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ORIGINAL ARTICLE

Radiotherapy for brainstem gliomas in children and adults: A single-institution experience and literature review

Kenji YOSHIDA,[1] Nor Shazrina SULAIMAN,[1] Daisuke MIYAWAKI,[1] Yasuo EJIMA,[1] Hideki NISHIMURA,[2] Takeaki ISHIHARA,[1] Yoshiro MATSUO,[1] Ryo NISHIKAWA,[1] Takashi SASAYAMA,[3] Akira HAYAKAWA,[4] Eiji KOHMURA[3] and Ryohei SASAKI[1]

[1]*Division of Radiation Oncology and Departments of* [3]*Neurosurgery and* [4]*Pediatrics, Kobe University Graduate School of Medicine, and* [2]*Department of Radiation Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan*

Abstract

***Aim*:** To evaluate the treatment results of radiotherapy (RT) in children and adults with brainstem gliomas (BSGs) and review the previous literature.

***Methods*:** Thirty patients (14 children, 16 adults) with BSG treated using RT were retrospectively evaluated. The median ages of the children and adults were 8 years (range: 2–16 years) and 49 years (range: 19–75 years), respectively. A histological diagnosis was obtained in 11 patients. The median total radiation dose was 56 Gy (range: 50–70 Gy) with a single fraction size of 1.8–2.0 Gy. Temozolomide was administered concurrently with RT in 14 patients.

***Results*:** Tumor progression after RT occurred in 26 patients (14 children and 12 adults). Four adults survived without tumor progression. The median survival times for children and adults were 8.5 and 39 months, respectively. The 1-, 2- and 3-year overall survival rates for children/adults were 29%/75%, 14%/68% and 0%/53%, respectively ($P = 0.001$), and the 1-, 2- and 3-year progression-free survival rates for children/adults were 14%/69%, 0%/49% and 0%/35%, respectively ($P < 0.001$). Grade 3 or higher acute and late toxicities did not occur.

***Conclusion*:** In this study, the prognosis of children with BSGs was considerably poorer than that of adults, and our results are consistent with those of previous studies. Efforts should be made to improve the survival outcomes of patients with BSGs, especially children.

Key words: brainstem glioma, children/adults, radiotherapy

INTRODUCTION

Brainstem glioma (BSG) accounts for 10%–20% of all brain tumors in children. The peak age is 7–9 years, with no gender predilection.[1–3] In contrast, BSG in adults is rare and accounts for <2% of gliomas, with a peak age of 40–70 years.[4–6] The most common type of BSG, as determined using magnetic resonance imaging (MRI), is diffuse intrinsic glioma arising in the pons, which accounts for 80% of all BSGs. Other types are generally defined as focal, dorsal exophytic or cervicomedullary.[7,8]

Correspondence: Dr Kenji Yoshida MD PhD, Division of Radiation Oncology, Kobe University Graduate School of Medicine, 7-5-2 Kusunokicho, Chuouku, Kobe City, Hyogo 650-0017, Japan. Email: kyoshi@med.kobe-u.ac.jp

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The brainstem is closely associated with circulation, respiration, consciousness, sensorimotor function and other essential life functions. Therefore, BSG can cause various symptoms such as dizziness, headache, altered consciousness, gait disturbance, dysphagia or a combination of these, which may lead to death.

Although radiotherapy (RT) is an essential therapeutic tool for BSG, the prognosis of BSG in children remains poor. Based on a systematic review of clinical trials, Hargrave et al. reported that 1-year survival rates range from 25% to 53%, whereas 2-year survival rates range from 5% to 23%.[9] Although a number of clinical trials have been undertaken, the role of chemotherapy or biological agents is not well defined.[10–12] Generally, the prognosis of BSG in adults is better than that in children. Guillamo et al. analyzed 48 adults, and reported that the 3-year survival rate was 66%.[5] However, because of the rarity of BSG in adults, no large clinical trials have been conducted, and the usefulness of chemotherapeutic and biological agents has also not been defined.

Owing to the poor prognosis of BSG and various safety concerns, the indication for surgical intervention is controversial. Therefore, MRI is usually the essential definitive diagnostic modality, and the MRI features of BSG are well established. However, the usefulness of stereotactic biopsy and resection has been reported in several studies.[13,14] For example, Rachinger et al. analyzed 46 adult patients with BSG, and reported that stereotactic biopsy was safe. Moreover, they noted that obtaining a valid tissue diagnosis was indispensable to formulate a treatment decision because radiological features alone are not reliable for diagnostic classification.[15]

In this study, the survival outcomes of children and adults with BSG treated using RT at our institution were retrospectively evaluated. We also reviewed the previous literature to investigate the current roles of RT, chemotherapeutic or biological agents and surgical intervention in the treatment of patients with BSG and to evaluate the prognostic factors.

METHODS

Patients

Between 1996 and 2014, 30 patients with BSG were treated at Kobe University Hospital. Of these patients, 14 were children (<18 years) and 16 were adults (≥18 years). The median ages of the children and adults were 8 years (range: 2–16 years) and 49 years (range: 19–75 years), respectively. Eleven patients (3 children and 8 adults) underwent a surgical approach, and histological diagnoses were determined. Biopsy was performed in seven patients (children: 1/14, adults: 6/16), and partial resection was performed in four patients (children: 2/14, adults: 2/16). The histological diagnoses in children were low-grade astrocytoma ($n = 1$, biopsy), anaplastic astrocytoma ($n = 1$, partial resection) and anaplastic ependymoma ($n = 1$, partial resection); those in adults were low-grade astrocytoma ($n = 2$, biopsy: 1, partial resection: 1), anaplastic astrocytoma ($n = 2$, biopsy) and glioblastoma multiforme ($n = 4$, biopsy: 3, partial resection: 1). A child with anaplastic ependymoma that was believed to originate from the fourth ventricle was included in this study because the tumor presented as diffuse BSG apparently involving the pons and medulla according to the MRI findings. Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Parameter	Children (<18 years) $n = 14$ (47%)	Adults (≥18 years) $n = 16$ (53%)
Age (years)		
Median (range)	8 (2–16)	49 (19–75)
Gender		
Male	5 (36%)	10 (63%)
Female	9 (64%)	6 (37%)
Karnofsky performance status		
≥80	2 (14%)	8 (50%)
50–70	3 (21%)	6 (38%)
≤40	5 (36%)	1 (6%)
NA	4 (29%)	1 (6%)
Surgical approach		
None	11 (79%)	8 (50%)
Biopsy	1 (7%)	6 (38%)
Partial removal	2 (14%)	2 (12%)
Histology		
Low grade astrocytoma	1 (7%)	2 (12%)
Anaplastic ependymoma	1 (7%)	0 (0%)
Anaplastic astrocytoma	1 (7%)	2 (12%)
Glioblastoma mutiforme	0 (0%)	4 (25%)
Unknown	11 (79%)	8 (50%)

NA, not available.

MRI findings

Pretreatment MRI was performed for all patients. The lesions were classified into three types (diffuse intrinsic, focal and exophytic) on the basis of T2-weighted images as described in previous reports.[3,7,8] Of the 30 tumors, 23 (76%) were classified as diffuse intrinsic, 2 (7%) as focal and 5 (17%) as exophytic. Gadolinium enhancement was performed for 29 patients, and 14 (47%, 5 children and 9 adults) showed enhancement. Regarding tumor location, tumors supposedly originating from the pons or

apparently invading the pons from the midbrain or medulla were defined as "involving the pons." Tumors supposedly originating from the midbrain and medulla without pons invasion were defined as "outside the pons." Of the 30 tumors, 25 (83%, 12 in children and 13 in adults) involved the pons, and the remaining 5 (2 in children and 3 in adults) were outside the pons.

Radiotherapy

In the 1990s, six patients were irradiated using the conventional lateral opposing technique. Since 2000, 24 patients have been irradiated using the three-dimensional conformal technique. Computed tomography (CT) was performed using a thermoplastic mask before RT planning commenced. The target and organs at risk (OARs) were delineated on the acquired CT images by referring to the MRI findings. If the tumor was partially resected before RT planning, delineation was performed with reference to the MRI images before and after resection. First, both gadolinium-enhanced lesions and high-intensity lesions on the T2-weighted images, representing the tumor body and peritumor infiltration with edema, were delineated as the gross tumor volume (GTV). The clinical target volume (CTV) was determined with a 0.5–2.0-cm margin from the area excluding bone. The planning target volume (PTV) was automatically delineated by adding a 0.5-cm margin to the CTV. The OARs, which included the chiasm, spinal cord, bilateral optic nerves, eyeballs and lens, were delineated. Subsequently, the RT field was set by adding a 0.5-cm margin to the PTV using a multileaf collimator to account for the radiation beam penumbra. The single fraction size was 1.8–2.0 Gy delivered once a day for 5 days a week for each patient. In general, field shrinking was performed at 40–45 Gy to protect the OARs. The median total dose for all patients was 56 Gy (range: 50–70 Gy), and the median overall treatment time (OTT) was 43.5 days (range: 34–49 days). The median total doses for children and adults were 60 Gy (range: 50–70 Gy) and 54 Gy (range: 50.4–60 Gy), respectively. The median OTTs for children and adults were 44 days (range: 38–49 days) and 43 days (range: 34–49 days), respectively. Children younger than 10 years were usually irradiated under intravenous sedation.

Combinations of chemotherapeutic agents

Of the 30 patients, 23 (76%, 11 children and 12 adults) were irradiated with the concurrent administration of chemotherapeutic agents. Temozolomide (TMZ) alone was administered to three children and seven adults, Nimustine hydrochloride (ACNU) alone was administered to four children, and interferon-β (IFN-β) alone was administered to two children and one adult. A combination of TMZ and IFN-β was administered to one child and three adults. A combination of ACNU and IFN-β was administered to one child. A combination of ACNU, IFN-β and vincristine was administered to one adult. A total of 14 patients (47%, 4 children and 10 adults) received TMZ either alone or in combination with other agents, concurrently with RT.

Statistics and evaluation of treatment-related toxicity and ethical considerations

Statistical analyses were performed using IBM SPSS Statistics 19 (IBM Corp, Armonk, NY, USA). Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. P values less than 0.05 were considered statistically significant. The follow-up period was calculated from the day of RT initiation. Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0.[16] This study was approved by the ethics committee at out institution.

RESULTS

Patient status after RT and survival

Of the 30 patients, 26 (87%, 14 children and 12 adults) experienced tumor progression after RT, and 23 died due to BSG (76%, 14 children and 9 adults). Three adults survived with tumor progression and had received salvage treatment or best supportive care at the time of analysis. Four adults survived without tumor progression. Of these patients who did not show progression, one had a tumor arising in the midbrain, two had tumors arising in the pons and one had tumors arising in the medulla.

The median survival time (MST) for all patients was 15 months (children: 8.5 months; adults: 39 months). The 1-, 2- and 3-year overall survival (OS) rates for all patients were 53%, 43% and 27%, respectively, and the 1-, 2- and 3-year progression-free survival (PFS) rates for all patients were 43%, 26% and 19%, respectively. The 1, 2- and 3-year OS rates for children/adults were 29%/75%, 14%/68% and 0%/53%, respectively (Fig. 1a, $P = 0.001$). The 1-, 2- and 3-year PFS rates for children/adults were 14%/69%, 0%/49% and 0%/35%, respectively (Fig. 1b, $P < 0.001$).

Additional survival analyses according to the type of tumor, pretreatment MRI enhancement and tumor location were performed. The 2-year OS/PFS rates for the patients with diffuse intrinsic and other (focal, exophytic)

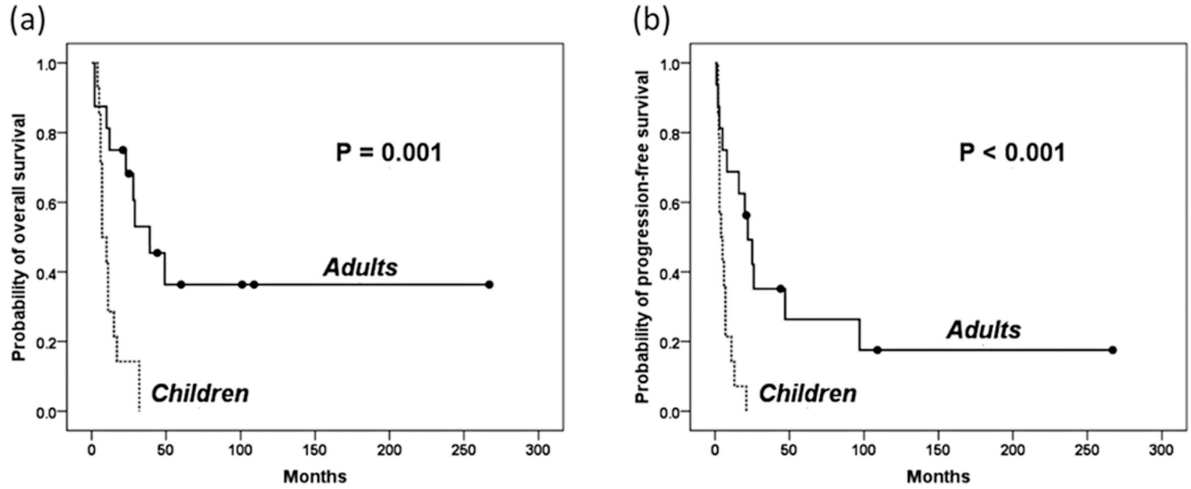

Figure 1 (a) Overall survival (OS) rates for children and adults. The 1-, 2- and 3-year OS rates for children/adults were 29%/75%, 14%/68% and 0%/53%, respectively. The difference between children and adults was significant ($P = 0.001$). (b) Progression-free survival (PFS) rates for children and adults. The 1-, 2- and 3-year PFS rates for children/adults were 14%/69%, 0%/49% and 0%/35%, respectively. The difference between children and adults was significant ($P < 0.001$).

tumors (23 and 7 patients, respectively) were 39%/57% and 26%/29%, respectively ($P = 0.84$ and 0.72, respectively). The 2-year OS/PFS rates for patients with and without pretreatment tumor enhancement (14 and 15 patients, respectively) were 50%/40% and 21%/33%, respectively ($P = 0.75$ and 0.35, respectively). The 2-year OS/PFS rates for patients with tumors involving the pons and outside the pons (25 and 5 patients, respectively) were 36%/80% and 24%/40%, respectively ($P = 0.18$ and 0.12, respectively). The 3-year OS/PFS rates for patients treated with and without TMZ were 34%/50% and 21%/31%, respectively ($P = 0.24$ and 0.09, respectively).

Treatment-related toxicity

None of the patients exhibited grade 3 or higher acute toxicity. Grade 2 toxicities were observed in only two adults: one had grade 2 nausea, dermatitis and alopecia, and the other exhibited grade 2 fatigue and anorexia. Most patients had minor acute toxicities, and all patients completed RT without delay. None of the children or adults experienced grade 2 or higher late toxicities.

DISCUSSION

In general, the prognosis of BSG in children is poorer than that in adults, which was also noted in our study. BSG also occurs with greater frequency in children than in adults. Therefore, various attempts have been made to improve treatment results, especially for children. In the field of RT, many dose escalation studies utilizing hyperfractionated RT have been undertaken and reported during the late 1980s through the 1990s (Table 2).[17–22] In these reports, the total doses ranged from 62.1 to 78.0 Gy, with a single fraction size of 1.00–1.26 Gy, using twice-daily irradiation. However, a survival benefit with the use of hyperfractionated RT could not be confirmed. In addition, children younger than 10 years old must be treated under intravenous sedation; therefore, when they receive hyperfractionated RT, intravenous sedation must also be performed twice daily. This is cumbersome for children and should be avoided unless hyperfractionated RT is found to have a significant advantage over conventional RT. The most recently reported standard dose for conventional RT is 54–60 Gy in 30 fractions over 6 weeks. However, in the late 2000s, several studies regarding hypofractionated RT were reported (Table 2).[23,24] For example, Jassens et al. performed a 1:1 matched cohort analysis comparing hypofractionated (39 Gy in 13 fractions or 44.8 Gy in 16 fractions, $n = 27$) and conventional (54 Gy in 30 fractions, $n = 27$) RT regimens. Although the use of hypofractionated RT did not improve the survival outcome, the authors concluded that this regimen was feasible, with no severe toxicity. The most significant benefit of hypofractionated RT was its shorter OTT compared with that of conventional RT (3 weeks *vs* 6 weeks).[24] As shown in Table 2, all children with BSG in the present study were treated with conventional RT, and the survival outcomes were consistent with those of previous studies. To confirm the efficacy and benefit of hypofractionated

Table 2 Results of hyper- and hypofractionated RT for BSGs in children

Author (year)	RT method	No. of patients (median age, years)	Dose (Gy)/fraction	MST (month)	Survival at 1 year (%)
Freeman (1988)[17]	Hyper	34 (7.2)	66/60	11	48
Freeman (1991)[18]	Hyper	57 (NA)	70.2/60	10	39.6
Freeman (1993)[19]	Hyper	39 (7.5)	75.6/60	10	39
Packer (1994)[20]	Hyper	66 (7.5)	78/78	NA	35
Mandell (1999)[21]	Conv *vs* Hyper	Conv: 66 (6.5)	Conv: 54/30	8.5	30.9
		Hyper: 64 (6.2)	Hyper: 70.2/60	8	27
Marcus (2003)[22]	Hyper	18 (8.5)	66/44	8.5	NA
Negretti (2011)[23]	Hypo	22 (5.9)	45/15	7.6	NA
Janssens (2013)[24]	Conv *vs* Hypo	Conv: 27 (7.3)	Conv: 54/30	9.4	NA
		Hypo: 27 (7.5)	Hypo: 39/13, 44.8/16	9	22
Current study (2015)	Conv	13 (8)	50–70	10	44

BSG, brainstem glioma; RT, radiotherapy; MST, median survival time; Hyper, hyperfractionated; Conv, conventional; Hypo hypofractinated.

Table 3 Results of RT and chemotherapeutic or biological agents for BSGs in children

Author (year)	No. of patients (median age, years)	Dose (Gy)/fraction	Combination	MST (month)	Survival at 1 year (%)
Broniscer (2004)[25]	33 (6.4)	55.8/31	TMZ, irinotecan	12	48
Sirachainan (2008)[26]	12 (4.4)	55.8–59.4/31–33	TMZ, cis-retinoic acid	13.5	58
Chiang (2010)[27]	18 (8.3)	54–60/30	TMZ	12.3	51
Kim (2010)[28]	17 (6)	50–54/25–30	TMZ, Thalidomide	12.7	58.3
Sharp (2010)[29]	15 (6.4)	54/30	TMZ	9.8	20
Cohen (2011)[10]	58 (7.7)	59.4/33	TMZ	9.6	40
Chassot (2012)[30]	21 (6.4)	54/30	TMZ	11.7	50
Haas-Kogan (2011)[11]	40 (5.5)	55.8/31	Tipifarnib	8.3	12.9
Pollack (2011)[12]	43 (7)	55.8/31	Gefinitib	NA	56.4
Current study (2015)	13 (8)	50–70/25–35	TMZ, ACNU, IFN-β, ACNU+ IFN-β	10	44

BSG, brainstem glioma; TMZ, temozolomide; MST, median survival time; NA, not available; ACNU, Nimustine hydrochloride; IFN, interferon.

RT, additional large randomized trials targeting BSGs in both children and adults should be performed. In the near future, hypofractionated RT might be a new alternative to conventional RT.

Many clinical trials have been undertaken to examine RT combined with various chemotherapeutic or biological agents for the treatment of gliomas, and TMZ with concomitant RT is currently the first choice not only for patients with glioblastoma multiforme, but also for those with other gliomas. Although no studies have been reported regarding the combination of TMZ and RT for the treatment of BSG in adults, several clinical trials exploring BSG treatments in children have been reported (Table 3).[10,25–30] Most of the previous studies described in Table 4 reported that TMZ and RT did not alter the poor prognosis of BSG in children. As shown in Table 3, children with BSG in the present study were treated with RT and various chemotherapeutic agents, and their survival outcomes were not different from those observed in other studies. Although the data are not shown in the table, 13 of 14 patients in the present study who received TMZ concurrently with RT experienced recurrence, and 11 died. One adult patient was alive without recurrence at the last follow-up. No significant difference in survival was observed between patients treated with and without TMZ. Owing to the small sample sizes in the studies listed in Table 4 and in the present study, further clinical trials with larger samples are needed to determine whether the combination of TMZ and RT is effective for BSG. In addition to TMZ, clinical studies examining other new agents such as tipifarnib and gefitinib have been undertaken.[11,12] However, the efficacy and safety of these agents remain to be confirmed. Therefore, additional data are needed to identify agents that are truly effective for BSG.

Table 4 Results of RT for BSG in adults

Author (year)	No. of patients (mean or median age, years)	Histological grade	MST (months)	Survivals (%)
Landolfi (1998)[31]	19 (40)	NA	54	45 (5-y)
Guillamo (2001)[5]	48 (34)	Low: 15 (31%), high: 17 (36%), NA: 16 (33%)	65	66 (3-y)
Salmaggi (2008)[6]	32 (31)	Low: 11 (35%), high: 9 (28%), NA: 12 (27%)	59	NA
Kesari (2008)[32]	101 (36)	Low: 31 (31%), high: 15 (15%): NA: 55 (54%)	85	58 (5-y)
Hundsberger (2014)[33]	21 (41)	Low: 8 (38%), high: 13 (62%)	low: 30.5, high: 11.5	NA
Dey (2014)[34]	240 (48.7)	High	7	19.7 (2-y)
Current study (2015)	16 (49)	Low: 2 (13%), high: 6 (37%), NA: 8 (50%)	39	53 (3-y)

BSG, brainstem glioma; MST, median survival time; NA, not available; MRI, magnetic resonance imaging; GBM, glioblastoma multiforme.

There are fewer studies about BSG in adults than in children. There are also limited studies comparing the treatment results for BSG between children and adults. As shown in Table 4, MSTs for BSG in adults were 7–85 months.[5,6,31–34] Studies that included a larger number of high grade tumors reported shorter MSTs.[33,34] Our results are fairly similar to these reports. On the contrary, as shown in Tables 2 and 3, MSTs for BSG in children were reportedly 7.6–13.5 months. Based on previous reports (Tables 2–4), the prognosis of children is apparently worse than that of adults; therefore, childhood is considered a strong unfavorable prognostic factor. In addition, a shorter symptom duration before diagnosis was considered an important unfavorable prognostic factor.[5,6,35–37] Regrettably, in our study, the symptom duration of more than half of the patients was not available, and an analysis could not be performed. Clinicians treating patients with BSG should pay careful attention to the duration of symptoms. AS described, studies including a large number of high grade tumors had worse treatment results and a high-grade tumor was also considered an important unfavorable prognostic factor.[5,32,38–40] To determine the tumor grade, surgical intervention (stereotactic biopsy or resection) is essential. Although the indication for surgical intervention should be determined carefully and consider both the safety and predicted prognosis of the patient, we favor the diagnostic accuracy of stereotactic biopsy compared to that of MRI alone.[13–15] In addition, several articles have reported that many focal BSGs could be resected radically with a better prognosis.[41,42] Thus, considering both safety and patient prognosis, surgical interventions should be performed by experienced neurosurgeons, if warranted. In our study, an analysis of the histological grade was not performed because histology data were only available for 11 of 30 patients.

The difference in histology is an important factor possibly explaining the poor prognosis of BSG in children. Reyes-Botero et al. reported that BSGs in adults represented heterogeneous tumor types, with a predominance of low-grade tumors, whereas grade IV was the most common BSG in children, reportedly observed in up to 50%–60%.[43] They indicated that the different histologic predominance probably correlates with the difference in survival outcomes between BSG in children and adults. In a clinical study, Ahmed et al. analyzed 662 biopsied BSG patients. There were 263 patients with low-grade tumors, but only 48 (18.3%) were children. Their report clearly showed a decreased frequency of low-grade BSG in children. However, survival outcomes in the 48 low-grade BSGs in this study were similar to those of adult BSGs, with a 5- and 10-year OS rate of 67% and 59%, respectively. Resection and a nondiffuse classification showed further improvement in outcome. Grade I tumors also had better outcomes than grade II tumors. Although the prognosis of BSG in children is poor because of the high frequency of grade IV tumors, low-grade BSG in children can still achieve outcomes comparable to adult BSG, as shown in that study.

Molecular biology has yielded important new findings. The K27M mutation in H3.3 histone (K27M-H3.3 mutation) in diffuse pontine glioma in children has been the subject of focus in recent studies.[44–46] The K27M-H3.1 mutation was also considered. Buczkowicz et al. reported that 42/66 (64%) and 8/66 (12%) cases showed K27M-

H3.3 and H3.1 mutations.[44] They also reported that patients with the K27M mutation in either histone H3.1 or H3.3 had a significantly worse OS than those without the mutation. These results indicate that the KM27-H3 mutation correlates with the poor prognosis of BSG in children and there is also the possibility of the new therapeutic approaches for BSG in children based on these molecular findings. In the future, molecular target therapy may achieve an improved outcome in unfavorable groups, such as high-grade, aggressive, grade II, unresectable and diffuse tumors in children. Because of rarity in adults, there are very few molecular studies on these tumors. Reyes-Botero et al. reported that the KM27-H3 mutation was also found in adult BSG, but with lower frequency, compared with pediatric BSG.[47] This may correlate with the heterogeneous histology, with predominance of low-grade tumors in adult BSG. Further investigations should determine whether adult BSGs have specific molecular features different from those in pediatric BSGs, such as the K27M-H3 mutation.

In conclusion, we found that the treatment outcomes of children with BSG were poorer than those of adults, and the results of our study were not different from the previous studies described in Tables 2–4. Based on these previous studies, various unfavorable prognostic factors were identified; of these factors, childhood was considered important. In addition, the duration of symptoms must be noted. The histological grade was also important. The difference in histological grade is one of the factors accounting for the difference in survival between children and adults with BSG. To improve the survival outcomes of patients with BSG, especially children, new methods of RT including hypofractionation, TMZ and other new agents should be used, and the indications for surgical intervention should be expanded, or a combination of these approaches should be adopted. Moreover, molecular biology of the K27M-H3 mutation has provided important information about BSG; therefore, investigation of new therapeutic approaches based on these findings must continue.

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