Clinical Features and Prognostic Factors of Pediatric Glioblastoma: Report of 38 Cases

Yang Jiao, Meng Wang, Xueyou Liu, Junkuan Wang, Zeming Wang, Wenzheng Luo, Yang Yu, Hongwei Sun

OBJECTIVE: **To better characterize children with glioblastoma, assess outcomes, and identify prognostic factors associated with overall survival and progression-free survival in a relatively large cohort from a single institution.**

METHODS: **For this retrospective review, 38 pediatric patients with a diagnosis of glioblastoma who were treated at The First Affiliated Hospital of Zhengzhou University between January 2015 and January 2020 were selected. Clinical and pathological characteristics, imaging, treatment, and survival variables were compared.**

RESULTS: **There were 24 boys and 14 girls with a median age of 11.5 years (range, 3–18 years). All patients underwent surgery, with gross total resection in 16 and subtotal resection in 22. Of patients, 18 received radiation combined with chemotherapy, 6 received radiation or chemotherapy alone, and 14 did not receive any adjuvant therapy. Contrast-enhanced magnetic resonance imaging of 21 patients showed rim enhancement, while heterogeneous enhancement was shown on imaging of the other 17 patients. Tumors were observed in hemispheric locations in 19 cases and in central locations in the others. Median overall survival was 10.5 months with a median progression-free survival of 6 months. Extent of resection, adjuvant therapy, and original site of tumor were identified as independent predictors for progression-free survival and overall survival on multivariate analysis. There were significant differences in prognosis among different enhancement characteristics; patients with rim-enhancing tumors had a better prognosis.**

CONCLUSIONS: **Pediatric glioblastoma carries a dismal prognosis. Maximum safe resection followed by adjuvant radiation with chemotherapy is considered standard treatment. Better outcomes are associated with hemispheric tumor locations and rim enhancement on magnetic resonance imaging.**

INTRODUCTION

Glioblastoma (GBM) is one of the most malignant tumors of the central nervous system with a 5-year survival rate of only 5%.[1] GBM is known to affect adults and is uncommon in children. Pediatric GBM accounts for 3%–7% of all primary brain tumors in children.[2-4] Pediatric GBM differs in many aspects, including clinical features, imaging, pathology, treatment, and prognosis, from adult GBM and has drawn wide attention of researchers in recent years.[3-6] However, because of the rarity of pediatric GBM, the number of cases as presented by previous studies, especially diagnosed and treated by a single institution, was inevitably limited, which required further research to develop on a broader data basis. We retrospectively analyzed 38 patients with pediatric GBM diagnosed and treated at our hospital between 2015 and 2020 to assess outcomes and identify prognostic factors associated with overall survival (OS) and progression-free survival (PFS).

MATERIALS AND METHODS

Patient Selection

Using an institutional database, 38 patients with histopathologically confirmed diagnosis of GBM at our hospital between 2015

Key words
- Clinical features
- Imaging features
- Long-term outcome
- Pediatric glioblastoma
- Treatment

Abbreviations and Acronyms
EOR: Extent of resection
GBM: Glioblastoma
GTR: Gross total resection
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
STR: Subtotal total resection

Department of Neurosurgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

To whom correspondence should be addressed: Hongwei Sun, M.D. [E-mail: sunhongweizzu1234@126.com]

Yang Jiao and Meng Wang are co–first authors.

Citation: World Neurosurg. (2021). https://doi.org/10.1016/j.wneu.2021.06.033

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

Available online: www.sciencedirect.com

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

and 2020 were selected for review. Primary GBM was newly diagnosed in all patients, and all patients were <18 years of age at the time of diagnosis. Cases of secondary GBM and spinal GBM were excluded. The clinical data of these patients were available for investigators by the approval of the institutional review board.

Data Collection

Data collection included age at diagnosis, sex, clinical manifestations (intracranial hypertension–related symptoms, seizure, and dyspraxia), original tumor sites (central locations including ventricles, thalamus, basal ganglia, brainstem, and cerebellum and hemispheric locations including brain lobes), extent of resection (EOR) (gross total resection [GTR] and subtotal resection [STR]), adjuvant therapy (radiotherapy combined with chemotherapy and other therapies, including chemotherapy only, radiotherapy only, and no therapy), imaging characteristics (rim enhancement and heterogeneous enhancement) (**Figure 1**),[7] postoperative immunohistochemistry indexes (ATRX and p53), and genetic testing (*IDH1* and *IDH2*). Patients were divided by age into 2 groups (≤10 years old and >10 years old); all underwent resection surgery. EOR was verified by comparing preoperative magnetic resonance imaging (MRI) with MRI performed within 72 hours after surgery. Postoperative radiotherapy was given, 2 Gy per day, 5 days per week, for a total dosage of 56–60 Gy. Temozolomide was prescribed for chemotherapy. Long-term outcomes included PFS and OS. OS was defined as time between the initial treatment and death or last follow-up. PFS was defined as time between the initial treatment and diagnosis of tumor recurrence. Follow-up was performed for all patients by telephone call once every 3 months or outpatient review on a timely basis. Q3

Statistical Analysis

Analysis was performed with PFS and OS as continuous variables, whereas age (≤10 years old vs. >10 years old), sex, original tumor sites, EOR, adjuvant therapies, and imaging features were taken as categorical variables. Kaplan-Meier method was used to estimate PFS and OS. Log-rank test was employed to compare survival distribution. Multivariate analysis was done using Cox proportional hazards model to simultaneously access the impact of multiple prognostic factors on survival. Differences were considered to be statistically significant when the *P* value was ≤0.05. All statistical analyses were performed using IBM SPSS Version 22.0 software (IBM Corporation, Armonk, New York, USA).

RESULTS

Clinical, Demographic, Imaging, and Pathological Features

A summary of clinical, demographic, imaging, and pathological features of 38 patients is presented in **Table 1**. There were 24 boys and 14 girls for a male-to-female ratio of 12:7. Fifteen patients were ≤10 years old and 23 patients were >10 years old, resulting in Q4 a median age of 11.5 years (range, 3–18 years). The median age of patients with hemispheric tumors was 12 years (range, 3–18 years), whereas the median age of patients with centrally located

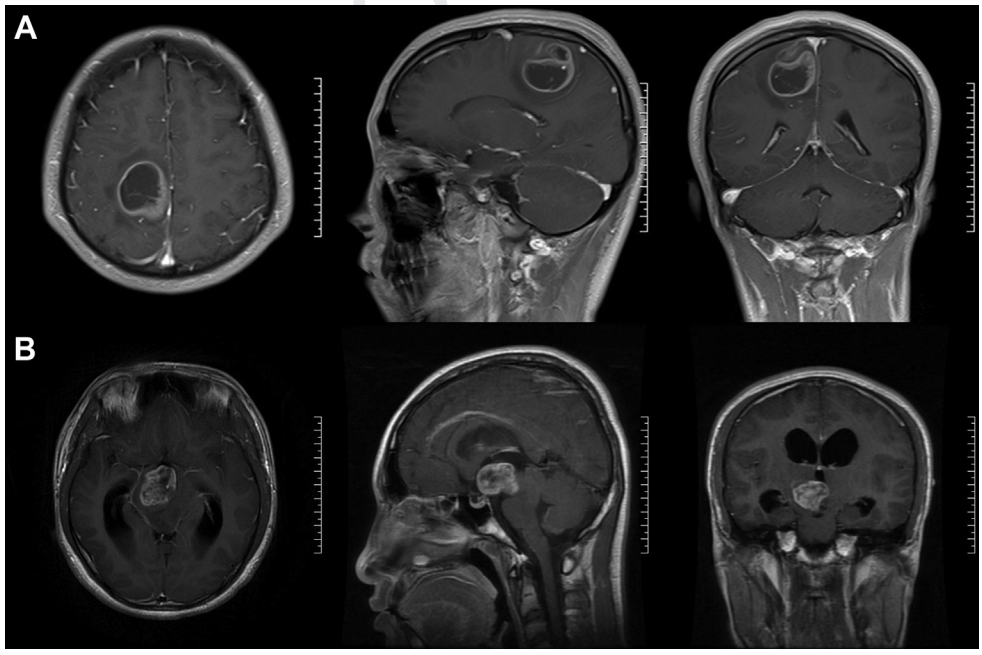

Figure 1. Typical magnetic resonance imaging showing rim enhancement and heterogeneous enhancement. (**A**) Rim enhancement is characterized by obvious surrounding annular hyperintense signal and central homogeneous hypointense signal. (**B**) Heterogeneous enhancement is characterized by heterogeneous hyperintense signal; there was no significant correlation between hyperintense and hypointense signal areas.

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

Table 1. Characteristics of 38 Patients with Pediatric Glioblastoma and Log-Rank Test for Kaplan-Meier Analysis

Characteristic	Number (%)	*P* Value PFS	*P* Value OS
Age, years		0.787	0.989
≤10	15 (39.5)		
>10	23 (60.5)		
Sex		0.851	0.677
Male	24 (63.2)		
Female	14 (36.8)		
EOR		0.001	0.001
GTR	16 (42.1)		
STR	22 (57.9)		
Adjuvant therapy		0.000	0.000
Chemoradiotherapy	18 (47.4)		
Other	20 (52.6)		
Chemotherapy alone	5		
Radiotherapy alone	1		
No adjuvant treatment	14		
Enhancement characteristics		0.012	0.012
Rim enhancing	21 (55.3)		
Heterogeneous enhancing	17 (44.7)		
Original site		0.000	0.011
Hemispheric location	19 (50)		
Central location	19 (50)		
Initial symptom			
Intracranial hypertension–related symptoms	23 (60.5)		
Dyspraxia	13 (34.2)		
Seizure	7 (18.4)		
ATRX			
Positive	14 (36.8)		
Negative	4 (10.5)		
Unknown	20 (52.6)		
p53			
Positive	17 (44.7)		
Negative	2 (5.3)		
Unknown	9 (23.9)		
IDH1			
Mutant	2 (5.3)		
Wild type	36 (94.7)		
IDH2			
Mutant	0 (0)		
Wild type	38 (100)		

PFS, progression-free survival; OS, overall survival; GTR, gross total resection; STR, subtotal resection; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection.

tumors was 11 years (range, 5–17 years). The difference between the 2 groups was not statistically significant (P = 0.075, Mann-Whitney U test). Tumors were observed in hemispheric locations in 19 cases (50%) and in central locations in 19 cases (50%). The median PFS and OS for the hemispheric tumor group were 10 and 15 months, respectively, compared with 3 and 6 months, respectively, for the centrally located tumor group. All patients presented with clinical symptoms in various degrees. Of patients, 23 (60.5%) had symptoms related to intracranial hypertension (headache, syncope, nausea, or vomiting), 7 (18.4%) had epilepsy, and 13 (34.2%) had dyspraxia. Contrast-enhanced MRI exhibited rim enhancement in 21 (55.3%) cases and heterogeneous enhancement in 17 (44.7%) cases. The median PFS and OS for the rim enhancement group were 7 and 15 months, respectively, compared with 4 and 6 months, respectively, for the heterogeneous enhancing group. Genetic testing showed *IDH1* mutation in 2 cases (5.3%); no *IDH2* mutation was identified. Immunohistochemistry results showed 14 cases positive for ARTX versus 4 negative cases and 17 cases positive for p53 versus 2 negative cases.

Treatment

Of 38 patients, 16 (42.1%) underwent GTR, and 22 (57.9%) underwent STR. Preoperative and postoperative T1-enhanced magnetic resonance images of a patient showing the same section exhibit surgical treatment (Figure 2). The median PFS and OS in patients who underwent GTR were 9.5 and 17 months, respectively, compared with 3 and 5.5 months, respectively, in patients who underwent STR. Regarding adjuvant therapy, 18 patients (47.4%) received radiotherapy with chemotherapy as postoperative regimen, 5 (13.2%) received temozolomide chemotherapy alone, 1 (2.63%) received radiotherapy alone, and 14 (36.9%) were not given any adjuvant therapy. The median PFS and OS in patients receiving chemoradiotherapy were 9.5 and 17 months, respectively, whereas median PFS and OS were 3 and 5.5 months, respectively, in patients receiving a single adjuvant therapy alone or not receiving any postoperative treatment. By the time of last follow-up, 4 patients (10.5%) were still alive, and 3 (7.9%) of these patients had no evidence of recurrence.

Kaplan-Meier Analysis of Survival

Kaplan-Meier survival estimates are presented in Figure 3. The average follow-up was 12.7 months (range, 2–48 months). The

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

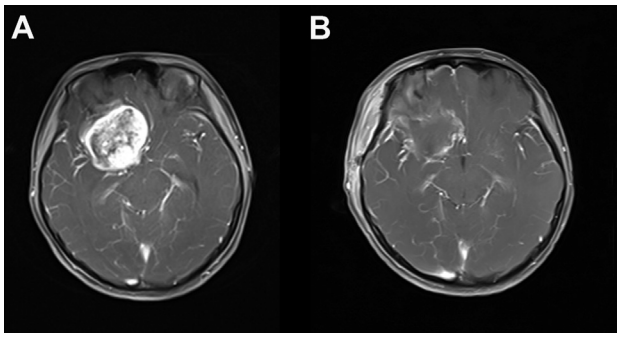

Figure 2. Magnetic resonance imaging exhibiting surgical treatment. (**A**) Preoperative T1-enhanced image of a patient shows that the tumor was characterized by heterogeneous enhancement. (**B**) Postoperative T1-enhanced image shows that gross total resection was achieved.

median PFS and OS were 6 and 10.5 months, respectively. OS rates at 6 months, 1 year, and 2 years were 65.8%, 38.4%, and 11%, respectively, whereas corresponding PFS rates were 47.4%, 16.7%, and 5.6%, respectively.

Kaplan-Meier Survival Analysis of Prognostic Factors

The original site of tumor ($P = 0.011$), enhancement characteristics ($P = 0.012$), EOR ($P = 0.001$), and adjuvant therapy ($P = 0.000$) were identified as significant prognostic factors of OS (Figure 4). Similarly, the original site of tumor ($P = 0.000$), enhancement characteristics ($P = 0.012$), EOR ($P = 0.001$), and adjuvant therapy ($P = 0.000$) were also identified as significant prognostic factors of PFS (Figure 5). GTR, adjuvant chemo radiotherapy, hemispheric location, and MRI rim enhancement predicted a better survival. Age and sex were not associated with outcomes.

Cox Proportional Hazards Model for Independent Risk Factors

A number of variables were involved in the multivariate analysis, including age, sex, EOR, MRI enhancement characteristics, original tumor location, and adjuvant therapy (Table 2). As a result, the original tumor location, EOR, and adjuvant therapy were identified as independent predictors of PFS and OS of patients with pediatric GBM.

DISCUSSION

Pediatric GBM has been a topic of discussion in recent years despite the extremely low incidence rate. This study was developed to better characterize children with GBM by evaluating clinical and pathological features, imaging characteristics, survival patterns, and prognostic factors. It featured a relatively larger size of samples provided by a single institution.

There is a general consensus that pediatric GBM has a poor prognosis. The median OS in our analysis for pediatric GBM was 10.5 months, much lower than 1–2 years reported by most previous publications.[8-10] Demographically, the median age of all patients in this study was 11.5 years, which is basically consistent with studies in other centers.[3-6,11] It was believed that pediatric GBM had a higher frequency in children >10 years of age. In most studies that were based on a database of a single hospital, the impact of age on the prognosis of pediatric GBM was not confirmed owing to limited samples. However, one exceptional study that included 1173 subjects revealed that younger age was associated with better survival.[12] In our study, there was no statistical difference in survival patterns between the 2 age groups (≤10 years and >10 years), suggesting that age was not a prognostic factor of pediatric GBM. The male-to-female ratio in our cohorts was 12:7, indicating a similar demographic pattern to that of adult GBM with males representing the majority of cases.[2-4,8,9] In addition, better survival was not associated with sex, which is consistent with other reports.[2,9,13]

We classified the primary site of tumors as hemispheric and central for children with GBM. Previous analyses tended to

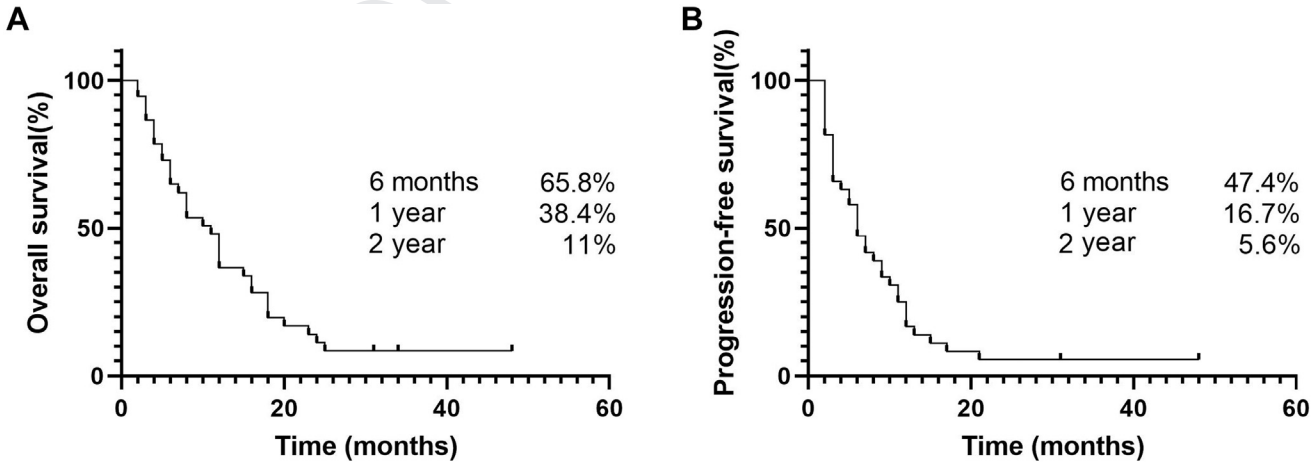

Figure 3. Kaplan-Meier curves for survival of 38 patients with pediatric glioblastoma. (**A**) Overall survival. (**B**) Progression-free survival.

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

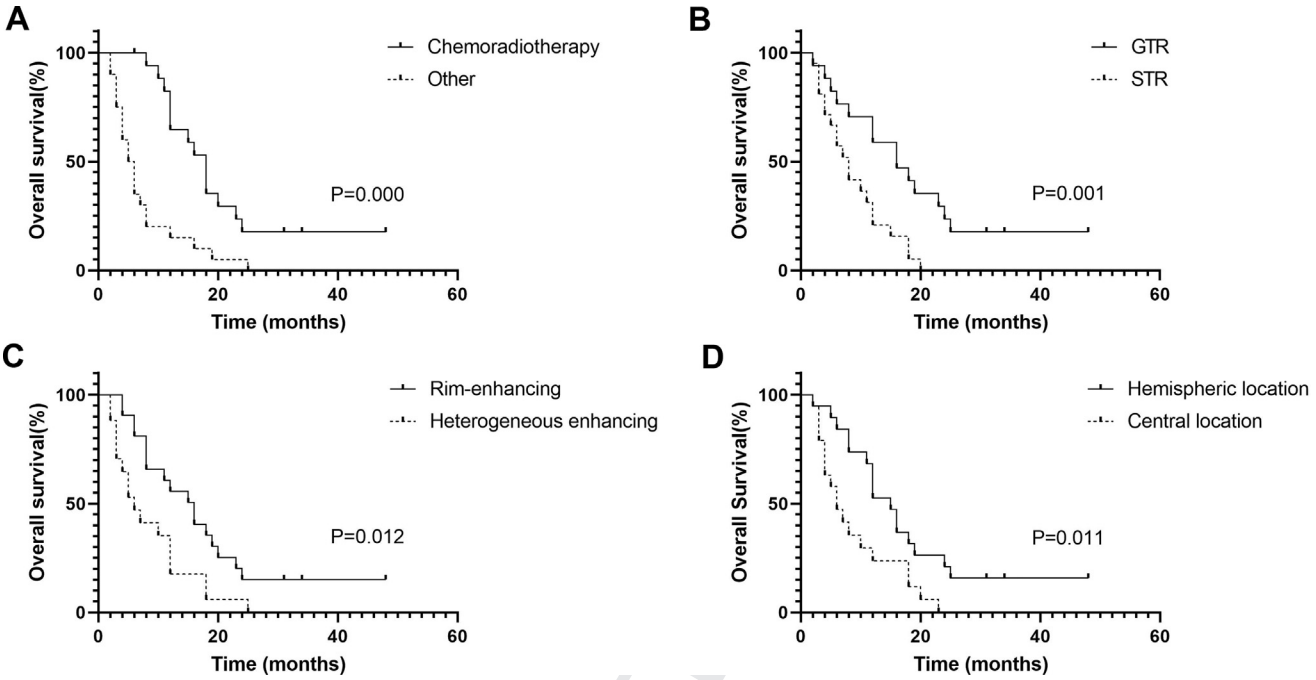

Figure 4. Kaplan-Meier curves for overall survival (OS). (**A**) OS based on adjuvant therapy ($P = 0.000$). (**B**) OS based on extent of resection ($P = 0.001$). (**C**) OS based on different enhancement characteristics ($P = 0.012$). (**D**) OS based on original site of tumors ($P = 0.011$). GTR, gross total resection; STR, subtotal resection.

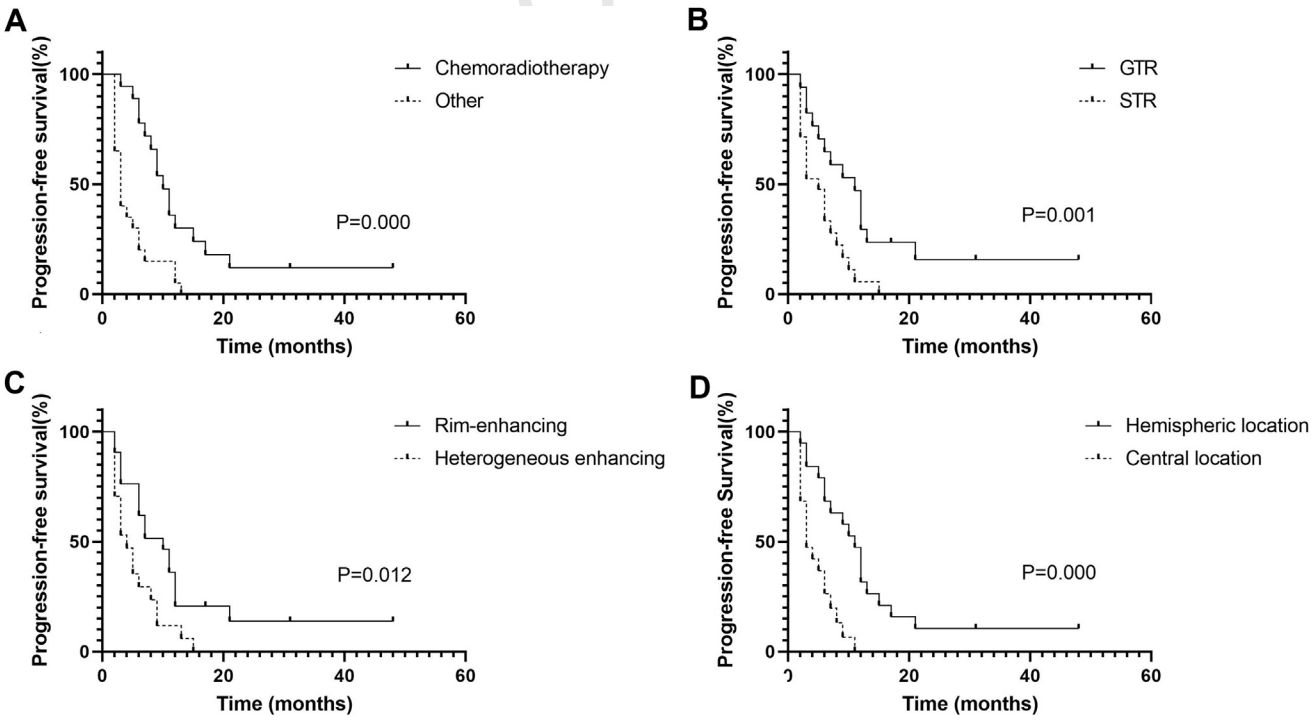

Figure 5. Kaplan-Meier curves for progression-free survival (PFS). (**A**) PFS based on adjuvant therapy ($P = 0.000$). (**B**) PFS based on extent of resection ($P = 0.001$). (**C**) PFS based on different enhancement characteristics ($P = 0.012$). (**D**) PFS based on original site of tumors ($P = 0.000$). GTR, gross total resection; STR, subtotal resection.

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

Table 2. Cox Proportional Hazards Model for Independent Risk Factors of Progression-Free Survival and Overall Survival

Prognostic Factors	PFS	OS
Age		
HR	0.937	0.960
95% CI	0.847–1.036	0.883–1.043
P value	0.205	0.335
Sex		
HR	1.314	1.126
95% CI	0.594–2.905	0.480–2.641
P value	0.500	0.785
EOR		
HR	3.103	2.769
95% CI	1.202–8.008	1.077–6.585
P value	0.019	0.034
Adjunctive therapy		
HR	6.556	5.748
95% CI	2.557–16.807	2.399–13.772
P value	0.000	0.000
Enhancement characteristics		
HR	1.129	1.521
95% CI	0.456–2.795	0.667–3.468
P value	0.793	0.318
Original site		
HR	5.464	2.584
95% CI	1.866–16.129	1.010–6.623
P value	0.002	0.048

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; EOR, extent of resection.

suggest that centrally located tumors had higher mortality compared with tumors with hemispheric locations.[12] This view was also confirmed by our study as expected. Centrally located tumors are very aggressive and associated with H3K27M mutations and were classified as H3 mutant diffuse midline glioma by the World Health Organization central nervous system tumor classification in 2016.

Most patients in our study exhibited initial symptoms of headache, syncope, nausea, or vomiting which were caused by increased intracranial pressure. In 2 cases, patients had facial paralysis associated with cranial nerve lesions. Patients with infratentorial tumors commonly had initial symptoms of somatic ataxia, dystonia, or dyskinesia. Depending on the location and growth rate of tumors, the initial symptom of pediatric GBM had not been exactly defined.[8]

IDH mutation has been widely accepted as a predictor of long survival for patients with GBM.[14,15] In our cohort, however, *IDH1* mutation occurred in 2 patients, aged 10 and 12 years, respectively, which differed distinctly from other descriptions in the literature that *IDH1* had a higher frequency in children >14 years of age.[15] The incidence of *IDH1* mutation in primary GBM is extremely low with an estimated rate of 5%, making it impossible in this study to statistically analyze the correlation between *IDH1* mutation and survival patterns. However, the view that *IDH1* mutation offers better survival for children with GBM is supported by our study. The 2 aforementioned patients with *IDH1* mutations had a prolonged survival. They were both alive and showed no evidence of recurrence at the time of their last follow-up, one of which was 31 months after diagnosis.

Imaging data provide important information for diagnosis. We are the first to analyze the relationship between the enhancement characteristics and prognosis of pediatric GBM in a relatively larger cohort. According to Choi et al.,[7] heterogeneous enhancement on contrast-enhanced MRI indicated worse outcomes for adult patients with GBM.[7] In our study, the median PFS and OS for patients with tumors with rim enhancement were 7 and 15 months, respectively. Median PFS and OS for patients with tumors with heterogeneous enhancement were 4 and 6 months, respectively. These differences were statistically significant, and pediatric patients with GBM tumors with rim enhancement have a better prognosis.

The importance of GTR in prolonged survival of patients with pediatric GBM has been addressed in almost all previous studies.[13,16,17] In our cohort, patients who underwent GTR had better PFS and OS compared with patients with STR. We recommend full use of microsurgery and intraoperative navigation as possible to improve the resection rate of tumors for better outcomes.

As concluded by this study, resection surgery and adjuvant chemoradiotherapy were independent predictors of OS and PFS that could distinctly prolong the survival of patients with pediatric GBM. Maximal safe resection of tumors followed by radiotherapy with concurrent chemotherapy is currently considered the standard treatment regimen.[6,9,18-20] The use of temozolomide as postoperative treatment for patients with GBM was first addressed by Stupp et al. in 2005.[21] Subsequent reports proved that temozolomide offered longer survival for children as it did for adults.[22] However, although we had actively recommended postoperative chemoradiotherapy to every patient, there was still a large number of patients who did not receive any postoperative adjuvant therapy owing to the high cost of treatment and the incurable status of GBM. If possible, we hope such standard treatment can become affordable to most families in the future.

CONCLUSIONS

This is a relatively large cohort of pediatric patients with GBM diagnosed and treated at a single center between 2015 and 2020. In general, pediatric GBM remains challenging to manage. No differences of PFS and OS were found based on age or sex. Origin site, EOR, and postoperative adjuvant treatment were independent predictors of OS and PFS. We should emphasize maximum safe resection combined with postoperative chemoradiotherapy as the prime treatment strategy. A better prognosis is related to

FLA 5.6.0 DTD ■ WNEU17375_proof ■ 28 June 2021 ■ 1:19 pm ■ ce

hemispheric tumor location and rim enhancement on preoperative enhanced MRI.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Yang Jiao: Conceptualization, Data curation, Writing - original draft. **Meng Wang:** Conceptualization, Writing - review & editing. **Xueyou Liu:** Writing - review & editing. **Junkuan Wang:** Writing - review & editing. **Zeming Wang:** XXX. **Wenzheng Luo:** Writing - review & editing. **Yang Yu:** Writing - review & editing. **Hongwei Sun:** Supervision, Writing - review & editing.

ACKNOWLEDGMENTS

We thank all the patients who trusted us and all the physicians and staff who assisted with this study.

REFERENCES

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol*. 2014;16(Suppl 4): iv1-iv63.
2. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol*. 2012; 14(Suppl 5):v1-v49.
3. Mahvash M, Hugo HH, Maslehaty H, Mehdorn HM, Stark AM. Glioblastoma multiforme in children: report of 13 cases and review of the literature. *Pediatr Neurol*. 2011;45:178-180.
4. Sánchez-Herrera F, Castro-Sierra E, Gordillo-Domínguez LF, et al. Glioblastoma multiforme in children: experience at Hospital Infantil de Mexico Federico Gomez. *Childs Nerv Syst*. 2009;25: 551-557.
5. Das KK, Mehrotra A, Nair AP, et al. Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. *Childs Nerv Syst*. 2012; 28:2055-2062.
6. Song KS, Phi JH, Cho BK, et al. Long-term outcomes in children with glioblastoma. *J Neurosurg Pediatr*. 2010;6:145-149.
7. Choi SW, Cho HH, Koo H, et al. Multi-habitat radiomics unravels distinct phenotypic subtypes of glioblastoma with clinical and genomic significance. *Cancers (Basel)*. 2020;12:1707.
8. Nikitović M, Stanić D, Pekmezović T, et al. Pediatric glioblastoma: a single institution experience. *Childs Nerv Syst*. 2016;32:97-103.
9. Perkins SM, Rubin JB, Leonard JR, et al. Glioblastoma in children: a single-institution experience. *Int J Radiat Oncol Biol Phys*. 2011;80:1117-1121.
10. Karremann M, Butenhoff S, Rausche U, Pietsch T, Wolff JE, Kramm CM. Pediatric giant cell glioblastoma: new insights into a rare tumor entity. *Neuro Oncol*. 2009;11:323-329.
11. Suri V, Das P, Pathak P, et al. Pediatric glioblastomas: a histopathological and molecular genetic study. *Neuro Oncol*. 2009;11:274-280.
12. Liu M, Thakkar JP, Garcia CR, et al. National cancer database analysis of outcomes in pediatric glioblastoma. *Cancer Med*. 2018;7:1151-1159.
13. Yang T, Temkin N, Barber J, et al. Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. *World Neurosurg*. 2013;79:537-544.
14. Antonelli M, Buttarelli FR, Arcella A, et al. Prognostic significance of histological grading, p53 status, YKL-40 expression, and IDH1 mutations in pediatric high-grade gliomas. *J Neurooncol*. 2010; 99:209-215.
15. Pollack IF, Hamilton RL, Sobol RW, et al. IDH1 mutations are common in malignant gliomas arising in adolescents: a report from the Children's Oncology Group. *Childs Nerv Syst*. 2011;27: 87-94.
16. Gupta S, Mallick S, Benson R, Haresh KP, Julka PK, Rath GK. Extent of surgical resection and adjuvant temozolomide improves survival in pediatric GBM: a single center experience. *Childs Nerv Syst*. 2017;33:951-956.
17. Adams H, Adams HH, Jackson C, Rincon-Torroella J, Jallo GI, Quiñones-Hinojosa A. Evaluating extent of resection in pediatric glioblastoma: a multiple propensity score-adjusted population-based analysis. *Childs Nerv Syst*. 2016; 32:493-503.
18. Klein R, Mölenkamp G, Sörensen N, Roggendorf W. Favorable outcome of giant cell glioblastoma in a child. Report of an 11-year survival period. *Childs Nerv Syst*. 1998;14:288-291.
19. Shinojima N, Kochi M, Hamada J, et al. The influence of sex and the presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme. *J Neurosurg*. 2004;101:219-226.
20. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group. *J Neurooncol*. 1989;7:165-177.
21. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
22. Donson AM, Addo-Yobo SO, Handler MH, Gore L, Foreman NK. MGMT promoter methylation correlates with survival benefit and sensitivity to temozolomide in pediatric glioblastoma. *Pediatr Blood Cancer*. 2007;48:403-407.

Conflict of interest statement: Funding was provided by Medical Science and Technology Project of Henan Province (SBGJ202003032).

Received 5 May 2021; accepted 7 June 2021

Citation: World Neurosurg. (2021). https://doi.org/10.1016/j.wneu.2021.06.033

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

*Available online: **www.sciencedirect.com***