation (HR 2.69, 95% CI 1.28-5.64), *MGMT* expression range of (30, 60%) (HR 0.34, 95% CI 0.13-0.88), and concurrent chemotherapy (HR 0.03, 95%CI 0.01-0.08) were found to be prognostic factors affecting the OS of multiple glioma patients. Multivariate Cox regression analysis incorporating factors with differences in the univariate Cox analysis identified pathological grade IV (HR 2.72, 95% CI 1.43-5.18) as a risk factor

Table IV. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

Before PSM	Univariable (N=264)			Multivariable (N=264)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender	0.83	0.61, 1.14	0.24			
Age	1.01	1.00, 1.03	0.026	1.02	1.00, 1.03	0.008
Pathological grade:						
IV	5.14	3.05, 8.65	<0.001	3.58	1.76, 7.28	<0.001
Lesion location:						
Left frontal lobe	0.90	0.61, 1.32	0.59			
Right frontal lobe	1.05	0.73, 1.51	0.78			
Left parietal lobe	1.22	0.62, 2.39	0.56			
Right parietal lobe	1.35	0.71, 2.55	0.36			
Left temporal lobe	1.24	0.84, 1.83	0.27			
Right temporal lobe	0.97	0.58, 1.60	0.90			
Left occipital lobe	0.35	0.09, 1.43	0.14			
Right occipital lobe	0.62	0.20, 1.95	0.42			
Left thalamus and basal ganglia	0.73	0.23, 2.27	0.58			
Right thalamus and basal ganglia	1.07	0.47, 2.42	0.87			
Corpus callosum	0.79	0.32, 1.92	0.60			
1p19q co-deletion	0.32	0.19, 0.56	<0.001	0.81	0.40, 1.62	0.55
IDH1:						
R132 mutation	1.47	0.72, 3.00	0.29	1.80	0.82, 3.98	0.14
IDH2:						
R172 mutation	0.61	0.09, 4.35	0.62			
TERT:						
C228T mutation	1.51	0.96, 2.37	0.077			
C250T mutation	0.61	0.34, 1.11	0.11			
ATRX mutation	1.07	0.73, 1.58	0.71			
MGMT:						
(8%, 30%)	1.07	0.47, 2.41	0.88			
(30%, 60%)	1.21	0.59, 2.47	0.60			
(60%, 100%)	2.13	0.53, 8.64	0.29			
p53 mutation	1.14	0.77, 1.69	0.51			
Ki67:						
(5%, 25%)	1.72	0.96, 3.09	0.068	1.32	0.72, 2.42	0.36
(25%, 50%)	2.12	1.17, 3.84	0.013	1.60	0.87, 2.95	0.13
(50%, 75%)	2.15	1.15, 4.03	0.017	1.31	0.68, 2.51	0.42
(75%, 100%)	1.11	0.32, 3.87	0.87	1.36	0.39, 4.83	0.63
NF1 Negative	1.23	0.17, 8.81	0.84			
Chemotherapy	0.08	0.05, 0.13	<0.001	0.09	0.05, 0.15	<0.001
After PSM	**Univariable (N=132)**			**Multivariable (N=132)**		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	0.62	0.38, 1.02	0.060			
Age	1.03	1.01, 1.05	0.002	1.03	1.01, 1.05	0.007
Pathological grade:						
IV	1.78	0.81, 3.92	0.15			
Lesion location:						
Left frontal lobe	0.97	0.55, 1.73	0.93			
Right frontal lobe	1.56	0.89, 2.75	0.12			
Left parietal lobe	1.47	0.59, 3.67	0.41			
Right parietal lobe	1.09	0.40, 3.01	0.86			
Left temporal lobe	0.92	0.46, 1.86	0.82			
Right temporal lobe	0.95	0.47, 1.92	0.89			
Left occipital lobe	0.29	0.04, 2.11	0.22			

Table continued

Table IV *(continued)*. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

After PSM	Univariable (N=264)			Multivariable (N=264)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Right occipital lobe	0.73	0.10, 5.27	0.75			
Left thalamus and basal ganglia	0.44	0.06, 3.16	0.41			
Right thalamus and basal ganglia	1.03	0.32, 3.28	0.96			
Corpus callosum	0.58	0.14, 2.38	0.45			
No *1p19q* co-deletion	1.21	0.60, 2.44	0.60			
IDH1:						
R132 mutation	1.36	0.14, 13.2	0.79			
Wild type	1.47	0.46, 4.69	0.51			
IDH2:						
Wild type	1.29	0.18, 9.31	0.80			
TERT:						
C250T mutation	1.03	0.42, 2.53	0.95			
Wild type	0.77	0.39, 1.53	0.46			
ATRX:						
Wild type	0.65	0.38, 1.11	0.11			
MGMT:						
(8%, 30%)	0.35	0.05, 2.49	0.29			
(30%, 60%)	0.78	0.24, 2.48	0.67			
p53 Wild type	1.11	0.60, 2.03	0.74			
Ki67:						
(25%, 50%)	2.51	0.76, 8.34	0.13			
(50%, 75%)	3.28	0.98, 11.0	0.054			
(75%, 100%)	2.47	0.69, 8.82	0.16			
(5%, 25%)	1.92	0.32, 11.5	0.47			
Bevaczumab	0.42	0.15, 1.17	0.10			
NF1 Negative	0.98	0.13, 7.10	0.98			
Chemotherapy	0.13	0.05, 0.32	<0.001	0.17	0.07, 0.42	<0.001

[1]HR = Hazard Ratio, CI = Confidence Interval.

for OS. The application of concurrent chemotherapy reduced the risk of death by 97% (HR 0.03, 95% CI 0.10-0.27).

After PSM: A lesion located in the right parietal lobe and Ki67 expression in the range (5%, 25%) (HR 5.55, 95% CI 1.08-28.4) were found to be prognostic factors affecting the OS of patients by univariate Cox analysis. Including factors with differences identified by the univariate Cox analysis into the multivariate Cox regression analysis revealed that lesion location in the right parietal lobe (HR 3.74, 95% CI 1.12-12.5) was a risk factor for OS (Table VI).

Cox Regression Analysis of Factors Affecting PFS in Patients with Multiple Gliomas

Before PSM: Pathological grade IV (HR 3.23, 95% CI 1.84-5.67), *IDH1* mutation (HR 0.44, 95% CI 0.23-0.84), *TERT*c250T mutation (HR 2.87, 95% CI 1.42-5.81), Ki67 expression range of (5%, 25%) (HR 3.09, 95% CI 1.04-9.18), Ki67 expression range of (25%, 50%) (HR 2.98, 95% CI 1.03-8.63), Ki67 expression range of (75%, 100%) (HR 3.69, 95% CI 0.82-16.7), and concurrent chemotherapy (HR 0.03, 95% CI 0.01-0.09) were found to be prognostic factors affecting patients' PFS by univariate Cox analysis. The multivariate Cox regression analysis incorporating factors with differences revealed in the univariate Cox analysis found that pathological grade IV (HR 3.00, 95% CI 1.51-5.98) was a risk factor for PFS. Meanwhile, concurrent chemotherapy reduced the risk of death by 96% compared to without chemotherapy (HR 0.04, 95% CI 0.10-0.12).

After PSM: According to univariate Cox analysis, the prognostic factors affecting patients' PFS included lesions located in the corpus callosum (HR 6.61, 95% CI 1.41-31.0) and pathological grade IV (HR 2.32, 95% CI 1.13-4.75). Including factors with differences identified by the univariate Cox analysis in the multivariate Cox regression analysis revealed lesion location in the corpus callosum (HR 7.43, 95% CI 1.38-40.0) and patho-

Table V. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

Before PSM	Univariable (N=264)			Multivariable (N=264)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	0.90	0.68, 1.19	0.45			
Age	1.01	1.00, 1.02	0.064			
Pathological grade:						
IV	5.20	3.38, 7.99	<0.001	4.14	2.17, 7.89	<0.001
Lesion location:						
Left frontal lobe	1.00	0.71, 1.41	>0.99			
Right frontal lobe	1.06	0.77, 1.47	0.71			
Left parietal lobe	1.08	0.59, 1.99	0.80			
Right parietal lobe	1.24	0.68, 2.29	0.49			
Left temporal lobe	1.30	0.91, 1.86	0.15			
Right temporal lobe	0.81	0.51, 1.29	0.38			
Left occipital lobe	0.59	0.22, 1.58	0.29			
Right occipital lobe	0.45	0.14, 1.42	0.17			
Left thalamus and basal ganglia	0.79	0.29, 2.15	0.64			
Right thalamus and basal ganglia	1.14	0.54, 2.43	0.73			
Corpus callosum	0.74	0.33, 1.66	0.46			
1p19q co-deletion	0.39	0.25, 0.61	<0.001	1.59	0.83, 3.04	0.16
IDH1:						
R132 mutation	1.78	0.91, 3.50	0.094	1.42	0.66, 3.02	0.37
IDH2:						
R172 mutation	1.94	0.48, 7.83	0.35			
TERT:						
C228T mutation	2.11	1.41, 3.15	<0.001	1.22	0.76, 1.94	0.40
C250T mutation	0.64	0.39, 1.06	0.085	0.72	0.42, 1.25	0.24
ATRX Mutation	1.07	0.76, 1.51	0.71			
MGMT:						
(8%, 30%)	0.98	0.46, 2.09	0.95			
(30%, 60%)	1.79	0.97, 3.30	0.063			
(60%, 100%)	1.57	0.39, 6.35	0.53			
p53 Mutation	1.18	0.83, 1.68	0.35			
Ki67						
(5%, 25%)	1.60	0.96, 2.67	0.074	1.48	0.87, 2.52	0.15
(25%, 50%)	2.39	1.43, 4.02	<0.001	2.23	1.27, 3.92	0.005
(50%, 75%)	2.25	1.30, 3.90	0.004	1.65	0.92, 2.95	0.090
(75%, 100%)	0.88	0.30, 2.58	0.81	0.86	0.28, 2.60	0.79
NF1 Negative	1.47	0.21, 10.5	0.70			
Chemotherapy	0.13	0.08, 0.21	<0.001	0.17	0.10, 0.27	<0.001
After PSM	**Univariable (N=98)**			**Multivariable (N=98)**		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	0.82	0.46, 1.44	0.49			
Age	1.02	1.00, 1.04	0.073			
Pathological grade:						
IV	1.94	1.06, 3.52	0.031	1.49	0.74, 2.99	0.26
Lesion location						
Left frontal lobe	0.99	0.49, 1.99	0.97			
Right frontal lobe	1.91	1.06, 3.42	0.030	1.86	1.00, 3.45	0.048
Left parietal lobe	1.99	0.48, 8.26	0.34			
Right parietal lobe	0.32	0.04, 2.34	0.26			
Left temporal lobe	1.29	0.62, 2.68	0.49			
Right temporal lobe	0.58	0.23, 1.47	0.25			

Table continued

Table V *(continued)*. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

After PSM	Univariable (N=98)			Multivariable (N=98)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Left occipital lobe	0.80	0.11, 5.80	0.82			
Right occipital lobe	0.00	0.00, Inf	>0.99			
Left thalamus and basal ganglia	0.54	0.07, 3.96	0.55			
Right thalamus and basal ganglia	0.00	0.00, Inf	>0.99			
Corpus callosum	0.80	0.19, 3.32	0.76			
1p19q co-deletion	0.71	0.38, 1.32	0.28			
IDH1:						
R132 mutation	2.14	0.65, 7.04	0.21			
TERT:						
C228T mutation	3.27	1.35, 7.93	0.009	1.93	0.66, 5.63	0.23
C250T mutation	0.58	0.20, 1.63	0.30	0.44	0.13, 1.50	0.19
ATRX mutation	1.10	0.57, 2.12	0.77			
MGMT:						
(8%, 30%)	0.00	0.00, Inf	>0.99			
(30%, 60%)	1.79	0.55, 5.82	0.33			
p53 mutation	1.58	0.82, 3.05	0.17			
Ki67:						
(5%, 25%)	1.44	0.60, 3.48	0.41	1.79	0.73, 4.41	0.20
(25%, 50%)	2.38	0.94, 6.05	0.067	2.93	0.95, 8.99	0.060
(50%, 75%)	3.44	1.26, 9.38	0.016	3.98	1.40, 11.3	0.010
(75%, 100%)	1.08	0.13, 8.83	0.94	1.83	0.21, 16.0	0.58
NF1 Negative	0.77	0.11, 5.59	0.79			
Chemotherapy	0.56	0.07, 4.46	0.58			
Bevaczumab	0.35	0.08, 1.43	0.14			

[1]HR = Hazard Ratio, CI = Confidence Interval.

logical grade IV (HR 2.55, 95% CI 1.21-5.38) as risk factors affecting PFS (Table VII).

The theory of 'initiation and promotion' was first proposed by Willis in 1960[6], suggesting that the formation and development of multicentric gliomas undergo two main stages of 1) genetically driven neoplastic transformation of normal brain tissue and 2) neoplastic proliferation in various locations of normal brain tissue under external stimuli. In contrast, Claes et al[7] argued from the histopathological perspective that all multifocal gliomas and most multicentric gliomas are more likely caused by the ability of glioma cells to invade normal brain tissue and to metastasize distantly. Currently, the prevailing view is that the formation of multiple gliomas is associated with their active invasive process[8]. In clinical practice, glioma recurrences are mostly local, with a few ectopic recurrences. Some ectopic recurrence cases can be explained by tumor cell dissemination along white-matter tracts or cerebrospinal fluid[4]. However, some ectopic recurrences cannot be explained by known development pathways. This is possibly due to the heterochrony of multicentric gliomas, i.e., lesions that are of the same origin but manifest as successive occurrences, being multicentric at the time of onset, but some lesions and microscopic pathways are not yet detectable by state-of-the-art imaging techniques[9]. This may also be one reason for the poor therapeutic effect of gliomas and could be a future research direction for glioma treatment. The results of this study indicate that most multifocal gliomas disseminate along the white-matter tracts, followed by membranous structures, such as the subependymal and small vascular spaces, while dissemination along the meninges is rarer. Moreover, in individual recurrent cases, recurrent lesions were found to be tiny nodules without enhancement on T1-weighted sequences at the time of initial treatment, which suggests that tiny lesions without enhancement should be treated cautiously.

Most multiple gliomas are pathologically glioblastomas, and the histological types of individual lesions in multiple gliomas are similar to those of single gliomas of the same pathological grade. The mutation of tumor-suppressor gene *TP53* is most commonly found in all human malignancies[10]. Scholars[11] have shown that *p53* mutation is

Table VI. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

Before PSM	Univariable (N=94)			Multivariable (N=94)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	0.94	0.57, 1.57	0.82			
Age	1.01	0.99, 1.03	0.25			
Pathological grade:						
IV	3.38	1.90, 6.03	<0.001	2.72	1.43, 5.18	0.002
Lesion location						
Left frontal lobe	1.45	0.88, 2.41	0.15			
Right frontal lobe	1.37	0.83, 2.27	0.22			
Left parietal lobe	0.59	0.34, 1.03	0.063			
Right parietal lobe	1.73	0.97, 3.07	0.063			
Left temporal lobe	1.26	0.54, 2.96	0.59			
Right temporal lobe	0.94	0.51, 1.74	0.85			
Left occipital lobe	0.49	0.15, 1.57	0.23			
Right occipital lobe	2.00	0.27, 14.9	0.50			
Left thalamus and basal ganglia	0.53	0.22, 1.24	0.14			
Right thalamus and basal ganglia	2.76	0.98, 7.77	0.055			
Corpus callosum	1.68	0.40, 7.09	0.48			
1p19q co-deletion	0.24	0.03, 1.71	0.15			
IDH1:						
R132 mutation	0.44	0.23, 0.83	0.012	0.68	0.29, 1.64	0.40
TERT:						
C228T mutation	1.47	0.62, 3.47	0.38	0.76	0.29, 1.97	0.57
C250T mutation	2.69	1.28, 5.64	0.009	1.01	0.42, 2.44	0.97
ATRX mutation	1.22	0.52, 2.85	0.64			
MGMT:						
(8%, 30%)	0.82	0.46, 1.47	0.51	0.98	0.50, 1.92	0.95
(30%, 60%)	0.34	0.13, 0.88	0.026	0.56	0.16, 1.98	0.37
(60%, 100%)	2.84	1.07, 7.59	0.37	4.35	1.43, 13.2	0.9
p53 mutation	1.88	0.62, 3.05	0.17			
Ki67:						
(5%, 25%)	2.93	0.99, 8.68	0.052			
(25%, 50%)	2.69	0.93, 7.82	0.068			
(50%, 75%)	2.32	0.74, 7.31	0.15			
(75%, 100%)	3.44	0.76, 15.5	0.11			
NF1 Negative	1.79	0.76, 4.25	0.18			
Chemotherapy	0.03	0.01, 0.08	<0.001	0.03	0.01, 0.12	<0.001
After PSM	**Univariable (N=64)**			**Multivariable (N=64)**		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	1.09	0.48, 2.50	0.83			
Age	1.00	0.97, 1.04	0.98			
Pathological grade:						
IV	2.22	0.97, 5.11	0.060			
Lesion location						
Left frontal lobe	0.95	0.32, 2.81	0.93			
Right frontal lobe	0.94	0.40, 2.21	0.88			
Left parietal lobe	0.70	0.29, 1.65	0.41			
Right parietal lobe	5.58	2.01, 15.5	<0.001	3.74	1.12, 12.5	0.032
Left temporal lobe	1.75	0.63, 4.86	0.28			
Right temporal lobe	0.87	0.34, 2.22	0.77			
Left occipital lobe	0.70	0.21, 2.38	0.57			
Right occipital lobe	0.00	0.00, Inf	>0.99			

Table continued

Table VI *(continued)*. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

After PSM	Univariable (N=64)			Multivariable (N=64)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Left thalamus and basal ganglia	0.60	0.22, 1.64	0.32			
Right thalamus and basal ganglia	1.72	0.22, 13.3	0.60			
Corpus callosum	4.52	0.55, 37.0	0.16			
1p19q co-deletion	0.71	0.09, 5.38	0.74			
IDH1:						
R132 mutation	0.58	0.25, 1.34	0.20			
TERT:						
C228T mutation	0.00	0.00, Inf	>0.99			
C250T mutation	7.52	0.83, 67.9	0.072			
MGMT:						
(8%, 30%)	1.08	0.40, 2.92	0.88			
(30%, 60%)	0.43	0.12, 1.62	0.21			
(60%, 100%)	9.17	2.05, 41.1	0.4			
Ki67:						
(5%, 25%)	5.55	1.08, 28.4	0.040	1.41	0.20, 10.1	0.73
(25%, 50%)	2.34	0.49, 11.1	0.29	1.77	0.32, 9.87	0.52
(50%, 75%)	1.94	0.38, 10.0	0.43	1.75	0.33, 9.22	0.51
(75%, 100%)	1.76	0.16, 19.9	0.65	1.13	0.08, 16.5	0.93
NF1 Negative	5.45	0.72, 41.1	0.10			

[1]HR = Hazard Ratio, CI = Confidence Interval.

a key factor causing glioma recurrence. The *NF1* gene directs the *in vivo* synthesis of neurofibromin, which regulates the *RAS* signaling pathway and further affects the development of many benign or malignant tumors. In gliomas, *NF1* mutation (tumor-suppressor mutation) is often accompanied by mutations of other genes (e.g., *ATRX, TP53, PIK3CA/B, IL15, TERT,* and *FGF1*). Mutations in these genes together affect the downstream *Raf-MEK-ERK* and *PI3K-Akt-mTOR* pathways. The pathogenesis of gliomas involves a complex network of genes, pathways, and metabolism, whose exact mechanism remains unclear[12]. In addition, *TP53* and *NF1* play complementary roles in the development and progression of glioma[13]. The results of this study show no significant difference in the positive rate of *p53* mutation between multifocal and multicentric gliomas. The positive rate of *NF1* mutation in multifocal gliomas was 6%, while that in multicentric gliomas was up to 33%. Meanwhile, 3 out of the 12 cases of multicentric gliomas showed the co-mutation of *p53* and *NF1*, while none of the 82 cases of multifocal gliomas had this co-mutation.

At present, multiple molecular markers have been proven to be helpful in determining the prognosis and therapeutic response of glioma patients[14]. However, there is limited genomics research on multiple gliomas. Liu et al[15] studied 30 cases of multiple gliomas and found that none had *IDH1* or *ATRX* mutations. Furthermore, the gene *CYB5R2* was significantly correlated with the survival rate of multiple glioma patients, and multiple gliomas had some underlying epigenetic features related to poor prognosis. Dono et al[16] studied 33 cases of multiple glioblastomas, among which about 6% of patients had *IDH* mutations. Karlowee et al[17] studied 16 patients with multiple gliomas and found that *IDH1* mutation, *PTEN* expression and *1p19q* co-deletion were all negative; 5 of the 14 cases (35.7%) were p53-positive, and 4 (28.6%) were *ATRX*-negative. The results of this study showed that, among the 82 multifocal glioma cases, those with *1p19q* co-deletion and *IDH1* mutation accounted for 5 and 24%, respectively, while neither *1p19q* co-deletion nor *IDH1* mutation were detected in multicentric gliomas. In addition, the positive expression rate of *MGMT* promoter methylation and *ATRX* mutation showed no significant difference between the two groups. After PSM, the *TERT* gene mutation was also not significantly different between the two groups. To our knowledge, this study is the first to include *1p19q, IDH, TERT, ATRX, MGMT, p53,*

Table VII. Cox regression analysis of factors affecting PFS in patients with multiple gliomas before and after PSM.

Before PSM	Univariable (N=94)			Multivariable (N=94)		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	1.07	0.65, 1.76	0.80			
Age	1.01	0.99, 1.03	0.27			
Pathological grade:						
IV	3.23	1.84, 5.67	<0.001	3.00	1.51, 5.98	0.002
Lesion location:						
Left frontal lobe	1.53	0.93, 2.52	0.10			
Right frontal lobe	1.21	0.74, 2.00	0.45			
Left parietal lobe	0.66	0.39, 1.13	0.13			
Right parietal lobe	1.62	0.92, 2.87	0.10			
Left temporal lobe	1.46	0.62, 3.41	0.39			
Right temporal lobe	0.95	0.51, 1.75	0.87			
Left occipital lobe	0.45	0.14, 1.44	0.18			
Right occipital lobe	1.52	0.21, 11.1	0.68			
Left thalamus and basal ganglia	0.54	0.23, 1.28	0.16			
Right thalamus and basal ganglia	2.23	0.80, 6.22	0.13			
Corpus callosum	1.27	0.30, 5.34	0.74			
1p19q co-deletion	0.21	0.03, 1.49	0.12			
IDH1:						
R132 mutation	0.44	0.23, 0.84	0.012	0.54	0.22, 1.32	0.18
TERT:						
C228T mutation	1.30	0.55, 3.08	0.55	0.79	0.30, 2.11	0.64
C250T mutation	2.87	1.42, 5.81	0.003	1.17	0.52, 2.66	0.70
ATRX Mutation	1.12	0.48, 2.61	0.79			
MGMT:						
(8%, 30%)	1.02	0.58, 1.81	0.95			
(30%, 60%)	1.34	0.13, 0.88	0.7			
(60%, 100%)	1.66	1.37, 9.77	0.9			
ki67:						
(5%, 25%)	3.09	1.04, 9.18	0.042	1.28	0.35, 4.71	0.72
(25%, 50%)	2.98	1.03, 8.63	0.044	0.95	0.22, 4.02	0.94
(50%, 75%)	2.54	0.82, 7.90	0.11	0.67	0.15, 2.96	0.59
(75%, 100%)	3.69	0.82, 16.7	0.090	0.64	0.10, 4.32	0.65
NF1 Negative	1.68	0.72, 3.96	0.23			
Chemotherapy	0.03	0.01, 0.09	<0.001	0.04	0.01, 0.12	<0.001
After PSM	**Univariable (N=64)**			**Multivariable (N=64)**		
Factor	**HR[1]**	**95% CI[1]**	***p*-value**	**HR[1]**	**95% CI[1]**	***p*-value**
Gender:						
Female	1.64	0.79, 3.41	0.19			
Age	1.01	0.98, 1.03	0.61			
Pathological grade:						
IV	2.32	1.13, 4.75	0.021	2.55	1.21, 5.38	0.014
Lesion location:						
Left frontal lobe	1.61	0.79, 3.29	0.19			
Right frontal lobe	1.05	0.52, 2.14	0.89			
Left parietal lobe	0.70	0.33, 1.47	0.34			
Right parietal lobe	1.66	0.67, 4.10	0.27			
Left temporal lobe	2.09	0.71, 6.16	0.18			
Right temporal lobe	1.06	0.45, 2.48	0.90			
Left occipital lobe	0.44	0.10, 1.85	0.26			
Right occipital lobe	0.00	0.00, Inf	>0.99			
Left thalamus and basal ganglia	0.51	0.17, 1.50	0.22			
Right thalamus and basal ganglia	1.18	0.16, 8.84	0.87			

Table continued

Table VII *(continued)*. Cox regression analysis of factors affecting OS in patients with solitary glioma before and after PSM.

After PSM	Univariable (N=64)			Multivariable (N=64)		
Factor	HR[1]	95% CI[1]	*p*-value	HR[1]	95% CI[1]	*p*-value
Corpus callosum	6.61	1.41, 31.0	0.017	7.43	1.38, 40.0	0.020
1p19q co-deletion	0.80	0.11, 5.94	0.83			
IDH1:						
R132 mutation	0.80	0.38, 1.68	0.55			
TERT:						
C228T mutation	0.42	0.06, 3.13	0.40			
C250T mutation	1.20	0.16, 8.94	0.86			
ATRX mutation	0.34	0.05, 2.53	0.29			
MGMT:						
(8%, 30%)	1.57	0.69, 3.60	0.28			
(30%, 60%)	0.75	0.27, 2.12	0.59			
(60%, 100%)	1.6	3.89, 79.2	0.1			
ki67:						
(5%, 25%)	3.31	0.89, 12.3	0.074			
(25%, 50%)	2.51	0.70, 9.04	0.16			
(50%, 75%)	1.79	0.42, 7.53	0.43			
(75%, 100%)	3.49	0.57, 21.4	0.18			
NF1 Positive	0.16	0.02, 1.20	0.074			

[1]HR = Hazard Ratio, CI = Confidence Interval.

ki67, and *NF1* as relevant factors for comparing patients with solitary gliomas and those with multiple gliomas.

Scholars[18] have shown that the clinical prognosis for multiple gliomas is worse than that for solitary gliomas. Guerrini et al[19] studied 16 patients with multiple gliomas with a median OS of 8.7 months, finding that age ≤70 years, postoperative Karnofsky performance status (KPS) ≥70 and GTR/ subtotal resection (STR) were significant factors in a good prognosis. Haque et al[20] showed a median OS of 12.8 and 8.3 months ($p < 0.001$) for solitary and multiple glioblastoma patients, respectively. In multivariate analyses, factors associated with improved OS included solitary disease, radiotherapy and chemotherapy. Our current study showed that the mOS rates for solitary and multiple glioma patients were 21.6 and 21 months (p=0.045), respectively, and there was no statistically significant difference in the mOS between multifocal and multicentric glioma patients. In the multivariate analysis, age and pathological grade IV were identified as risk factors affecting OS ($p< 0.05$), and applying concurrent chemotherapy reduced the risk of death by 83%. There have not been standard guidelines for the treatment of multiple gliomas, and the applied treatment mode is the same as that for solitary gliomas. Kasper et al[21] suggested that craniotomy with maximum safe resection was beneficial, with >27.7% of patients achieving longer survival. Our study revealed that lesion location in the right parietal lobe [hazard ratio (HR) 3.74, 95% confidence interval (CI) 1.12-12.5] was a risk factor affecting the OS in multiple glioma patients and lesion location in the corpus callosum and pathological grade IV were risk factors affecting PFS ($p < 0.05$). This may be related to the surgical difficulty in these areas and, thus, the challenge of performing a complete resection of lesions in these locations.

Conclusions

This era of precision medicine based on technological advances requires more accurate molecular pathology information. There remain many controversial viewpoints and unresolved issues. Extensive studies have focused on imaging diagnosis and prognosis prediction, and further research is required to reveal the specific mechanisms of their development, especially in patients with multiple gliomas. Advances in treatment have done little to improve patient survival, reinforcing the need for us to develop highly targeted treatments to improve patient prognosis.

Conflict of Interest
The authors declare that they have no conflict of interests.

Informed Consent
Individual written consent was waived due to the non-interventional and retrospective nature of this study.

Ethics Statement
This study has been approved by the Ethics Committee of Henan Cancer Hospital (2022-540-001).

Data Accessibility
The data supporting this study is open-access and can be found in the corresponding databases described in the paper.

Authors' Contributions
All authors contributed equally to this article. H. WU was the chief investigator and was responsible for the data analysis. All authors developed the study design and contributed to the writing of the final manuscript.

Funding
This study was supported by the Key Science and Technology Project of Henan Province (222102310253), Natural Science Foundation of Henan Province of China (222300420575 and 232300420231), Project of Henan Province Medical Science Technology (SB201901112).

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