Brainstem Infiltration Predicts Survival in Patients With High-grade Gliomas Treated With Chemoradiotherapy

SHIMPEI ANAMI¹, JUNYA FUKAI², MIZUKI HAMA¹, AZUSA AWAYA¹, TAKAYA INAGAKI¹, TAKAHIRO CHIBA¹, YASUTAKA NODA¹, YONEHIRO KANEMURA^{3,4}, NAOYUKI NAKAO² and TETSUO SONOMURA¹

¹Department of Radiology, Wakayama Medical University, Wakayama, Japan;

²Department of Neurological Surgery, Wakayama Medical University, Wakayama, Japan;

³Department of Biomedical Research and Innovation, Institute for Clinical Research, National Hospital Organization Osaka National Hospital, Osaka, Japan;

⁴Department of Neurosurgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

Abstract. *Background/Aim:* High-grade gliomas have a poor prognosis despite standard treatment. The aim of the study was to identify new prognostic factors to select patients who need more intense treatment. *Patients and Methods:* Forty-three consecutive patients underwent surgery plus chemoradiotherapy for pathologically diagnosed high-grade gliomas (grade III, IV). *Results:* The median survival time was 989 days, and the 1-year survival rate was 87.6%. Among patients with grade IV disease, the median survival time, 1-year, and 2-year survival rate were 814 days, 82.6%, and 58.7%, respectively. In the univariate analysis, unmethylated MGMT promoter ($p=0.0495$), brainstem infiltration ($p=0.0004$), basal ganglia as the primary lesion site ($p=0.0056$), 3-dimensional conformal radiotherapy ($p=0.0286$), and <50 Gy ($p=0.0049$) were associated with a poor prognosis. In the multivariate analysis, only brainstem infiltration retained significance (HR for death, 0.21; 95% CI=0.06-0.70; $p=0.011$). *Conclusion:* Brainstem infiltration is a novel prognostic factor for poor prognosis in patients with high-grade gliomas.

High-grade gliomas account for approximately 15% of all primary brain tumours in Japan (1). They are a curative challenge with poor treatment outcomes, particularly for those classified as glioblastomas (grade IV); the 1-, 2-, and 5-year survival rates are 60%, 25%, and 10%, respectively (1). The standard treatment modality for high-grade gliomas is surgery

followed by chemoradiotherapy (2). However, because high-grade gliomas are highly invasive, residual tumours are inevitable. The degree of surgical resection markedly affects prognosis; thus, surgery should be aimed toward the highest possible degree of resection (3). Temozolomide is the standard chemotherapeutic for high-grade gliomas (4).

Postoperative radiotherapy significantly improves the prognosis of patients with high-grade gliomas. Extended local irradiation with 60 Gy in 30 fractions is usually administered. Higher doses and better outcomes may be achieved using other protocols; these protocols are currently under investigation and include intensity-modulated radiation therapy (IMRT), stereotactic radiotherapy (SRT), heavy ion radiotherapy, and boron neutron capture therapy (BNCT) (5-8). Despite its usefulness, radiotherapy may not be well tolerated by and may cause serious adverse events in elderly patients and patients with a poor general condition. For these patients, the hypo-fractionated radiation method has become the standard approach as it yields fewer severe adverse effects than other methods but has the same prognostic benefit (9).

The presence of MGMT promoter methylation in the tumour increases the efficacy of temozolomide and improves prognosis (10). Additional novel prognostic factors include point mutations in the IDH gene and co-deletion of the short arm of chromosome 1 and the long arm of chromosome 19 (11-13). Recent advances in molecular biology have led to revision of the classification of central nervous system (CNS) tumours.

The purpose of this study was to identify new prognostic factors for high-grade gliomas.

Patients and Methods

Study design and patients. This retrospective study was approved by our institutional review board (approval number 2944) and was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

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Correspondence to: Shimpei Anami, MD, Department of Radiology, Wakayama Medical University, 811-1, Kimiidera, Wakayama, Wakayama, Japan. Tel: +81 734410605, Fax: +81 734410605, e-mail: anami131@wakayama-med.ac.jp

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Forty-four consecutive patients underwent chemoradiation at our institution between January 2014 and October 2019. Among them, one patient was excluded based on the exclusion criteria [no specific events during a follow-up of <60 days or a diagnosis based on magnetic resonance imaging (MRI) rather than on pathology]. As a result, 43 patients were eligible for this analysis, all of whom were pathologically diagnosed with high-grade gliomas at our institution.

Our study population comprised 19 men and 24 women, with a median age of 62 years (range=18-80 years) (Table I). Thirty-seven patients had a good general condition, as indicated by an Eastern Cooperative Oncology Group-performance status (ECOG-PS) of 0 or 1, and 6 patients had a poor general condition (ECOG-PS of ≥ 2). Seventeen and 26 patients had World Health Organization (WHO) grade III and IV disease, respectively, and 21/22 patients had unmethylated *MGMT* promoter tumours (cut off value for methylation: 1%) (14). The median tumour size was 41 mm (range=5-92 mm). Ten patients had brainstem infiltration on MRI at the time of initial diagnosis, and two of them had the H3F3A-K27 mutation. The primary tumour location was the basal ganglia in 8 patients.

Treatment. Surgery consisted of total or subtotal resection in 28 patients and biopsy in 15 patients. All patients received temozolomide as chemotherapy. Forty-one patients underwent IMRT, and two underwent 3-dimensional conformal radiotherapy (3D-CRT). The median radiation dose was 60 Gy (range=29.37-60 Gy). The radiation treatment was hypo-fractionated in 10 patients.

Molecular diagnosis. The molecular diagnosis of all patients was performed by the Kansai Molecular Diagnosis Network for CNS Tumours (14).

Statistical analysis. Data are reported as median (range) or number (percentage). In time-to-event analyses, overall survival was calculated from the date of surgery to the date of emergence of the event. Overall survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Potential prognostic factors were evaluated using the Cox proportional hazards model, and the results are reported as hazard ratios and corresponding 95% confidence intervals. Significant factors identified in the univariate analyses were included in the multivariate model. All analyses were performed using JMP software (version 14; SAS Institute, Cary, NC, USA), and differences with *p*-values <0.05 were considered statistically significant.

Results

Eighteen patients died of primary disease. The general condition of one of these patients deteriorated during treatment, and treatment was therefore discontinued. The median observation period for the surviving 25 patients was 492 days (range=99-1,979 days).

The median overall survival time for all patients was 989 days, and the 1- and 2-year survival rates were 87.6% and 67.3%, respectively (Figure 1A). For patients with WHO grade IV disease, the median survival time was 814 days, and the 1- and 2-year survival rates were 82.6% and 58.7%, respectively (Figure 1B). For patients with grade III disease, the progression-free survival rate was 64.7% at 1 year and

Table I. *Clinicopathological patient characteristics (n=43).*

Characteristic	Value
Age (years), median (range)	62 (18-80)
Gender, n	
Male	19
Female	24
ECOG-PS, n	
0	15
1	22
2	2
3	2
4	2
WHO grade, n	
Grade III	17
Grade IV	26
<i>MGMT</i> promoter, n	
Methylated	22
Unmethylated	21
IDH1	
Mutant	10
Wild-type	33
TERT promoter	
Mutant	25
Wild-type	18
Maximum tumour diameter (mm), median (range)	41 (5-92)
Brainstem infiltration	
Yes	10
No	33
Primary site	
Basal ganglia	8
Others	35
Extent of surgical resection	
GTR/STR/PR	28
Biopsy	15
Irradiation technique	
IMRT	41
3D-CRT	2
Total prescription dose (Gy)	60 (29.37-60)
Number of fractions, median (range)	25 (11-30)
GTV (cm ³)	26 (3-143)
CTV1 (cm ³)	144 (6-408)
CTV2 (cm ³)	307 (40-733)

ECOG-PS, Eastern Cooperative Oncology Group-performance status; *MGMT*, *O*⁶-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; GTR, gross total resection; STR, subtotal resection; PR, partial resection; IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; GTV, gross tumour volume; CTV1, clinical target volume 1 (GTV+15 mm) and cerebral oedema; CTV2, GTV/cerebral oedema + 15 mm.

43.7% at 2 years; for patients with grade IV disease, it was 53.7% and 35.8%, respectively.

In univariate analysis, five factors negatively impacted survival: unmethylated *MGMT* promoter (*p*=0.0495), brainstem infiltration (*p*=0.0004), basal ganglia as the primary lesion site (*p*=0.0056), 3D-CRT (*p*=0.0286), and

Figure 1. Overall survival after surgery. (A) In the overall cohort, the median survival time was 989 days, and the 1- and 2-year overall survival rates were 87.6% and 67.3%, respectively. (B) In the patients with World Health Organization grade IV tumours, the median survival time was 814 days, and the 1- and 2-year overall survival rates were 82.6% and 58.7%, respectively. Meanwhile, the rates were 94.1% and 78.7%, respectively, in patients with grade III tumours.

radiation dose <50 Gy ($p=0.0049$) (Table II, Figure 2). In patients with and without brainstem infiltration, the median survival time was 363 days and 1,022 days; the 1-year survival rate, 60% and 96.7%; and the 2-year survival rate, 36% and 77.2%, respectively. Age, ECOG-PS, genetic mutations other than *MGMT* promoter methylation, and irradiation volume (gross tumour volume and clinical target volume 1 and 2) had no effect on survival rates.

Because the total radiation dose was low in patients with a poor general condition and the number of 3D-CRT cases was small, only *MGMT* promoter methylation, brainstem infiltration, and basal ganglia as the primary lesion site were examined in the multivariate analysis. Of these, brainstem infiltration was the only significant independent predictor of poor survival (HR for death, 0.21; 95% CI=0.06-0.70; $p=0.011$) (Table III).

Figure 2. Postoperative survival by predictors of prognosis in the univariate analysis. Brainstem infiltration (A), basal ganglia as the primary site (B), and unmethylated *MGMT* promoter (C).

Discussion

The standard treatment modality for high-grade gliomas is surgery plus postoperative chemoradiation (2, 3). The prognostic factors for patients with this disease include age, Karnofsky Performance Score, surgical resection rate, and *MGMT* promoter methylation (10, 15). *MGMT* promoter methylation is considered a favourable prognostic factor

Table II. Univariate analysis of the influencing factors of overall survival.

Clinicopathological parameter	Patients (n=43)	Univariate analysis			
		1-year survival rate (%)	2-year survival rate (%)	HR (95% CI)	p-Value
Age (years)					
<70	30	83.3	60.9	1	0.30
≥70	13	100.0	87.5	0.52 (0.15-1.80)	
Gender					
Male	19	83.3	66.7	1	0.68
Female	24	91.1	66.9	0.82 (0.32-2.10)	
ECOG-PS					
0, 1	37	91.4	67.9	1	0.10
2~	6	64.3	64.3	2.61 (0.84-8.16)	
WHO grade					
Grade III	17	94.1	78.7	1	0.14
Grade IV	26	82.6	58.7	2.19 (0.78-6.17)	
MGMT promoter					
Methylated	22	100.0	79.6	1	0.0495
Unmethylated	21	72.7	52.0	2.63 (1.00-6.90)	
IDH1					
Mutant	10	100.0	88.9	1	0.16
Wild-type	33	83.5	59.9	2.42 (0.70-8.40)	
TERT promoter					
Mutant	25	87.0	64.6	1	0.76
Wild-type	18	88.2	72.2	1.16 (0.45-3.02)	
Maximum diameter of tumour (mm)					
≤40	23	91.7	70.8	1	0.84
>40	19	81.3	61.4	1.10 (0.43-2.80)	
Brainstem infiltration					
Yes	10	60.0	36.0	1	0.0004
No	33	96.7	77.2	0.14 (0.05-0.41)	
Primary site					
Basal ganglia	8	75.0	45.0	1	0.0056
Others	35	90.6	72.9	0.234 (0.08-0.65)	
Extent of surgical resection					
GTR/STR/PR	28	88.5	65.5	1	0.65
Biopsy	15	85.7	70.1	1.24 (0.48-3.21)	
Irradiation technique					
IMRT	41	89.8	69.0	1	0.0286
3D-CRT	2	0.0	0.0	15.00 (1.33-169.58)	
Total prescription dose (Gy)					
≤50	33	85.7	28.6	1	0.0449
>50	10	87.9	76.9	0.32 (0.11-0.97)	
GTV volume (cm ³)					
≤30	20	89.5	72.9	1	0.20
>30	16	78.6	50.0	1.92 (0.71-5.23)	
CTV1 volume (cm ³)					
≤150	21	100.0	76.9	1	0.39
>150	20	71.1	53.3	1.53 (0.58-3.98)	
CTV2 volume (cm ³)					
≤300	14	85.7	66.8	1	0.26
>300	16	87.5	80.2	0.49 (0.14-1.68)	
MIB1 index					
≤20	28	88.3	66.0	1	0.62
>20	15	86.7	69.3	1.27 (0.49-3.32)	
Brainstem compression					
Yes	5	60.0	60.0	1	0.25
No	38	91.4	67.9	0.48 (0.13-1.68)	
Midline shift					
Yes	16	80.4	62.5	1	0.55
No	27	92.0	69.5	1.37 (0.49-3.85)	
Bevacizumab					
Yes	23	85.4	64.6	1	0.41
No	20	90.0	69.3	0.66 (0.24-1.77)	

HR, Hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; WHO, World Health Organization; MGMT, O⁶-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; GTR, gross total resection; STR, subtotal resection; PR, partial resection; IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; GTV, gross tumour volume; CTV1, clinical target volume 1 (GTV+15 mm) and cerebral oedema; CTV2, GTV/cerebral oedema +15 mm; MIB1, Mind bomb 1.

Table III. Multivariate analysis of the influencing factors of overall survival.

Parameter	Multivariate analysis	
	HR (95% CI)	p-Value
MGMT promoter		
Methylated	1	0.55
Unmethylated	1.42 (0.45-4.46)	
Brainstem infiltration		
Yes	1	0.011
No	0.21 (0.06-0.70)	
Primary site		
Basal ganglia	1	0.21
Others	0.47 (0.14-1.54)	

HR, Hazard ratio; CI, confidence interval; MGMT, *O*⁶-methylguanine-DNA methyltransferase.

because it enables a good response to temozolomide. Owing to recent advances in molecular biology, the WHO reclassified high-grade gliomas based on *IDH* mutations, *TP53* mutations, and chromosome 1p19q co-deletion (16). New prognostic factors such as *TERT* promoter mutations have also been reported (17).

Among the genetic mutations tested in this study, only *MGMT* promoter methylation significantly correlated with survival in the univariate analysis; it was not, however, significant in the multivariate analysis. Furthermore, patients with *IDH* mutants tended to have a better prognosis, but the difference was not significant. We believe that significant differences may be observed by increasing the sample size or extending the observation period. Tumour factors related to tumour location, namely brainstem infiltration and basal ganglia as the primary lesion site, negatively correlated with survival in the univariate analysis; in the multivariate analysis, only brainstem infiltration retained significance. Drumm *et al.* reported that brainstem infiltration is a common cause of death in patients with glioblastoma, with 66% of glioblastoma patients having brainstem infiltration on autopsy (18). In their study, patients with brainstem infiltration survived significantly longer (17.4 months) than those without brain infiltration (9 months, $p=0.002$). It is thought that rapid growth of the primary lesion caused the death of the latter patients before brainstem infiltration could occur. The reason our results differ from those of Drumm *et al.* (18) is unclear. Possibilities include selection bias in previous studies, differences in surgical removal rates, and a higher incidence of *MGMT* promoter methylation in the non-brainstem infiltration group in our study. In fact, in our study, *MGMT* promoter methylation was found in 2 out of 10 patients (20%) in the brainstem infiltration group and in 20 out of 33 patients (61%) in the non-brainstem infiltration

group. Although the reason for this is not yet known, *MGMT* promoter methylation has been reported to be lower in brainstem gliomas, which may be similar to the results of this study (19, 20). Furthermore, although further studies are needed, brainstem infiltration and brainstem gliomas have low *MGMT* promoter methylation, which may affect the efficacy of treatment. We defined brainstem infiltration as a high fluid-attenuated inversion-recovery signal on MRI. Even small brainstem infiltrations may significantly impact prognosis; thus, local control is key to improving the prognosis of patients with high-grade gliomas.

Local control can be achieved with various treatment modalities. Tanaka *et al.* reported that increasing the local dose to 80-90 Gy yielded a median survival time of 16.2 months in patients with malignant gliomas (21). Iuchi *et al.* reported a median survival time of 20 months and improved local control rates in glioblastoma patients receiving simultaneous integrated boost-IMRT (68/40/32 Gy in 8 fractions); however, local recurrence progressed to disseminated recurrence, and the rate of brain necrosis was high (40%) (5). Consistent with this finding, high doses of radiation were associated with brain necrosis in the study by Tanaka *et al.* (21).

Brainstem necrosis is the most serious and life-threatening complication in patients with brainstem infiltration. Administration of more than 60 Gy to the micro-infiltration area (brainstem) is considered dangerous and should be avoided, even if IMRT or heavy ion radiotherapy is used in addition to SRT. BNCT is the preferred primary radiotherapy technique for patients with brainstem infiltration because it delivers a high dose to tumour cells and a low dose to normal tissues. However, there have been few reports on BNCT for malignant gliomas. Yamamoto *et al.* reported excellent outcomes with a median survival time of 25.7 months for BNCT of primary glioblastoma and suggest that BNCT is beneficial not only in cases with brainstem infiltration, but also in those with organs subject to dose tolerance restrictions such as the optic nerve and optic chiasm (7).

Another treatment option is the concurrent use of bevacizumab during radiotherapy. Radiation-induced brain damage is caused by a vicious cycle of radiation-induced endothelial cell damage, hypoxia in peri-tumour tissues, and brain oedema and by increased expression of vascular endothelial growth factor (VEGF) (22). In the randomised trial conducted by Levin *et al.*, bevacizumab significantly reduced the occurrence of radiation-induced brain oedema and improved clinical symptoms (23). Although this result requires verification, it suggests that the radiotherapy dose can be increased when bevacizumab is concurrently administered. Gilbert (24) and Chinot *et al.* (25) reported that bevacizumab and radiotherapy plus temozolomide had an additive effect on the progression-free survival rate but not on the overall survival rate in patients with glioblastoma. In

their study, the progression-free survival rate was better in the bevacizumab group than in the placebo group during the first 2 years after treatment. Most patients with brainstem infiltration in the present study died within 2 years after treatment due to focal enlargement and thus may benefit greatly from concomitant use of bevacizumab and radiotherapy. However, bevacizumab has been shown to increase tumour invasiveness (26, 27), suggesting that its inhibitory effects on VEGF activity may insufficiently prevent tumour infiltration through the white matter. Therefore, bevacizumab administration must be carefully considered in cases of high-grade glioma with brainstem infiltration. In addition, although rare, brainstem gliomas have been reported in patients with neurofibromatosis type 1, and mitogen-activated extracellular signal-regulated kinase inhibitors may be an option for these patients (28, 29).

Because tumour control is difficult, treatments that shorten the treatment period, such as hypo-fractionated radiation, may be useful. Hypo-fractionated delivery of 40 Gy is often used in elderly patients or patients with a poor general condition, as its benefits are comparable to those of standard treatments (9). Moreover, it has fewer side-effects and is thus a viable treatment option for patients with brainstem infiltration who, as shown here, have an extremely poor prognosis.

This study had certain limitations, including its retrospective design and relatively small sample size. Despite these limitations, the results clearly indicate that patients with brainstem infiltration have a poor prognosis; thus, more effective approaches to increasing the radiation dose while avoiding severe adverse effects are needed.

In conclusion, brainstem infiltration independently worsens the prognosis of patients with high-grade gliomas and thus may be a novel prognostic factor.

Conflicts of Interest

None to be declared.

Authors' Contributions

Shimpei Anami collected and analysed the data and drafted the manuscript. Shimpei Anami, Junya Fukai, Mizuki Hama, Azusa Awaya, Takaya Inagaki, Takahiro Chiba, Yasutaka Noda and Naoyuki Nakao mainly treated patients.

Junya Fukai, Yonehiro Kanemura, Naoyuki Nakao and Tetsuo Sonomura provided critical revisions of the manuscript. Junya Fukai and Tetsuo Sonomura supervised the project. All Authors read and approved the final manuscript.

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