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Clinical and Genetic Features of Brainstem Glioma in Adults: A Report of 50 Cases in a Single Center

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Background and Purpose Brainstem gliomas (BSGs) in adults are rare brain tumors with dismal outcomes. The aim of this study was to determine the clinical and genetic features in a series of BSGs and their association with the prognosis.

Methods Fifty patients who underwent a stereotactic biopsy between January 2016 and April 2018 at a single institution were collected. Data on clinicopathological characteristics were analyzed and factors associated with patient survival were identified using a Cox regression model.

Results The median age at diagnosis was 55.5 years, and 62% of the patients were male. Glioblastoma (44%) accounted for the largest proportion of BSGs, and oligodendroglioma (2 of 50) was rarely encountered. The *IDH* mutation (6 of 44) occurred infrequently in astrocytomas, and *IDH*-mutant tumors harbored both *ATRX* loss and *MGMT* promoter methylation at a relatively low level. Wild-type *IDH* astrocytomas were identified as having high rates of 1p/19q codeletion (5 of 38) and loss of heterozygosity 1p (8 of 38) or 19q (8 of 38) only. In diffuse midline glioma *H3K27M* mutant, *MGMT* promoter methylation occurred in three of four cases. Patients were offered radiotherapy and/or concurrent/adjuvant temozolomide chemotherapy, and their median survival time was 13 months. Multivariate analysis revealed that a low tumor grade, absence of tumor enhancement, duration of symptoms ≥3 months, Karnofsky performance status ≥70, and *ATRX* loss conferred a survival advantage.

Conclusions Adult BSGs showed different molecular genetic characteristics, but also resembled supratentorial gliomas in their clinical features associated with oncological outcomes.

Key Words brain stem neoplasms, glioma, molecular epidemiology, prognosis.

INTRODUCTION

Brainstem gliomas (BSGs) are relatively rare tumors of the central nervous system that are more common in children,[1] accounting for less than 2% of adult gliomas.[2,3] Imaging findings show that adult BSGs are most frequently identified in the pons (60–63%) and also occur in the medulla oblongata (25%) and the midbrain (12–15%), with a combination of these brain structures being involved in most cases.[3] Based on radiographic characteristics, adult BSGs have been subdivided into diffuse intrinsic, focal, and exophytically growing tumors, among which infiltrative gliomas represent the most common pathological subtype.[4,5] Due to the challenging location, the scope of surgical treatment for these infiltrative tumors is limited to stereotactic biopsy. Treatment efforts have focused on investigating adjuvant therapies, such as radiotherapy and chemotherapy.[6] Although the prognoses have been improving, adult patients with high-grade BSG still face a dismal course, with the median survival time reported to range from 5.7 months to 16 months.[6,7] Moreover, few studies have focused on the biological characteristics, which has hampered the development of

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therapeutic strategies and improvements in the survival of patients.

The above-described situation indicates that further investigations of intrinsic traits in adult BSGs are urgently needed. The main purposes of this study were to determine the clinical and pathological features of adult BSGs and identify prognostic factors influencing overall survival (OS), with the aim of improving the management of these patients.

METHODS

Patients and specimens

Patients were collected at the Sixth Medical Center of Chinese PLA General Hospital between January 2016 and April 2018. These patients visited our center by themselves or were referred from other hospitals in Beijing, China. Due to the diffusely infiltrative nature of the neoplasm, the participants were not candidates for tumor resection, but all underwent MRI-guided or CT-guided stereotactic biopsy. Sufficient tumor specimens were obtained for pathological diagnose, while part of each tissue sample was sent out fresh for the DNA detection of a gene panel (Supplementary Table 1 in the online-only Data Supplement) as dictated by the institutional pathology protocol. Additionally, the status of *MGMT* promoter methylation was detected by bisulfite sequencing.

Subjects were included in our study when they met the following criteria: 1) radiological imaging showing that the center of the tumor bulk intrinsically resided in the brainstem, and 2) age of ≥18 years at the time of the initial diagnosis. Patients were not eligible if they presented with a history of other tumors or received chemotherapy or had radiotherapy prior to the biopsy. Brainstem diffuse astrocytic and oligodendroglial tumors were diagnosed by two experienced pathologists independently according to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System.

Other clinical data were obtained from the institutional medical database, including: 1) age at the time of diagnosis, 2) sex, 3) main symptoms and their duration, 4) Karnofsky performance status (KPS), 5) location of tumor epicenter, 6) MRI findings (tumor size and tumor enhancement), 7) postoperative treatment, and 8) length of follow-up.

The study protocol was approved by the Tissue Committee and Research Ethics Board of Chinese PLA General Hospital (NGH-01581-C00712). All patients or their legal guardians signed the written informed-consent form about the acquisition and use of human tissue in this study, which compiled with the National Regulations of Clinical Samples in China.

Statistical analysis

The clinical data are described statistically as percentages, means, and medians. Complete follow-up information was recorded. OS was calculated in months from the initial date of diagnosis to the time of death, regardless of cause. Survival was estimated using the Kaplan-Meier method, and variables related to survival were analyzed using log-rank test. Factors for which $p<0.2$ in the univariate analysis were included in the analysis performed using the multivariate Cox stepwise regression model.

All analyses were conducted using the SPSS software program (versions 18.0, SPSS, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Male sex and grade IV tumors predominate in adult BSGs

Fifty patients with diffusely infiltrative BSG were eligible for inclusion in the analysis (Table 1). According to the WHO classification, 52% of the tumors were grade IV [22 glioblastoma (GBM) and 4 diffuse midline glioma (DMLG) *H3K27M*-mutant (*H3K27M*-mut)], 24% (n=12) were grade III anaplastic astrocytoma (AA), 22% (n=11) were grade II diffuse astrocytoma (n=9) or oligodendroglioma (n=2), and only 1 case was diagnosed as grade I pilocytic astrocytoma. The age at the time of diagnosis was 53.6±16.9 years (mean±SD; range from 24–93 years), and 62% of the patients were male (n=31). Most of the BSGs were centered in the pons (80%, n=40), 7 tumors were in the midbrain, and the remaining 3 cases mainly involved the medulla oblongata. Moreover, at least two brainstem structures were invaded in 40% of the patients.

The medical histories indicated that the median duration of symptoms was 3 months (range=0.5–25 months). The presenting signs and symptoms mainly included cranial nerve dysfunction and long-tract signs. Headaches and other manifestations caused by obstructive hydrocephalus were also observed. The median KPS at diagnosis was 80 (range=40–100), and 32 participants had a KPS of >70. MRI showed contrast-enhanced masses in 52% of the BSGs (n=26), and the maximum diameter of the tumors ranged from 9.9 mm to 29.3 mm, with a median of 19.4 mm.

Wild-type IDH astrocytomas account for the vast majority of adult BSGs and present with a high rate of loss of heterozygosity of 1p and/or 19q

Gene panel sequencing revealed that *IDH1/2* mutation occurred in 6 of 44 astrocytic gliomas and 1 of 2 oligodendroglial tumors, but in no DMLG *H3K27M*-mut (Fig. 1).

Table 1. Clinical features of 50 brainstem gliomas in adult

Grade	Type (number)	Sex		Age (years)		Duration of symptoms (months)		KPS		Tumor epicenter		
		Male	Female	≥55	<55	≥3	<3	≥70	<70	Midbrain	Pons	Medulla
WHO IV	GBM (22)	14 (63.6)	8 (36.4)	16 (72.7)	6 (27.3)	8 (36.4)	14 (63.6)	12 (54.5)	10 (45.5)	2 (9.1)	18 (81.8)	2 (9.1)
	DMLG (4)	3 (75.0)	1 (25.0)	3 (75.0)	1 (25.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	0 (0)
WHO III	AA (12)	7 (58.3)	5 (41.7)	8 (66.7)	4 (33.3)	9 (75.0)	3 (25.0)	7 (58.3)	5 (41.7)	1 (8.3)	10 (83.4)	1 (8.3)
WHO II	DA (9)	5 (55.6)	4 (44.4)	2 (22.2)	7 (77.8)	6 (66.7)	3 (33.3)	9 (100.0)	0 (0)	1 (11.1)	8 (88.9)	0 (0)
	O (2)	1 (50.0)	1 (50.0)	0 (0)	2 (100.0)	2 (100.0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)	2 (100.0)	0 (0)
WHO I	PA (1)	1 (100.0)	0 (0)	0 (0)	1 (100.0)	1 (100.0)	0 (0)	1 (100.0)	0 (0)	1 (100.0)	0 (0)	0 (0)
Total, %		62	38	58	42	56	44	64	36	14	80	6

Grade	Type (number)	Tumor enhancement		Diameter (cm)		Radiotherapy		Chemotherapy		Status		Median OS (months)
		Yes	No	≥2	<2	Yes	No	Yes	No	Dead	Alive	
WHO IV	GBM (22)	14 (63.6)	8 (36.4)	10 (45.5)	12 (54.5)	22 (100.0)	0 (0)	22 (100.0)	0 (0)	21 (98.0)	1 (2.0)	9.5
	DMLG (4)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	4 (100.0)	0 (0)	4 (100.0)	0 (0)	4 (100.0)	0 (0)	7.5
WHO III	AA (12)	6 (50.0)	6 (50.0)	3 (25.0)	9 (75.0)	12 (100.0)	0 (0)	12 (100.0)	0 (0)	10 (83.3)	2 (16.7)	17.5
WHO II	DA (9)	4 (45.4)	5 (55.6)	5 (55.6)	4 (45.4)	9 (100.0)	0 (0)	5 (55.6)	4 (45.4)	7 (77.8)	2 (22.2)	32.0
	O (2)	0 (0)	2 (100.0)	2 (100.0)	0 (0)	2 (100.0)	0 (0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	37.0
WHO I	PA (1)	0 (0)	1 (100.0)	0 (0)	1 (100.0)	1 (100.0)	0 (0)	0 (0)	1 (100.0)	0 (0)	1 (100.0)	38.0
Total, %		52	48	44	56	100	0	88	12	86	14	

Data are presented as *n* (%).
AA: anaplastic astrocytoma, DA: diffuse astrocytoma, DMLG: diffuse midline glioma, GBM: glioblastoma, KPS: Karnofsky performance status, O: oligodendroglioma, OS: overall survival, PA: pilocytic astrocytoma, WHO: World Health Organization.

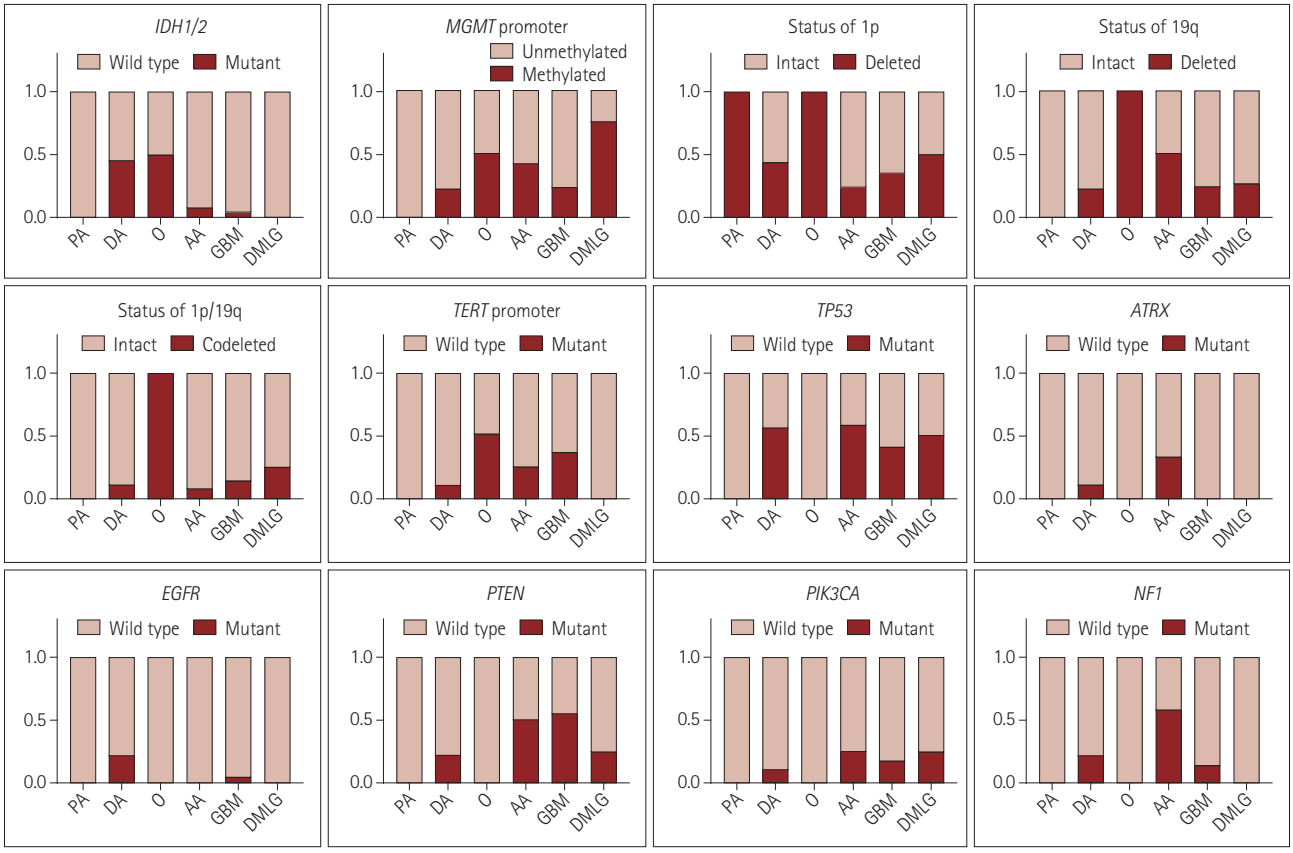

Fig. 1. Common genetic alterations detected in BSGs. The proportion of each genetic alteration is shown for different BSG subtypes. AA: anaplastic astrocytoma, BSG: brainstem glioma, DA: diffuse astrocytoma, DMLG: diffuse midline glioma, GBM: glioblastoma, O: oligodendroglioma, PA: pilocytic astrocytoma.

In the *IDH* mutant (*IDH*-mut) astrocytomas, *TP53* mutation occurred in five cases and only two tumors harbored both *ATRX* loss and *MGMT* promoter methylation. Among this subgroup, an AA with an R172S mutation in *IDH2* showed *TP53* mutation, *ATRX* loss, *MGMT* promoter methylation and *PIK3CA* mutation, while three of the other five *IDH1-R132H* mutated astrocytomas had a loss of heterozygosity (LOH) of 1p only (Supplementary Table 2 in the online-only Data Supplement).

In the wild-type *IDH* astrocytic subgroup, 18 of 38 tumors carried a *TP53* mutation, and 12 cases harbored a *TERT* promoter C228T/C250T mutation, but only 3 were identified with *ATRX* loss. *ATRX* loss and *TERT* promoter mutation were mutually exclusive. *MGMT* promoter methylated tumors accounted for 26.3% (10 of 38) of this subgroup. More than half of the patients (21 of 38) in this subgroup harbored LOH of 1p or 19q, and codeletion of 1p/19q was identified in 5 of these cases. *PTEN* and *NF1* mutations were found in 10 and 12 wild-type *IDH* astrocytomas, respectively. *EGFR*, *RB1*, and *PIK3CA* mutations were identified in three, three and seven tumors, respectively. Either *MSH2* or *MSH6* mutation was identified in four cases, all of whom also carried a *TP53* mutation. *EGFR* amplification occurred in seven astrocytic gliomas with a median amplification time of 7.1, and three of these tumors also exhibited *CDK4* amplification. Amplifications of *CDK4*, *PDGFRA*, and *MET* were presented in five, three, and two cases, respectively.

In the subgroup of oligodendrogliomas, the wild-type *IDH* and 1p/19q codeleted tumor did not display any common genetic alterations, while another *IDH*-mut and 1p/19q codeleted one harbored *TERT* promoter mutation and *MGMT* promoter methylation.

In the subgroup of DMLG *H3K27M*-mut, no mutations of *IDH1/2*, *ATRX*, or *TERT* promoter were found. *MGMT* promoter methylation was present in three of four cases, of which one harbored *TP53* mutation, *PTEN* mutation, and *PDGFRA* amplification with a change of 10.6-fold, and the other two carried LOH of 1p and codeletion of 1p/19q. The *MGMT* promoter unmethylated tumor showed of a *TP53* mutation.

No mutations in *BRAF V600E*, *CDK4*, *CDK6*, *CDKN2A*, *CDKN2B*, *MYCN*, or *PMS2* and no gene rearrangement in *BRAF*, *FGFR3*, *RELA*, or *YAP1* were found in any of the tumors in our cohort. Common genetic alterations in each pathological subtype are listed in Table 2, and the details of the genetic findings are also given in Supplementary Table 2 (in the online-only Data Supplement).

Adult patients with BSGs suffer undesirable outcomes

All the patients underwent a stereotactic biopsy, and those patients who developed symptomatic hydrocephalus received a ventriculo-peritoneal shunt at the diagnosis or during follow-up. When the diagnosis was made, all BSG patients were offered 30 cycles of radiotherapy with a total dose of 54–60 Gy, and patients with wild-type *IDH1/2* grade II tumor or high-grade glioma (HGG) were also suggested to receive temozolomide chemotherapy (Stupp protocol). The 50 patients were followed up for 0.5 months to 42 months (median=13.3 months), and 43 patients had died at the final follow-up. The median OS of all adult BSGs was 13 months.

The OS differed significantly between with the pathological grade, being shorter in grade IV (median=9 months) than in grade III (median=17.5 months) and grade II (median=33 months) (Fig. 2). Kaplan-Meier log rank testing also showed that age ≥55 years, KPS <70, HGG, presence of tumor enhancement, duration of symptoms <3 months, temozolomide chemotherapy and *PTEN* mutation were associated with a worse prognosis (Fig. 2). However, sex, tumor location, tumor

Table 2. Common genetic alterations in adult brainstem gliomas and supratentorial gliomas

Pathological types	*MGMT* promoter methylation		*TERT* promoter mutation		*ATRX* loss		*TP53* mutation		*PTEN* mutation		Codeletion of 1p and 19q	
	Cohort	Ref.[10]	Cohort	Ref.[10]	Cohort	Ref.[10]	Cohort	Ref.[11]	Cohort	Ref.[11]	Cohort	Ref.[11]
GBM, IDH-wt	24 (5/21)	~40	38 (8/21)	>75	0 (0/21)	3	38 (8/21)	20	57 (12/21)	24	14 (3/21)	0
GBM, IDH-mut	0 (0/1)	~90	0 (0/1)	12	0 (0/1)	78	100 (1/1)	83	0 (0/1)	0	0 (0/1)	50
Astrocytoma (grade II and III), IDH-wt	31 (5/16)	~55	25 (4/16)	>60	19 (3/16)	12	50 (8/16)	20	50 (8/16)	23	13 (2/16)	11
Astrocytoma (grade II and III), IDH-mut	40 (2/5)	~85	0 (0/5)	5	40 (2/5)	63	80 (4/5)	69	0 (0/5)	0	0 (0/5)	5
Oligodendroglioma (grade II and III)	50 (1/2)	~65-100	50 (1/2)	94	0 (0/2)	3	0 (0/2)	13	0 (0/2)	0		
DMLG	75 (3/4)		0 (0/4)		0 (0/4)		50 (2/4)		25 (1/4)		25 (1/4)	

Data are presented as % (*n*).
GBM: glioblastoma, DMLG: diffuse midline glioma, mut: mutant, Ref: reference, wt: wild type.

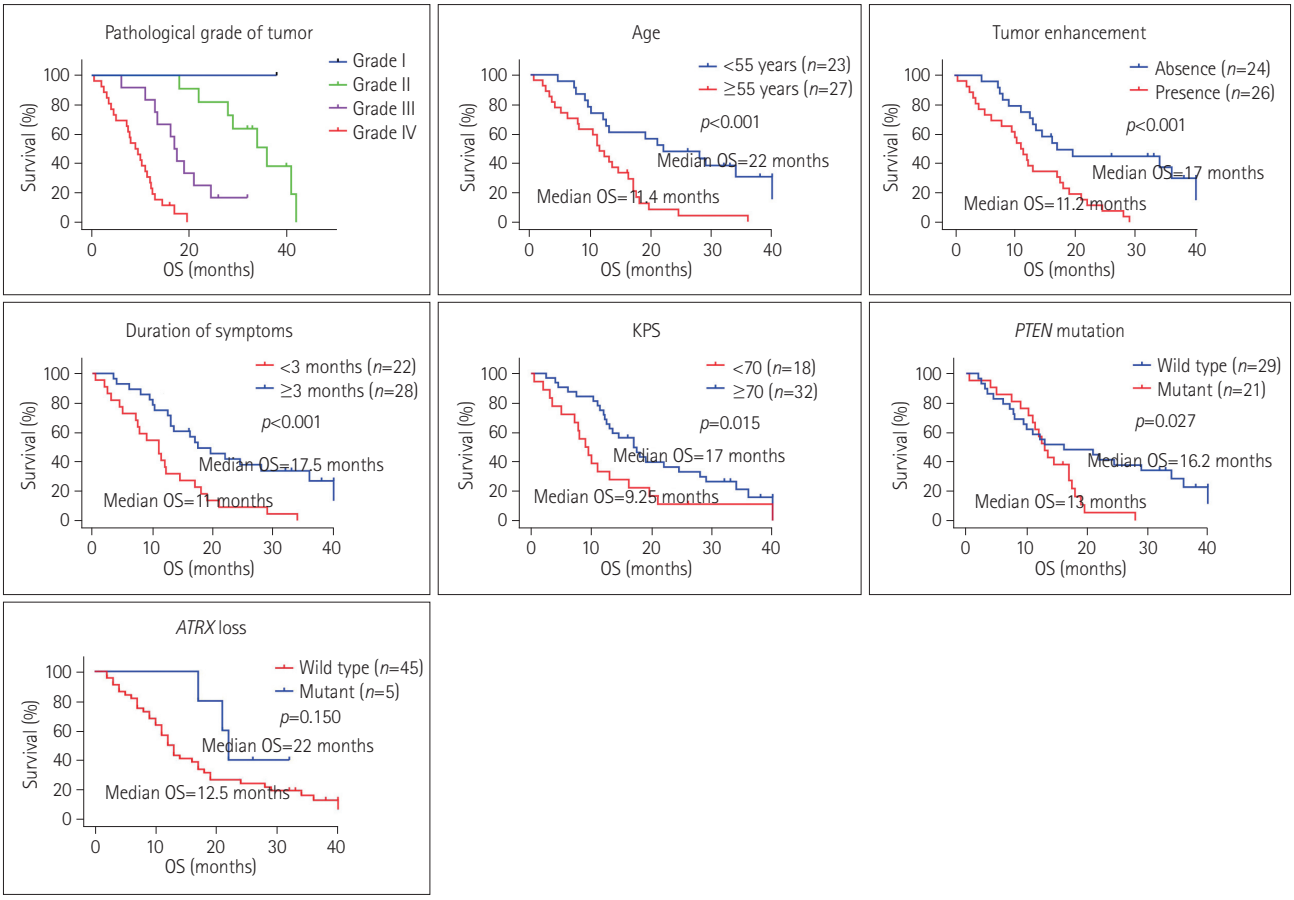

Fig. 2. Clinicopathological factors associated with OS of brainstem glioma patients. Kaplan-Meier curves were used to analyze the relationships of age, KPS, tumor grade, tumor enhancement, duration of symptoms, *PTEN* mutation, and *ATRX* loss with the OS of all patients. OS: overall survival, KPS: Karnofsky performance status.

diameter, *MGMT* promoter methylation, *IDH1/2* mutation, LOH of 1p/19q, *TERT* promoter mutation, *TP53* mutation, *EGFR* amplification, *NF1* mutation, and *PIK3CA* mutation had no significant impact on survival in the adult BSG patients. After adjusting for the confounding effects of each variable in the multivariate analysis, low tumor grade, absence of tumor enhancement, duration of symptoms ≥3 months, and KPS ≥70 conferred a survival advantage for patients (Table 3). Although not significant in the univariate analysis, *ATRX* loss was also identified as an independent factor predicting a favorable prognosis (Table 3).

The findings of the subgroup analyses of the Cox model are presented in Supplementary Tables 3, 4, and 5 (in the online-only Data Supplement). These tables indicate that grade IV and tumor enhancement were independent risk predictors in patients with brainstem HGG, KPS<70, high tumor grade, duration of symptoms <3 months, tumor enhancement, and *ATRX* loss were independent risk predictors in brainstem astrocytoma patients; and absence of tumor enhancement was an independent factor predicting a favorable outcome in brainstem GBM patients.

DISCUSSION

This study retrospectively analyzed the general features and genetic characteristics of 50 adult BSGs at a single institution and identified prognostic factors that may be helpful in improving the management of these patients.

The anatomic characteristics of brainstem tumors mean that controversy remains about whether to perform a stereotactic biopsy procedure due to the presumed risk for histological diagnosis of lesions located in this area.[8] A meta-analysis of 735 patients found that a stereotactic biopsy was valuable in diagnosing these patients, with a 96% success rate and a very low rate of procedure-related complications (0.6%).[9] This was confirmed in the present study, since 50 adult BSG patients who underwent a stereotactic biopsy were accurately diagnosed, despite a glioma having been considered an intratumoral heterogeneous tumor, and the only complication was a minor hemorrhage in 1 patient. Moreover, the

Table 3. Results of univariate and multivariate analyses of factors associated with OS of 50 patients with brainstem gliomas

Variable	Univariate analysis	Multivariate analysis			
	p	HR	95% CI	Median OS (months)	*p*
Age (≥55 years vs. <55 years)	0.001			11.4 vs. 22.0	0.197
Sex (female vs. male)	0.578			14.5 vs. 13.0	
Grade (HGG vs. LGG)	<0.001	15.109	3.604–63.335	11.0 vs. 36.0	<0.001
KPS (≥70 vs. <70)	0.015	0.317	0.147–0.686	17.0 vs. 9.0	0.004
Course of disease (≥3 months vs. <3 months)	0.001	0.401	0.201–0.802	17.5 vs. 11.0	0.010
Diameter (≥2 cm vs. <2 cm)	0.729			12.0 vs. 14.5	
Location (pons vs. midbrain vs. medulla)	0.989			13.5 vs. 13.0 vs. 12.2	
Tumor enhancement (yes vs. no)	0.001	2.892	1.355–6.173	11.0 vs. 17.0	0.006
Chemotherapy (yes vs. no)	0.012			12.2 vs. 34.0	0.424
IDH (mutant vs. wild type)	0.107			29.0 vs. 12.5	0.328
MGMT promoter (methylated vs. unmethylated)	0.508			16.2 vs. 13.0	
1p/19q (LOH vs. intact)	0.460			11.4 vs. 13.0	
TERT promoter (mutant vs. wild type)	0.656			11.4 vs. 13.5	
ATRX (mutant vs. wild type)	0.150	0.107	0.027–0.418	22.0 vs. 12.5	0.001
TP53 (mutant vs. wild type)	0.977			13.0 vs. 16.2	
PTEN (mutant vs. wild type)	0.029			13.0 vs. 16.2	0.722
NF1 (mutant vs. wild type)	0.619			17.0 vs. 12.2	
PIK3CA (mutant vs. wild type)	0.891			12.5 vs. 13.5	
EGFR amplification (yes vs. no)	0.309			11.0 vs. 13.5	

CI: confidence interval, HGG: high-grade glioma, HR: hazard ratio, KPS: Karnofsky performance status, LGG: low-grade glioma, LOH: loss of heterozygosity, OS: overall survival.

use of a stereotactic biopsy also allowed successful tissue sampling for molecular characterization, which primarily was incorporated into the definition of brain tumors according to the 2016 WHO classification. We can also briefly report on the distribution and genetic features of reclassified diffuse gliomas of the brainstem in adult patients.

Based on previous studies and the present findings, both supratentorial and brainstem GBMs constitute the majority of adult gliomas located in their respective areas.[10] Consistent with the findings for supratentorial GBMs, *IDH* mutations (1 of 22, 4.5%) were rarely found in adult brainstem GBMs.[11] Moreover, *IDH* mutations were infrequently seen in our brainstem WHO grade-II and -III diffuse gliomas (6 of 23, 26.1%), in contrast to rates of up to 70% in supratentorial WHO grade-II and -III astrocytic and oligodendroglial tumors.[11] Several recent studies have suggested that non-*IDH1*-R132H mutations (*IDH1*-R132C/G and *IDH2*-R172S/G), which constitute only 5% of *IDH* mutations in adult supratentorial gliomas, occur more frequently in adult BSGs.[12,13] In the present study, an R172S mutation in *IDH2* was detected in one AA (WHO grade III). All of the IDH mutations were present in patients younger than 50 years, showing that our findings are consistent with previous reports of *IDH* mutations mainly occurring in young adults, and being rare in patients older than 55 years.[14]

Regarding astrocytomas, there is robust evidence that *IDH* mutations usually occur together with a loss-of-function mutation in *TP53* and *ATRX* genes.[15,16] We also found a high prevalence of *TP53* mutation in the *IDH*-mut astrocytic group (5 of 6, 83.3%) resembling their supratentorial counterparts; however, a lower proportion of *ATRX* loss was detected in the *IDH*-mut astrocytomas (2 of 6, 33.3%) compared with that in cerebral astrocytomas (96%),[13] indicating genetic differences between these two entities.[17] Moreover, patients with *ATRX* loss had a longer OS in our group analyzed using the Cox model (Table 3 and Supplementary Table 4 in the online-only Data Supplement). Similar findings were obtained in cerebral gliomas, with *ATRX* loss identified as a subgroup of *IDH*-mut astrocytic tumors with a better prognosis and associated with a high survival rate in the GBM group.[18,19] Given that all *ATRX* losses occurred in astrocytomas at grades II and III and were weakly related to *IDH* mutation in our cohort, the results suggest that *ATRX* alteration refines the classification of adult brainstem astrocytomas; this needs to be investigated further in a larger sample.

IDH mutations and codeletion of chromosomes 1p and 19q are associated with the oligodendroglial histological type, which is enriched for wild-type *TP53* and *TERT* promoter mutation.[17] However, this oligodendroglial entity is rarely encountered in the brainstem of either pediatric or adult patients,[20,21] with only one eligible case found in our cohort. We might be able to report the second case of a brainstem oligo-

dendroglioma with 1p/19q codeletion but wild-type *IDH1/2*,[21] which showed different genetic alterations from the *IDH*-mut one and warranted further investigations. It is particularly interesting that 1p/19q codeletion was also found not to correspond to a diagnosis of oligodendroglioma. A retrospective study of 359 fibrillary astrocytomas found that 11 tumors (3.1%) had 1p/19q codeletion and only 1 of these cases demonstrated *IDH1* mutation.[22] In addition, 19 and 35 of the 359 cases harbored losses only on chromosomes 1p and 19q, respectively.[22] Though 1p/19q codeletion is evidently rarely detected in adult BSGs, brainstem astrocytic gliomas with wild-type *IDH* in our study frequently had 1p/19q codeletion (5 of 38, 11.4%), which mainly occurred in GBM (3 of 21, 14%), and increased trends of LOH of 1p only (13 of 38, 25%) and LOH of 19q only (8 of 38, 18.2%) in the wild-type IDH subgroup and LOH of 1p only (3 of 6, 50%) in the IDH-mut subgroup were also found. Genomic instability might account for complete 1p/19q codeletion in GBM; moreover, our findings revealing oligodendroglioma components in a few GBM cases according to the 2007 morphological criteria might explain the high rate of codeleted 1p/19q. Besides, TP53 mutation appearing at a high rate (3 of 5, 60%) in the 1p/19q codeleted astrocytic tumors may help to avoid misclassification of such tumors as oligodendroglioma.[23]

More recently, landmark genomic studies have shown that diffuse intrinsic pontine glioma is driven by somatic mutations in histone H3, either H3.1 (*HIST1H3B/C*) or H3.3 variants (*H3F3A*), which defines distinct subgroup entities with different biological and clinical phenotypes and prognose.[24,25] These histone H3 mutations rarely occur in supratentorial gliomas, but they have been detected in a much higher proportion of adult diffuse intrinsic BSGs, such as in 53.6% (15 of 28) of samples harboring *H3F3A* K27M mutations.[12,26] Moreover, the presence of *H3K27M* mutation seemed to be strongly correlated with wild-type *IDH* and was potentially associated with a short survival time.[26] We then identified four BSGs (accounting for only 8% of our cohort) as DMLG *H3K27M*-mut, and *H3K27M* and IDH mutations were mutually exclusive in the subgroup that showed a poor prognosis similar to GBM patients (median OS=7.5 months vs. 9.5 months). This subgroup could harbor mutations in *TP53*, *PTEN*, *PIK3CA*, *PPM1D*, and methylated *MGMT* promoter (Supplementary Table 2 in the online-only Data Supplement), as well as *PDGFRA* amplification that tended to confer a proneural phenotype and a prometastatic gene expression pattern in tumors with *PDGFRA* activation.[24]

Another important biological marker is *MGMT* promoter methylation, which has been reported in 30−80% of supratentorial gliomas, but it has not been adequately evaluated in adult BSGs.[27,28] Negativity for *MGMT* expression was identified in 35.3% of 34 adult high-grade BSGs.[27] Similarly, our study found *MGMT* promoter methylation in 25% of low-grade BSGs and approximately 34% of high-grade ones, indicating a low effective rate of response to alkylating agents such as temozolomide.[29] Moreover, only two out of six *IDH*-mut astrocytomas presented with *MGMT* promoter methylation in our study, while about 96% of supratentorial IDH-mut astrocytomas displayed *MGMT* promoter methylation.[13] Moreover, the rate of *MGMT* methylation was as high as 75% (three of four) in DMLG *H3K27M*-mut, which contrasts to previous reports of *H3K27M*-mut gliomas rarely (<5%) having a methylated *MGMT* promoter.[30] This discrepancy is probably due to the smallness of our sample and the average proportion of methylated CpG sites in *MGMT* promoter being less than 20% in the four DMLG *H3K27M*-mut (3.25%, 11%, 18%, and 18%, with a cutoff value of 10%), in contrast with this proportion being up to 80−100% in other subtypes of gliomas. PI3K signaling is a critical regulator of glioma progression, and it is activated by mutations in the *PI3KCA* or *PIK3R1* subunit and loss of tumor suppressor *PTEN* that is present in 15−40% of GBMs.[31] In our cohort, the incidence of *PTEN* mutations was high in the GBM group (12 of 22, 54.5%) and the loss of *PTEN* was mutually exclusive with IDH mutations, pointing to the most aggressive type of glioma and the worst prognosis of the patients. The *PTEN* mutation was associated with a shorter OS of adult patients with BSG compared with wild-type *PTEN* (Fig. 2).

Furthermore, univariate analysis identified that several clinical factors were associated with a prolonged OS, including being younger than 55 years, low tumor grade, absence of tumor enhancement, duration of symptoms ≥3 months and KPS ≥70, and the latter four factors were seen to be favorable independent predictors of survival. Age <55 years was excluded from the multivariate analysis since high-grade tumors tended to occur in the older patients of our cohort. Previous studies of clinical prognostic factors of adult BSG patients have obtained consistent findings.[32,33] Likewise, these factors have been demonstrated to be prognostically significant in predicting survival in supratentorial gliomas,[34] indicating that the clinical course could be at least partly shared by gliomas located in different areas.

In contrast with therapeutic regimens containing surgery and postoperative radiotherapy being applied to most supratentorial gliomas, there is still no consensus on the effective treatments for adult BSGs. The role of resection (excluding a stereotactic biopsy that is mainly applied for diagnostic purposes) in the treatment of diffuse BSGs is controversial, due to the significant morbidity and mortality associated with operations in the highly eloquent region. With the application of electrophysiological monitoring, navigation, and neuroim-

aging, the microsurgical resection of such lesions via a brainstem safe entry zone may become feasible.

A recent study of 502 adult brainstem HGGs from the Surveillance, Epidemiology, and End Results Program (SEER) database concluded that for surgically accessible tumors, partial resection and gross total resection are associated with three- and fourfold increases in OS, respectively, relative to biopsy only.[7] However, the value of resection in improving the survival of adult BSG patients needs further verification. Radiotherapy with concurrent or adjuvant chemotherapy is currently the most commonly treatment.

Another analysis based on the National Cancer Database collected 422 adult patients with high-grade BSG, and found that median OS was longer for radio-chemotherapy (14.2 months) than radiation alone (5.7 months) and no postoperative treatment (1.8 months).[6] However, we found that the median OS was shorter in patients receiving temozolomide than that in patients without chemotherapy (12.2 months vs. 34 months), which was mainly due to all high-grade and wild-type *IDH* low-grade gliomas being in the chemotherapy group. Despite receiving these treatments, the conditions of the patients deteriorated, and so novel therapies such as targeted therapy and immunotherapy are required to prolong their survival in the future.

Some limitations of this study need to be considered. Firstly, this was a retrospective study and so its findings are not as reliable as those of a randomized controlled trial. Secondly, the total number of participants is small and the pathological types were highly heterogeneous, with both of these features reducing the power of the statistical analyses, especially for the multivariate models. Thirdly, adjuvant treatments such as targeted therapy and immunotherapy were not applied to these patients, and so their effects could not be evaluated in this study.

It was conclusively found that adult BSGs have different molecular genetic characteristics (Table 2), but also that some of their clinical features associated with the oncological prognosis partly resemble those of supratentorial gliomas.[34] Further studies including large populations are needed to explore more comprehensive profiles of adult BSGs and incorporate specific markers when stratifying patients and developing therapeutic regimens, in order to improve the OS of this population.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.2.220.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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