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

Haipeng Liu, MS, Liangfang Shen, MD*, Xinqiong Huang, MD, Guangying Zhang, MD

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.

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.\(^{[6]}\) 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 status.\(^{[13,14]}\) However, most existing reports focus on high grade gliomas rather than low grade lesions, and grade II gliomas remain poorly understood.\(^{[15]}\)

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, 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 consensus 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, ganglioglioma 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 ± 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
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
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 <7 cm and ≥7 cm groups suggested significant differences between the 2 groups. These data suggest that tumor size ≥7 cm is the most important factor in influencing patient prognosis in grade II glioma.

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

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. 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.

### 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 (0.483,3.201) | .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 (0.00, 149.043) | .443 | |
| Seizure before surgery | 1.471 (0.44, 4.823) | .524 | |
| Multiple lesions | 4.904 (0.618, 38.915) | .132 | |
| Lesion diameter ≥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 (0.054,3.029) | .414 | |
| Tumor across cranial midline in T2 images | 1.032 (0.301, 3.333) | .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) | .177 |
| Postoperative treatment | Radiotherapy + chemotherapy | 2.409 (0.303, 19.146) | .406 | |
| | Chemotherapy | 2.806 (0.177, 47.454) | .456 | |

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

### 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) | .583 |
| Female    | 1.657 (0.616,4.455) | .317 | 0.996 (0.317, 3.124) | .994 |
| Preoperative KPS, <70 | 0.466 (0.06,3.598) | .464 | |
| Seizure before surgery | 1.256 (0.47, 3.362) | .649 | |
| Multiple lesions | 3.914 (0.502, 30.499) | .193 | |
| Lesion diameter ≥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 | 1.961 (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 | 1.965 (0.732, 5.23) | .181 | |
| Edema | 21.838 (0.001, 570904.000) | .552 | |
| Edema across cranial midline | 2.239 (0.835, 6) | .109 | |
| Cystic changes | 0.027 (0.00, 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, 57.903) | .373 | |

CI = confidence interval, HR = hazard ratio, KP = Karnofsky performance.
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 predicted OS and EFS. Therefore, tumor diameter could be used as a prognostic parameter in these patients.

### Author contributions

Conceptualization: Haipeng Liu.

Data curation: Haipeng Liu, Xinqiong Huang.

Formal analysis: Haipeng Liu, Liangfang Shen.

Investigation: Guangying Zhang.

Methodology: Xiangfeng Shen.

Project administration: Xinqiong Huang.

Supervision: Guangying Zhang.

Writing – original draft: Haipeng Liu.

Writing – review & editing: Haipeng Liu, Liangfang Shen.

### References

[1] Chen R, Smith-Cohn M, Cohen AL, et al. Glioma subclassifications and their clinical significance. Neurotherapeutics 2017;14:284–97.

[2] Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803–20.

[3] Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109.

[4] Claus EB, Walsh KM, Wiercicki JK, et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus 2015;38:E6. DOI: 10.3171/2014.10.FOCUS12367.

[5] Kumthekar P, Rauzer J, Singh S. Low-grade glioma. Cancer Treat Res 2015;163:73–87.

[6] Oberheim Bush NA, Chang S. Treatment strategies for low-grade glioma in adults. J Oncol Pract 2016;12:1235–41.

[7] Ferracci FX, Michaud K, Duffau H. The landscape of postsurgical recurrence patterns in diffuse low-grade gliomas. Crit Rev Oncol Hematol 2019;138:148–55.

[8] Schiff D, Brown PD, Giannini C. Outcome of adult low-grade glioma: the impact of prognostic factors and treatment. Neurology 2007;69:1366–73.

[9] Forst DA, Naed BV, Leefer JS, et al. Low-grade gliomas. Oncologist 2014;19:403–13.

[10] Cui Y, Li G, Yan M, et al. The effects of gene polymorphisms on glioma prognosis. J Gene Med 2017;19:343–52.

[11] Wahl M, Phillips JJ, Molinaro AM, et al. Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. Neuro Oncol 2017;19:242–51.
[12] Purohit B, Kamli AA, Kollia SS. Imaging of adult brainstem gliomas. Eur J Radiol 2015;84:709–20.
[13] Pope WB, Brandal G. Conventional and advanced magnetic resonance imaging in patients with high-grade glioma. Q J Nucl Med Mol Imaging 2018;62:239–53.
[14] Wu CX, Lin GS, Lin ZX, et al. Peritumoral edema on magnetic resonance imaging predicts a poor clinical outcome in malignant glioma. Oncol Lett 2015;10:2769–76.
[15] Zhou H, Vallieres M, Bai HX, et al. MRI features predict survival and molecular markers in diffuse lower-grade gliomas. Neuro Oncol 2017;19:662–70.
[16] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[17] Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
[18] Bogdanska MU, Bodnar M, Piotrowska MJ, et al. A mathematical model describes the malignant transformation of low grade gliomas: prognostic implications. PLoS One 2017;12:1–24.
[19] Murphy ES, Leyrer CM, Parsons M, et al. Risk factors for malignant transformation of low-grade glioma. Int J Radiat Oncol Biol Phys 2018;100:965–71.
[20] Schiff D. Low-grade Gliomas. Continuum (Minneap Minn) 2017;23:1564–79.
[21] Wang TJ, Mehta MP. Low-grade glioma radiotherapy treatment and trials. Neurosurg Clin N Am 2019;30:111–8.
[22] Schiff D. PCV in low-grade gliomas: benefit from old drugs in an evolving disease entity. Neuro Oncol 2016;18:755–6.
[23] Fisher BJ, Hu C, Macdonald DR, et al. Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys 2015;91:497–504.
[24] Bush NA, Butowsky N. The effect of molecular diagnostics on the treatment of glioma. Curr Oncol Rep 2017;19:26.
[25] Brat DJ, Verhaak RG, et al. Cancer Genome Atlas Research NComprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015;372:2481–98.
[26] Dixit K, Raizer J. Newer strategies for the management of low-grade gliomas. Oncology (Williston Park) 2017;31:680–2. 684–685.