

Maximal tumor diameter in the preoperative tumor magnetic resonance imaging (MRI) T2 image is associated with prognosis of Grade II Glioma

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Abstract

Factors associated with the prognosis of low-grade glioma remain undefined. In this study, we examined whether the maximal tumor diameter in the preoperative tumor magnetic resonance imaging (MRI) T2 image is associated with the prognosis of grade II gliomas patients, aiming to provide insights into the clinical prediction of patient outcome.

We retrospectively analyzed the clinical data of patients with Grade II glioma, who were hospitalized in Xiangya Hospital, Central South University, from 2011 to 2016. Kaplan–Meier and Cox proportional hazards analyses were performed to determine the association between maximal tumor diameter and prognosis.

A total of 90 patients with grade II glioma were included in this study. Mean patient age was 37.7 ± 13.0 years, and 58.9% of them were male. Kaplan–Meier survival analysis of overall survival (overall survival [OS], $P = .009$) and event-free survival (EFS, $P = .002$) revealed statistically significant differences between the patients with lesion diameter < 7 cm and those with lesion diameter ≥ 7 cm. The maximal tumor diameter in the preoperative tumor MRI T2 image was identified as a prognostic factor of OS ($P = .013$), while constituting an independent risk factor for EFS ($P = .002$) alongside elevated histological grade after recurrence ($P = .006$).

The maximal tumor diameter in the preoperative tumor MRI T2 image independently predicts OS and EFS in patients with grade II glioma.

Abbreviations: CI = confidence interval, EFS = event-free survival, HR = hazard ratio, OS = overall survival, PACS = picture archiving and communication system, WHO = World Health Organization.

Keywords: astrocytoma, glioma, magnetic resonance imaging, prognosis, survival analysis

1. Introduction

Gliomas are the most frequent primary tumors of the brain and the spinal cord.^[1] Prior to the updated World Health Organization (WHO) classification in 2016, which introduced molecular biology based parameters,^[2] the main classification of gliomas was based on histology and clinical findings.^[3] Both classification methods assign gliomas into grades I to IV.^[2,3]

Grade I tumors are most often found in children, generally benign and frequently curable with complete surgical resection,

while grade II–IV are more common in adults.^[4] Patients with grade II glioma, also known as low-grade glioma, have slower tumor growth and better prognosis compared with those with high grade gliomas.^[5]

Standard care for patients with low-grade glioma includes maximal safe resection, and high-risk patients undergo a combination of both radiation and chemotherapy after surgery.^[6] Some patients can achieve relatively long event-free survival (EFS) and overall survival (OS) after the standardized treatment. With a better understanding of the molecular basis of these tumors, more targeted and improved treatments are likely to be developed.^[4] However, low-grade glioma still shows high recurrence, disability and mortality rates.^[7]

There are a number of factors that may be associated with the prognosis of low-grade glioma, including age ≥ 40 , astrocytic tumor type, tumor size ≥ 6 cm, tumor crossing the midline, and the presence of neurologic deficit at diagnosis.^[8,9] It is now becoming more apparent that various genetic factors play important roles not only in diagnosis but also in the development and prognosis of glioma.^[10,11] However, imaging examination remains the best tool for clinical diagnosis.^[12] In high-grade glioma, magnetic resonance imaging (MRI) features are associated with patient prognosis, including the size, location and number of tumors, as well as enhancement, necrosis and edema statuses.^[13,14] However, most existing reports focus on high grade gliomas rather than low grade lesions, and grade II gliomas remain poorly understood.^[15] Therefore, more effort is needed to explore factors associated with the prognosis of grade II glioma.

The aim of this study was to determine whether the maximal tumor diameter in the preoperative tumor MRI T2 image is

Editor: Mihnea-Alexandru Găman.

The study was approved by the ethics committee of Xiangya Hospital, and the need for informed consent was waived because of its retrospective nature.

The authors have no conflicts of interests to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Liu H, Shen L, Huang X, Zhang G. Maximal tumor diameter in the preoperative tumor magnetic resonance imaging (MRI) T2 image is associated with prognosis of Grade II Glioma. *Medicine* 2021;100:10(e24850).

Received: 16 December 2019 / Received in final form: 30 December 2020 / Accepted: 28 January 2021

<http://dx.doi.org/10.1097/MD.00000000000024850>

associated with the prognosis of grade II gliomas patients, further to provide insights into the clinical prediction of patient outcome.

2. Methods

2.1. Patients

In this retrospective cohort study, we collected the data of patients with grade II glioma, who were treated by surgery and confirmed by pathological testing in Xiangya Hospital, Central South University (China), from January 2010 to December 2016. Inclusion criteria were:

1. age ≥ 18 years;
2. first-line treatment patients with grade II glioma treated by surgery and confirmed by postoperative pathological test;
3. complete clinical and imaging data.

Exclusion criteria were:

1. preoperative radiotherapy and chemotherapy;
2. second primary malignant tumors.

Grading of specimens was based on the WHO classification (Grade I–IV).^[3] The study was approved by the ethics committee of Xiangya Hospital, and the need for informed consent was waived because of its retrospective nature.

2.2. MR examination

Preoperative MRI examination was performed on Siemens instruments (1.5T or 3T), with Gd-diethylenetriamine penta-acetic acid as the contrast agent. The scan layer thickness was 1.5 mm. The data were collected, uploaded to the workstation, and processed with the MRI post processing software and the picture archiving and communication system (PACS). After postprocessing and remodeling, the basic measurements were obtained.

Imaging features, such as tumor diameter, whether the tumor crossed the cranial midline, the presence of cystic changes or necrosis, and the degree of edema, were independently measured and recorded by an experienced associate chief radiologist and an experienced chief oncologist. Any disagreement was resolved by consensual discussion. The tumor diameter was measured as follows: in the PACS, the tumor diameter was assessed in the transverse plane of MRI T2-weighted image series and averaged. The edema was segmented into 7 categories based on

1. peritumoral edema extension: < 1 cm from the tumor margin or ≥ 1 cm;
2. edema shape, as rounded or irregular;
3. necrosis, as none, mild, or severe;
4. cyst, as none, small, or large;
5. enhancement, as not marked or marked;
6. tumor crossing the brain midline, as no or yes, that is, extending into the other side of the cerebral hemisphere;
7. edema crossing the brain midline, as no or yes;
8. size: < 5 cm or ≥ 5 cm maximum diameter.^[14]

2.3. Surgery and pathological examination

All the patients received radical surgical resection, performed by an experienced chief neurosurgeon.

Postoperative adjuvant radiotherapy included conformal radiotherapy, intensity-modulated radiotherapy, whole brain radio-

therapy and Gamma Knife stereotactic radiosurgery. The dose was 1.8 to 2.0 Gy/time, 5 times/week for 5 to 6 weeks. The maximal and minimal doses for the planning target volume were 60 Gy and 48 Gy, respectively. Mannitol/glycerol fructose and dexamethasone were administered during radiotherapy based on patient response to reduce brain edema. Synchronous or adjuvant chemotherapy was administered during radiotherapy. Synchronous chemotherapy involved the oral intake of Temozolomide at a dose of 75 mg/m²-d. Adjuvant chemotherapy followed the Stupp protocol,^[16] including the oral intake of Temozolomide at a dose of 150 mg/m²-d for phase I and 200 mg/m²-d for phase II, d1-d5 Q4W. Pathological diagnosis followed the WHO 2007 guideline.^[3]

2.4. Clinical data collection

Clinical data were collected, including gender, age, disease onset, onset symptoms, preoperative Karnofsky performance score, surgical time and details, pathological results (non-astrocytoma included oligodendroglioma, anaplastic oligo-astrocytomas, ganglioneuroma and ependymoma) and postoperative treatment.

2.5. Definitions and follow-up

The follow-up information of all eligible patients was obtained by telephone calls. The last follow-up was performed in December 2017. Overall survival (OS) was determined from the date of the initial surgical operation to death. Recurrence was defined as tumor enlargement by more than 10% in volume postoperatively. Event-free survival (EFS) was defined as the period between the initial operation and tumor recurrence or death. The diagnosis of adverse reactions of the nervous system was based on CTCAE version 3.0.^[17]

2.6. Statistical analysis

All analyses were performed with SPSS 23.0 (IBM Corp., Armonk, NY). Continuous variables were first tested for normality of distribution. Those with normal distribution were presented as mean \pm standard deviation, and compared by the *t* test. Otherwise, data were presented as median (range), and the Mann–Whitney *U* test was used for comparison. Categorical variables were presented as frequency and percentage, and assessed by the Chi Squared test. Survival curves were plotted by the Kaplan–Meier method, and differences were assessed by the log-rank test. The Cox's proportional hazards model was used to identify factors independently affecting survival. $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among the 90 patients finally included, 14 died throughout the trial, while 76 remained alive with no lost to follow-up. Their baseline information is presented in Table 1. Their mean age was 37.7 ± 13.0 years, and 58.9% of the patients were male.

3.2. Factors associated with OS

Univariate analysis of factors associated with OS is shown in Table 2. The only factor with a significant association with OS was lesion diameter ≥ 7 cm (hazard ratio [HR] = 4.902, 95% confidence interval [CI] 1.3–18.488; $P = .019$). There were no significant associations with age, gender, and other clinical

Table 1**Baseline information of the patients with grade II glioma.**

Characteristics	Lesion diameter <7 cm (N=60)	Lesion diameter ≥7 cm (N=30)	P
Baseline information			
Age in years, mean ±SD	36.1 ± 14.1	41.0 ± 9.9	.089
Age, n (%)			.367
≤40	36 (60%)	15 (50%)	
>40	24 (40%)	15 (50%)	
Gender, n (%)			.05
Male	39 (65%)	13 (43.33%)	
Female	21 (35%)	17 (56.67%)	
Preoperative KPS, Median (IQR)	80 (75,80)	80 (70,80)	.767
Preoperative KPS, n (%)			.682
<70	4 (6.67%)	3 (10%)	
≥70	56 (93.33%)	27 (90%)	
Seizure before surgery, n (%)	28 (46.67%)	13 (43.33%)	.765
Multiple lesions, n (%)	0 (0%)	2 (6.67%)	.114
Lesion site, n (%)			
Frontal lobe + parietal lobe	8 (13.33%)	5 (16.67%)	.753
Frontal lobe + occipital lobe	1 (1.67%)	0 (0%)	>.999
Frontal lobe + temporal lobe	7 (11.67%)	11 (36.67%)	.005
Parietal lobe + occipital lobe	1 (1.67%)	1 (3.33%)	>.999
Parietal lobe + temporal lobe	2 (3.33%)	5 (16.67%)	.039
Occipital lobe + temporal lobe	1 (1.67%)	1 (3.33%)	>.999
Imaging features			
Enhanced T1 contrast-enhanced images, n (%)	28 (50.91%)	13 (44.83%)	.596
Tumor across cranial midline in T1 images, n (%)	13 (21.67%)	15 (50%)	.006
Tumor across cranial midline in T1 contrast-enhanced images, n (%)	7 (12.28%)	7 (25%)	.212
Tumor across cranial midline in T2 images, n (%)	14 (23.33%)	15 (50%)	.011
Edema, n (%)	56 (94.92%)	30 (100%)	.548
Edema across cranial midline, n (%)	13 (21.67%)	15 (50%)	.006
Cystic changes, n (%)	10 (16.67%)	4 (13.33%)	.767
Surgical Pathology			
Surgical approach, n (%)			.538
Total surgical removal	52 (86.67%)	24 (80%)	
Subtotal surgical removal	8 (13.33%)	6 (20%)	
Histological types, n (%)			>.999
Non-Astrocytoma	18 (30%)	9 (30%)	
Astrocytoma	42 (70%)	21 (70%)	
Lesion diameter in cm, Median (IQR)	4.89 (3.67,6.23)	7.805 (7.52,8.85)	<.001
Postoperative volume, cm ³ , median (IQR)	0.25 (0,13.3)	26.7 (0,54.8)	.006
Postoperative treatment, n (%)			.678
Radiotherapy + chemotherapy	44 (74.58%)	23 (79.31%)	
Chemotherapy	5 (8.47%)	1 (3.45%)	
Neither	10 (16.95%)	5 (17.24%)	

IQR = interquartile range, KPS = Karnofsky performance score, SD = standard deviation.

factors. Multivariate analysis also showed that only lesion diameter ≥7 cm was independently associated with OS (HR = 5.897, 95% CI 1.451–23.969; $P = .013$; Table 2).

3.3. Factors associated with EFS

Univariate analysis of factors associated with EFS is shown in Table 3. Lesion diameter ≥7 cm was also associated with EFS (HR = 4.673, 95% CI 1.611–13.556; $P = .005$). There were no significant associations with age, gender, and other clinical factors. Multivariate analysis (Table 3) showed that lesion diameter ≥7 cm was independently associated with EFS (HR = 5.065, 95% CI 1.593–16.11; $P = .006$).

3.4. Survival analysis according to lesion size

Kaplan–Meier survival analysis was performed with the patients grouped according to lesion diameter into the <7 cm and ≥7 cm

categories (Fig. 1). Although median OS for both groups separated by lesion diameter could not be determined, the log rank test yielded a P value of .009, suggesting a statistically significant difference between the 2 groups (Fig. 1A). We were also unable to determine median EFS in patients with lesion diameter <7 cm, while median EFS was 54.5 (95% CI, 36.55–72.45) months in those with lesion diameter ≥7 cm (log rank test $P = .002$), suggesting a statistically significant difference between the 2 groups.

4. Discussion

The aim of this study was to determine whether the maximal tumor diameter in the preoperative tumor MRI T2 image is associated with the prognosis of grade II gliomas patients. The results showed that the maximal tumor diameter was significantly associated with OS in both univariate and

Table 2**Univariate and multivariate Cox analyses of factors associated with overall survival in patients with grade II glioma.**

Variables	Univariate			Multivariate		
	HR	95%CI	P	HR	95% CI	P
Age, >40	1.585	(0.483,5.201)	.448	1.005	(0.274, 3.681)	.994
Female	0.733	(0.213,2.518)	.622	0.457	(0.11, 1.888)	.279
Preoperative KPS, <70	0.04	(0.000, 149.043)	.443			
Seizure before surgery	1.471	(0.449, 4.823)	.524			
Multiple lesions	4.904	(0.618, 38.915)	.132			
lesion diameter \geq 7 cm	4.902	(1.3, 18.488)	.019	5.897	(1.451, 23.969)	.013
Enhanced T1 contrast-enhanced images	0.773	(0.235, 2.539)	.671			
Tumor across cranial midline in T1 images	1.041	(0.304, 3.567)	.949			
Tumor across cranial midline in T1 contrast-enhanced images	0.424	(0.054, 3.329)	.414			
Tumor across cranial midline in T2 images	1.032	(0.301, 3.533)	.961			
Edema	21.728	(0.000, 5425479.865)	.627			
Edema across cranial midline	1.16	(0.339,3.978)	.813			
Cystic changes	0.033	(0.000, 22.040)	.305			
Subtotal surgical removal	1.847	(0.488, 6.996)	.367			
Non-Astrocytoma	0.219	(0.028, 1.709)	.147	0.242	(0.031, 1.901)	0.177
Postoperative treatment						
Radiotherapy + chemotherapy	2.409	(0.303, 19.146)	.406			
Chemotherapy	2.896	(0.177, 47.454)	.456			

CI = confidence interval, HR = hazard ratio, KP = Karnofsky performance.

multivariate analyses, and was also a risk factor for EFS alongside elevated histological grade after recurrence. Kaplan–Meier survival analysis of OS and EFS in patients divided into the lesion diameter <7cm and \geq 7cm groups suggested significant differences between the 2 groups. These data suggest that tumor size \geq 7cm is the most important factor influencing patient prognosis in grade II glioma.

The prognosis of low-grade glioma has been suggested to be associated with various factors, including age \geq 40, astrocytic tumor type, tumor size \geq 6cm, tumor crossing the midline, and neurological deficit at diagnosis.^[8,9] The current results showed that of all these factors, only tumor size \geq 7cm was an

independent factor associated with OS and EFS in this population. The discrepancy may be due to the different populations studied, and previous studies often included patients with grade I glioma within their populations.^[9]

While not an independent factor associated with OS, elevated histological grade after recurrence was a factor related to EFS in this study. Low-grade glioma progression to a higher grade is known as malignant transformation, and considered a major cause of death.^[18] A study assessing risk factors for malignant transformation in patients with low-grade glioma reported older age, male sex, multiple tumor locations, use of chemotherapy alone, and presence of residual disease to be significant.^[19]

Table 3**Univariate and multivariate Cox analyses of factors related to event-free survival in patients with grade II glioma.**

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age, >40	0.932	(0.346,2.512)	.889	0.735	(0.246, 2.202)	0.583
Female	1.657	(0.616,4.455)	.317	0.996	(0.317, 3.124)	.994
Preoperative KPS, <70	0.466	(0.06,3.595)	.464			
Seizure before surgery	1.256	(0.47, 3.362)	.649			
Multiple lesions	3.914	(0.502, 30.499)	.193			
lesion diameter \geq 7 cm	4.673	(1.611, 13.556)	.005	5.065	(1.593, 16.11)	.006
Enhanced T1 contrast-enhanced images	0.751	(0.279, 2.021)	.571			
Tumor across cranial midline in T1 images	1.981	(0.742, 5.291)	.173			
Tumor across cranial midline in T1 contrast-enhanced images	0.647	(0.146, 2.866)	.567			
Tumor across cranial midline in T2 images	1.955	(0.732, 5.22)	.181			
Edema	21.838	(0.001, 570994.000)	.552			
Edema across cranial midline	2.239	(0.835, 6)	.109			
Cystic changes	0.027	(0.000, 4.362.)	.164			
Subtotal surgical removal	1.72	(0.553, 5.351)	.349			
Non-Astrocytoma	0.147	(0.019, 1.111)	.063	0.142	(0.019, 1.082)	.06
Postoperative treatment						
Radiotherapy + chemotherapy	3.752	(0.493, 28.579)	.202			
Chemotherapy	3.558	(0.219, 57.933)	.373			

CI = confidence interval, HR = hazard ratio, KP = Karnofsky performance.

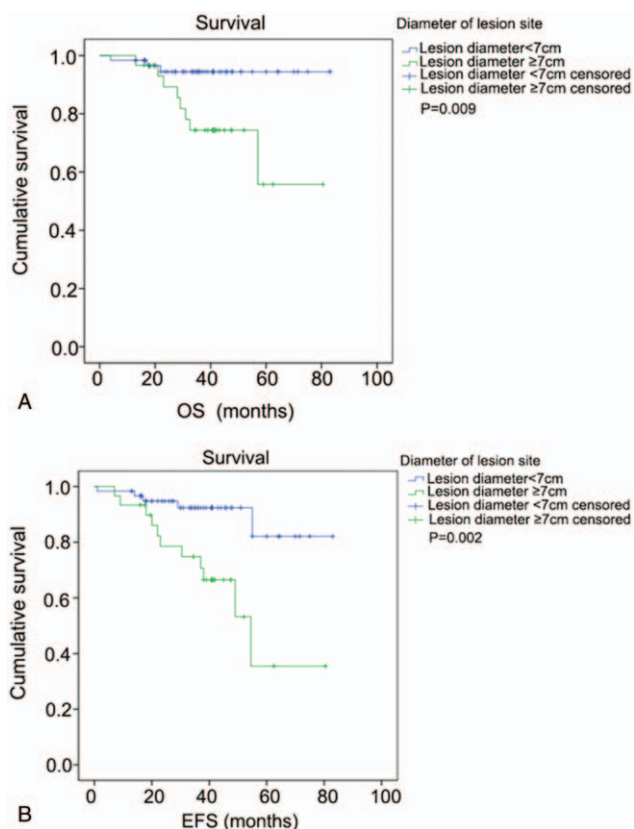


Figure 1. Kaplan–Meier survival curves for overall survival (OS) and event free survival (EFS) in patients with grade II glioma. A: OS analysis according to lesion diameter (<7 cm or ≥7 cm) showed a significant difference between the groups by the log rank test ($P=.009$). B: EFS analysis according to lesion diameter (<7 cm or ≥7 cm) showed a significant difference between the groups by the log rank test ($P=.002$).

Further investigation is needed to evaluate malignant transformation.

MRI examination remains the best tool for clinical diagnosis.^[12] In high-grade glioma there are clear associations of MRI features with patient prognosis, including the size, location and number of tumors, and enhancement, necrosis and edema statuses.^[13,14] However, few studies have focused on low-grade gliomas. A study found that no enhancement and a smooth non-enhancing margin on MRI are predictive of longer EFS, while a smooth non-enhancing margin is a significant predictor of longer OS.^[15] These authors also suggested that textural analyses of MRI data could predict *IDH1* mutation, 1p/19q codeletion, histological grade, and tumor progression, emphasizing the importance of MRI.^[15] However, the latter study also included grade III glioma patients, which may explain the difference in results from the current study.

Suggested treatment for grade II glioma remains a fairly controversial subject because of the slow development of these tumors alongside the risk of treatment.^[20] Over recent years the treatment has changed subtly. Surgical removal of the tumor, if possible, remains an important first step in treatment but radiotherapy plays a vital role in many patients.^[21] Recent evidence also suggests a possible large survival advantage of combined chemotherapy and radiation, raising questions about using chemotherapy alone as an initial treatment strategy.^[20,22]

The patients in this study were treated by surgical resection, which fully removes the tumor if possible, and radiotherapy; in addition, most of them also received chemotherapy. Therefore, this follows current opinion for optimal treatment, despite being a retrospective cohort study. The treatment of low-grade glioma is likely to develop further as the molecular basis of the disease is comprehensively understood and new treatments are developed, including better tolerated chemoradiotherapy regimens.^[23,24]

This study had some limitations. The sample size was relatively small, and data from multiple centers would provide more evidence to support these results. As a retrospective study, selection bias was possible, and all the patients were treated prior to the updated WHO guidelines that include molecular biology information in the classification of gliomas.^[2] The different molecular subtypes of low-grade glioma have been shown to have distinct prognoses based on *IDH1* and *IDH2* gene mutational and 1p/19q codeletion statuses.^[25,26] Therefore, assessing the molecular subtypes of this population may provide important information related to patient survival.

In conclusion, this retrospective analysis of clinical factors related to prognosis in patients with grade II glioma indicated that the maximal tumor diameter in the preoperative tumor MRI T2 image could independently predict OS and EFS. Therefore, tumor diameter could be used as a prognostic parameter in these patients.

Author contributions

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