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Clinical characteristics and prognostic factors of adult brainstem gliomas

A retrospective analysis of histologically-proven 40 cases

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Abstract

To illustrate the clinical characteristics and prognostic factors of adult patients pathologically confirmed with brainstem gliomas (BSGs). Clinical data of 40 adult patients pathologically diagnosed with BSGs admitted to Beijing Shijitan Hospital from 2009 to 2022 were recorded and retrospectively analyzed. The primary parameters included relevant symptoms, duration of symptoms, Karnofsky performance status (KPS), tumor location, type of surgical resection, diagnosis, treatment, and survival. Univariate and multivariate analyses were evaluated by Cox regression models. The gliomas were located in the midbrain of 9 patients, in the pons of 14 cases, in the medulla of 5 cases, in the midbrain and pons of 6 cases and invading the medulla and pons of 6 cases, respectively. The proportion of patients with low-grade BSGs was 42.5%. Relevant symptoms consisted of visual disturbance, facial paralysis, dizziness, extremity weakness, ataxia, paresthesia, headache, bucking, dysphagia, dysacousia, nausea, dysphasia, dysosmia, hypomnesia and nystagmus. 23 (57.5%) patients accepted stereotactic biopsy, 17 (42.5%) patients underwent surgical resection. 39 patients received radiotherapy and 34 cases were treated with temozolomide. The median overall survival (OS) of all patients was 26.2 months and 21.5 months for the median progression-free survival (PFS). Both duration of symptoms (P = .007) and tumor grading (P = .002) were the influencing factors for OS, and tumor grading was significantly associated with PFS (P = .001). Duration of symptoms for more than 2 months and low-grade are favorable prognostic factors for adult patients with BSGs.

Abbreviations: BSGs = brainstem gliomas, KPS = Karnofsky performance status, MRI = magnetic resonance imaging, OS = overall survival, PFS = progression-free survival.

Keywords: adult, brainstem glioma, prognostic factor, survival

1. Introduction

Adult brainstem gliomas (BSGs) are rare malignant tumors in central nervous system and account for merely 2% of adult gliomas, significantly lower than 20% of pediatric brain tumors.[1] Unlike unfavorable prognosis in pediatric high-grade BSGs,[2] adult BSG patients can obtain different clinical outcomes. Based on magnetic resonance imaging (MRI) findings, BSGs can be divided into diffuse and local lesions according to whether the tumors infiltrate into 50% of the axial diameter of brainstem.[3] Furthermore, diffuse midline glioma is newly defined as H3 K27M-mutant by the WHO 2016 Classification, which is categorized as grade 4 by WHO, aiming to emphasize the role of molecular genetics.[4] In recent decades, MRI has been employed as the primary diagnostic tool for BSGs due to the low prevalence and the large number of essential nervous tissues located in the brainstem. Surgical resection can be avoided considering the potential risk of neurological dysfunction. However, the diagnostic discrepancy between MRI images and pathological results emphasizes the importance of tissue acquisition. Because of the low incidence, clinical data of adult and pediatric BSG patients are constantly combined for subsequent analysis, leading to the scarce data. In this study, clinical characteristics, treatment regimens, and prognostic factors of adult patients pathologically confirmed with BSGs between 2009 and 2022 were retrospectively analyzed, aiming to supplement evidence for clinical diagnosis and management of rare adult BSGs.

2. Materials and methods

2.1. Study design

Clinical data of 40 adult BSG patients (aged >18 years) with definite histopathological results treated in the Department of Oncology, Beijing Shijitan Hospital from 2009 to 2022 were

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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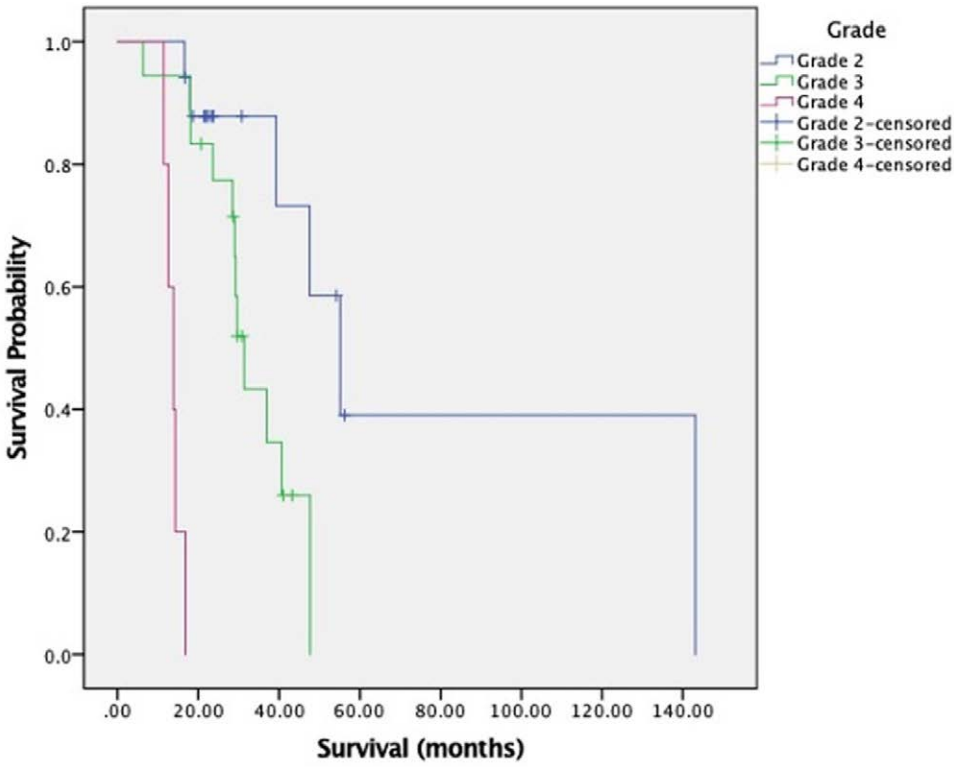

Figure 1. MRI demonstrating a nonenhanced diffused lesion in the pons (A) and contrast-enhanced lesions in the medulla (B). MRI = magnetic resonance imaging.

retrospectively analyzed. The study procedures were approved by the ethics committee of our hospital. Relevant data were collected from medical records of outpatients and inpatients as well as regular telephone follow-up.

2.2. Primary parameters

Primary parameters included gender, age, initial symptoms, duration of symptoms, Karnofsky performance status (KPS), tumor location, MRI imaging, type of surgical resection, histopathological diagnosis, treatment regimens, and survival. Overall survival (OS) was calculated from the histopathological diagnosis to death or the final date of follow-up until December 2022. Progression-free survival (PFS) was defined from the histopathological diagnosis to the date of CT scan or MRI evidence showing tumor recurrence.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago). Survival comparison between 2 groups was assessed by two independent samples *t* test. The survival curve was delineated by the Kaplan–Meier method. Univariate and multivariate analyses were evaluated by the Cox regression models. A *P* value of <.05 was considered statistically significant.

3. Results

3.1. Baseline data

A total of 20 male and 20 female patients were included. The median age at diagnosis was 37 years (range: 18–57 years) and the median KPS was 70 (range: 50–90). The tumors were located in the midbrain of 9 patients, in the pons of 14 cases, in the medulla of 5 cases, 6 cases of midbrain and pons invasiveness, 6 cases of medulla and pons infiltration, respectively.

3.2. Magnetic resonance imaging

MRI demonstrated a nonenhanced diffused lesion in the pons (Fig. 1A). The patient received stereotactic biopsy followed by 5040 cGy radiotherapy. Imaging findings indicated the status of stable disease. She refused temozolomide chemotherapy after radiation. In February 2016, the patient suffered from headache and extremity weakness. MRI showed enlarged tumors in the medulla (Fig. 1B).

3.3. Clinical features

Twenty-five patients had symptoms lasting for >2 months before admission, and enduring for <2 months in the remaining 15 patients. Initial clinical symptoms included visual disturbance (50.0%, diplopia in 13 cases, blurry vision in 7 cases), facial paralysis (32.5%, n = 13), dizziness (25.0%, n = 10), extremity weakness (25.0%, n = 10), ataxia (20.0%, n = 8), paresthesia (20.0%, n = 8), headache (17.5%, n = 7), bucking (17.5%, n = 7), dysphagia (10.0%, n = 4), dysacousia (7.5%, hearing loss in 2 cases, tinnitus in 1 case), nausea (7.5%, n = 3), dysphasia (5.0%, n = 2), dysosmia (2.5%, n = 1), hypomnesia (2.5%, n = 1), and nystagmus (2.5%, n = 1).

3.4. BSGs grading system

The proportion of patients with WHO grade 2 BSGs was 42.5% (14 cases of astrocytoma who were diagnosed before 2016, 3 cases of oligoastrocytoma), WHO grade 3 BSGs accounted for 45.0% (9 cases of anaplastic oligoastrocytoma, 2 cases of anaplastic oligodendroglioma, 7 cases of anaplastic astrocytoma), and 12.5% for WHO grade 4 BSGs (3 cases of glioblastoma and 2 patients who were diagnosed with diffuse midline glioma, H3 K27M-mutant after 2016). Among them, 11 patients received genetic testing. The status of IDH1 mutation, 1p/19q co-deletion, and MGMT promotor methylated of 11 cases were illustrated in Table 1.

Table 1

Clinical features of 40 adult brainstem glioma patients.

Variables		*N*	%
Gender			
	M	20	50.0
	F	20	50.0
Age (yr)	Median 37	Range 18~57	
KPS	Median 70	Range 50~90	
Location			
	Midbrain	9	22.5
	Pons	14	35.0
	Medulla	5	12.5
	Midbrain and pons	6	15.0
	Medulla and pons	6	15.0
Symptoms			
	Visual disturbances	20	50.0
	Facial paralysis	13	32.5
	Dizziness	10	25.0
	Extremity weakness	10	25.0
	Ataxia	8	20.0
	Paresthesia	8	20.0
	Headache	7	17.5
	Bucking	7	17.5
	Dysphagia	4	10.0
	Dysacousia	3	7.5
	Nausea	3	7.5
	Dysphasia	2	5.0
	Dysosmia	1	2.5
	Hypomnesia	1	2.5
	Nystagmus	1	2.5
Surgery			
	Biopsy	23	57.5
	Resection	17	42.5
	GTR	1	2.5
	STR	12	30.0
	PR	4	10.0
WHO grade			
Grade 2		17	42.5
	A	14	35.0
	O	3	7.5
Grade 3		18	45.0
	AOA	9	22.5
	AO	2	5.0
	AA	7	17.5
Grade 4		5	12.5
	GBM	3	7.5
	H3 K27M-mutant DMG	2	5.0
IDH1			
	Mutation	8	20.0
	Wild type	3	7.5
	Not available	29	72.5
MGMT promoter			
	Methylation	4	10.0
	Unmethylation	7	17.5
	Not available	29	72.5
1p/19q			
	Co-deletion	3	7.5
	Intact	8	20
	Not available	29	72.5
Initial treatment			
Radiotherapy			
	RT alone	9	22.5
	CRT	30	75.0
	Surveillance	1	2.5
Chemotherapy	TMZ (5/28 regimen)	34	85.0
Treatment after progression		28	70.0
Chemotherapy		20	50.0
	TMZ (7/14 regimen)	12	30.0
	Cisplatin	4	10.0
	Irinotecan	2	5.0
	Etoposide	2	5.0
Target therapy	Bevacizumab	6	15.0
Ventriculoperitoneal shunt		2	5.0
Cyber knife		1	2.5

A = astrocytoma, AA = anaplastic astrocytoma, AO = anaplastic oligodendrogliomas, AOA = anaplastic oligoastrocytomas, CRT = concurrent chemoradiotherapy, CT = chemotherapy, F = female, GBM = glioblastoma, GTR = gross total resection, H3 K27M-mutant DMG = Diffuse midline glioma, H3 K27M-mutant, IDH = isocitrate dehydrogenase, KPS = Karnofsky performance scale, M = male, MGMT = O(6)-methylguanine-DNA methyltransferase, O = oligodendroglioma, PR = partial resection, RT = radiotherapy, STR = subtotal resection, TMZ = temozlilomide.

3.5. Therapeutic regimen

Twenty-three (57.5%) patients underwent stereotactical biopsy, 17 (42.5%) patients received surgical resection including 1 case of total resection, 12 cases of subtotal resection, and 4 cases of partial resection. Postoperative complications mainly consisted of hydrocephalus (n = 2) and intracranial infection (n = 1). After pathological examination, 9 (22.5%) patients received radiotherapy alone, including 4 cases of high-grade gliomas because of abnormal liver function (n = 3) or thrombopenia (n = 1) and 5 cases of low-grade gliomas. Concurrent chemoradiotherapy was completed in 30 (75%) patients (11 low-grade BSGs and 19 high-grade BSGs) while only 1 (2.5%) patient underwent surveillance without any treatment due to refusal to receive radiotherapy. The dose of radiotherapy ranged from 4500 cGy to 6000 cGy. Thirty-four (85.0%) patients received temozolomide chemotherapy after radiation in the primary setting (4–12 cycles, 150–200 mg/m^2/d 5/28 regimen). Until the final follow-up, 28 (70.0%) patients developed disease progression. According to the KPS, 20 (50.0%) patients received secondary chemotherapy after tumor recurrence. In the initial period, 6 cases accepted radiotherapy alone, 14 cases received concurrent chemoradiotherapy followed by temozolomide. The optional regimens contained temozolomide (150 mg/m^2/d, 7/14 regimen, 2–4 cycles), irinotecan (120 mg/m^2/d every 2 weeks, 2–4 cycles), etoposide (100 mg/m^2/d, days 1–3, every 4 weeks, 2–4 cycles), and cisplatin (75 mg/m^2/d every 4 weeks, 2–4 cycles), 6 (15.0%) patients underwent bevacizumab target therapy (5 mg/kg, every 2 weeks, 2–14 cycles), 4 (10.0%) patients received intrathecal chemotherapy (methotrexate, 10 mg every week, 6–8 weeks), ventriculoperitoneal shunt was employed in 2 (5.0%) patients, and 1 (2.5%) patient treated with cyber knife (Table 1).

3.6. Survival analysis

A total of 23 patients died at the end of follow-up in December 2022. The survival rates by WHO grade were reported as follows: 64.7% (11/17) for grade 2, 33.3% (6/18) for grade 3 and 0% (0/5) for grade 4, respectively. The median OS for all patients was 26.2 months (range: 6.3–143.1 months) and the median PFS was 21.5 months (range: 2.3–88.4 months). The median OS for grade 3 patients was 29.4 months and 13.8 months for grade 4 ($P < .001$). The 1-year survival rate was 95.0% (38/40), 50.0% (20/40) for 2-year survival rate, and 27.5% (11/40) for 3-year survival rate. The median OS for patients undergoing surgical resection was 29.6 months (range: 6.3–47.6 months) and 23.3 months (range: 11.4–143.1 months) for those receiving biopsy ($P = .594$). The median PFS for patients undergoing surgical resection was 21.5 months (range: 2.3–41.0 months) and 21.4 months (range: 5.1–88.4 months) for those receiving biopsy ($P = .989$).

3.7. Prognostic factors

Univariate analysis demonstrated gender, duration of symptoms, and BSGs grading were associated with PFS and OS (Tables 2 and 3). Multivariate analysis showed duration of symptoms (HR = 0.261, 95%CI = 0.098–0.691, $P = .007$) and BSGs grading (HR = 0.050, 95%CI = 0.008–0.332, $P = .002$) were the prognostic factors for OS. Patients with a duration of symptoms of >2 months obtained better survival than those with a duration of symptoms of <2 months (Figs. 2 and 3). BSGs grading was the only prognostic factor of PFS (HR = 0.053, 95%CI = 0.010–0292, $P = .001$).

4. Discussion

Adult BSGs exhibit heterogeneous disease courses, diverse radiological manifestations, and variable outcomes. The onset

Table 2

Univariate analysis for progression-free survival by Cox regression models.

Variables	N	Median progression-free survival (mo)	HR	95% CI	*P*
Age			0.984	0.951–1.018	.350
Gender			2.233	1.021–4.884	.044
Male	20	19.4			
Female	20	23.6			
Symptom duration			0.456	0.221–0.981	.044
<2 mo	15	16.4			
>2 mo	25	22.3			
KPS			1.333	0.518–3.427	.551
<70	9	23.3			
≥70	31	21.4			
Grade			5.487	2.400–12.545	.001
2	17	23.3			
3	18	21.1			
4	5	7.2			
Surgery			1.714	0.783–3.749	.177
Biopsy	23	21.4			
Resection	17	21.5			

KPS = Karnofsky performance status.

Table 3

Univariate analysis for overall survival performed by Cox regression.

Variables	N	Median overall survival (mo)	HR	95% CI	*P*
Age			0.970	0.934–1.008	.121
Gender			3.537	1.412–8.862	.007
Male	20	22.6			
Female	20	30.2			
Symptom duration			0.351	0.151–0.817	.015
<2 mo	15	23.8			
>2 mo	25	28.5			
KPS			1.173	0.440–3.128	.750
<70	9	29.0			
≥70	31	23.6			
Grade			7.444	2.775–19.968	.001
2	17	23.3			
3	18	29.4			
4	5	13.8			
Surgery			1.803	0.723–4.500	.206
Biopsy	23	23.3			
Resection	17	29.6			

KPS = Karnofsky performance status.

age of adult BSG patients is ranged from 30 to 40 years old, and 60% of tumors arise from the pons and 45% to 50% for diffuse low-grade glioma.[1] BSGs lack specific manifestations. The most common symptoms of BSGs consist of visual disturbance, facial palsy, headache, limb weakness and hemiparesis,[2,3] which are consistent with the findings in the present study. More than 20% of patients may present with hydrocephalus due to the obstruction of cerebrospinal fluid circulation caused by tumors.[3] Ventriculoperitoneal shunt is the most common management to relieve headache symptoms. In this study, ventriculoperitoneal shunt was indwelled in 2 patients after disease progression, which is an immediate and effective option to improve the quality of life by lowering intracranial pressure.

MRI yields critical value in the imaging examination of BSG patients. Low-grade BSG is featured by hypointense areas on T1-weighted sequences and hyperintense signals on T2/FLAIR (Fluid Attenuation Inversion Recovery) images.[5] Other features, such as enhanced contrast lesions, necrosis, cysts, and surrounded edema, indicate high-grade BSGs, generally the more obvious contrast enhancement, the more severe malignant of the tumor. However, the rule is not always applicable due to only 0% to 25% of tumor cells could be stained with contrast agent.[4] Besides, approximately 31.2% of high-grade BSGs demonstrate nonenhancement.[5] Lymphomas, metastatic malignant tumors, abscesses, and demyelinating diseases also could demonstrate enhanced lesions.[6] Magnetic resonance spectroscopy may assist in differentiating the enhanced lesions which the choline/NAA ratio will elevate in BSGs.[7] Rachinger et al reported only 60.9% (28/46) of glial neoplasm in the brainstem suspected by imaging examination are finally confirmed by histopathological results. Furthermore, the predictive rate for low-grade glioma is 27% and 35% (7/20) for high-grade glioma,[3] highlighting the importance of pathological diagnosis. In our study, all patients underwent pathological diagnosis to avoid conclusive deviations, however, only 11 patients received genetic testing. Lack of molecular diagnosis was a study limitation.

It is challenging to perform total resection for BSG patients due to critical anatomical structure. Previously, the aim of surgical approach is to relieve clinical symptoms and reduce high cranial pressure. With the advancement of surgical technology, neurosurgeons are also attempting to explore a balance between tumor debulking associated with prolonged survival and the risk of surgical complications. Doyle J reported a greater extent of excision (gross total resection and subtotal resection) is

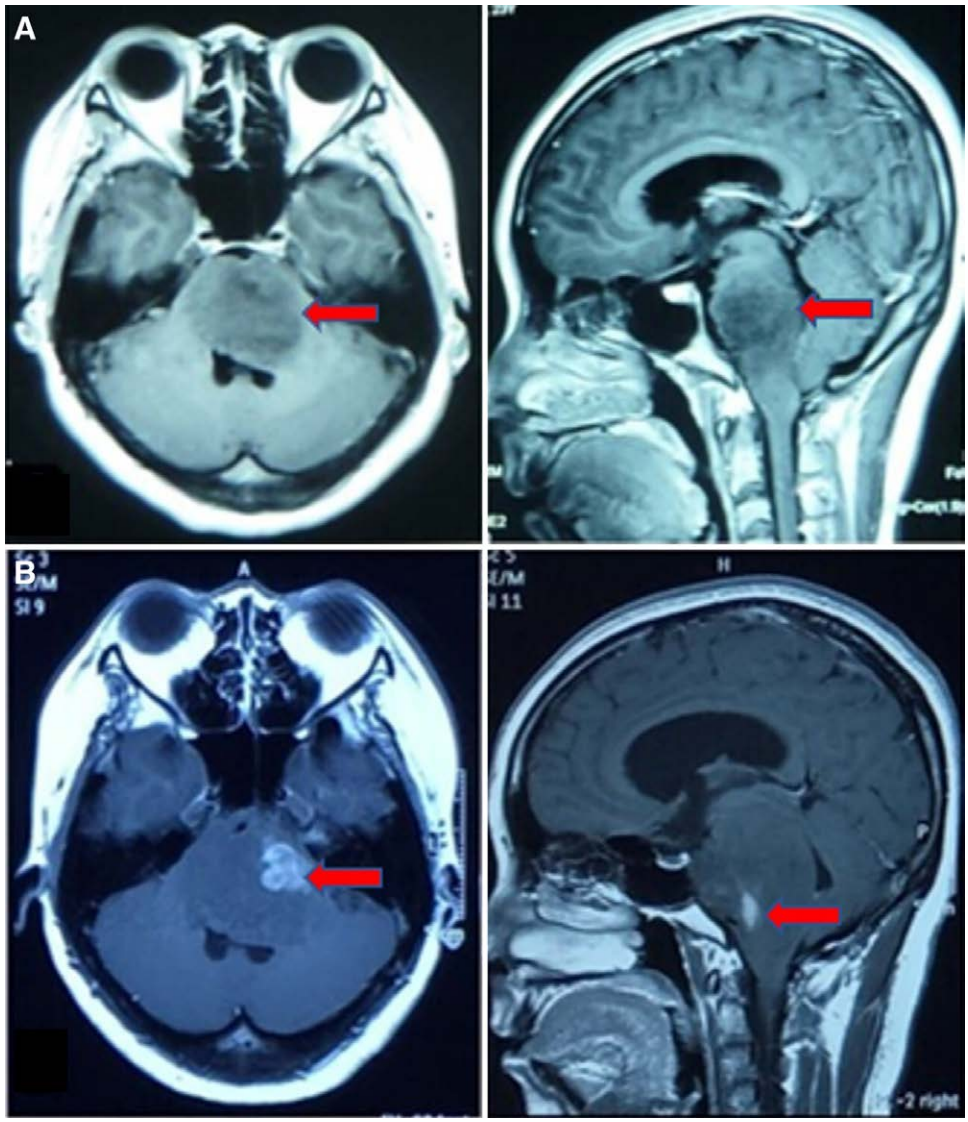

Figure 2. Survival analysis between patients with duration of symptoms of >2 mo and those of <2 mo.

associated with increased survival in high-grade BSGs (16 and 11 months), while the survival of biopsy patients is 8 months.[8] Besides, the incidence rate of permanent neurological damage caused by surgical resection is reported only 1.7%.[9] Expert consensus has been reached that surgical resection is recommended for BSGs.

In our study, the median survival for surgical patients was 29.6 months and 23.3 months for biopsy patients with no statistical difference, probably due to the small size and lack of subgroup analysis.

Radiation therapy is another indispensable standard treatment for adult BSGs, the recommended dose is 54 to 60 Gy in 1.8–2.0 Gy per fraction.[10] Park et al[11] reported hypofractionated radiotherapy (39/44.8 Gy in 13/16 fractions) presented with similar survival compared with conventionally fractionated radiotherapy (50.4–60 Gy) in diffuse intrinsic pontine gliomas. Due to the particularity of brainstem position and residual tumor tissue after surgery, the radiation dose varies significantly among individuals. In our cohort, the dose range was 45 to 60 Gy, depending on the resection extent, pathological grade, and KPS of patients.

For high-grade adult BSGs, concomitant chemoradiotherapy followed by temozolomide adjuvant chemotherapy (Stupp regimen) is the protocol of treatment.[12] In the present study, 30 patients received Stupp regimen, including 19 high-grade and 11 low-grade BSGs, whereas for low-grade adult BSGs, the survival benefit from concurrent chemoradiotherapy still needs more evidence.[5] It is certified that diffuse midline glioma, H3 K27-altered obtains worse survival. Meyronnet et al[13] reported histone H3 mutations are mutually exclusive with IDH1 R132H mutations, while uncommon mutations (R132C, R132G) are found in another study,[14] suggesting that adult BSGs presenting with specific genetic features distinguish from the supratentorial gliomas. Two preclinical compounds, indoximod which is an IDO1 inhibitor and imipridone ONC201 have already confirmed efficacy target H3K27M in vitro and in vivo.[15] Although only 2 patients were diagnosed with diffuse midline glioma, H3 K27M-mutant in our study, these findings still indicate that target therapy is a promising approach for these patients.

The recommended regimens for recurrent adult BSGs are also unsettled due to the scarce data. Another important reason is the deteriorated KPS of recurrent patients, most of them could no longer be able to withstand antitumor therapy (KPS < 60). As in our cohort, only 20 relapsed patients received chemotherapy, including temozolomide, cisplatin, etoposide, and irinotecan. Most of them repeatedly progressed after 2 to 4 cycles. Tyrosine kinase inhibitors were recommended for *NTRK* gene fusion or *BRAF* V600E mutation. Bevacizumab

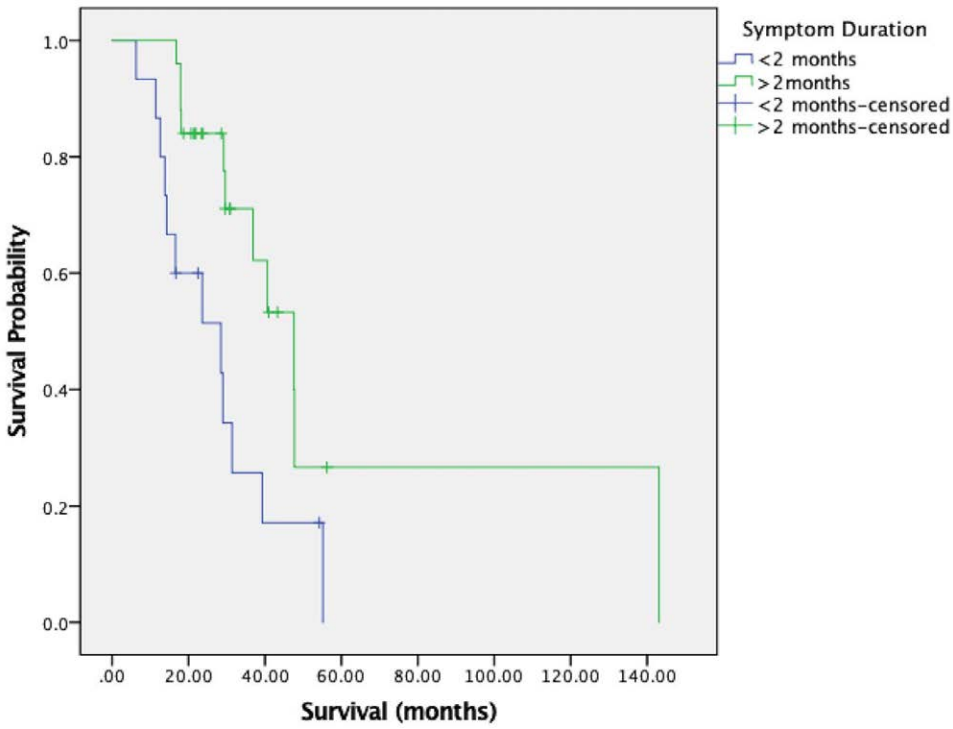

Figure 3. Survival analysis between patients with high-grade and low-grade BSGs. BSGs = brainstem gliomas.

has been shown to relieve hydrocephalus, decrease steroid doses, and improve the quality of life in patients with supratentorial glioma.[15] Theeler et al reported that 21% of (3/14) adult BSG patients achieve 6-month PFS after bevacizumab treatment.[16] Six patients receiving bevacizumab target therapy in our study showed significant physical improvement rather than survival benefit. Anti-PD-1 therapy, such as nivolumab or pembrolizumab has yielded prolonged survival in recurrent glioblastoma patients (14.3 months compared to the 10.1 months).[17] However, in CheckMate 143 Phase 3 randomized clinical trial, OS is similar between nivolumab and bevacizumab groups for recurrent glioblastoma (9.8 months vs 10.0 months).[18] The standard regimen for adult recurrent BSGs is still in exploratory stage.

The median OS is reported to be 54 months in adult BSGs, better than that of their pediatric counterparts.[19] Nevertheless, these studies mainly assess low-grade BSGs. In the present study, more than half of grade 2 patients survived, the median OS of grade 3 glioma patients was 29.4 months and 13.8 months for grade 4, which are similar to those of the supratentorial glioma patients. Prognostic factors for prolonged survival consisted of low-grade, duration of symptoms of >2 months and nonenhancement or necrosis on MRI.[1] Cox regression models also validated these findings in our study.

4.1. Study limitations

Several limitations have to be acknowledged in this study. This is a single-center study. The sample size is relatively small. Genetic information of only 11 patients is available. Different therapeutic regimens are adopted after tumor recurrence. The number of patients in each group is relatively low and unbalanced.

5. Conclusions

Although the difficulties in adult BSGs treatment are still unresolved, biopsy and surgical resection have been increasingly applied in the diagnosis and treatment of subclassification types of adult BSGs, such as local lesions rather than diffuse lesions. Radiotherapy, such as proton beam radiotherapy, molecular features of K27 mutation, and clinical trials will provide more potential therapeutic options in the future.

Author contributions

Conceptualization: Shan Li, Yanjie Zhao, Hongyan Huang.

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