Suggestions for Escaping The Dark Ages for Pediatric Diffuse Intrinsic Pontine Glioma Treated with Radiotherapy: Analysis of Prognostic Factors From The National Multicenter Study

Hyun Ju Kim

Gachon University Gil Medical Center Department of Radiation Oncology

Joo Ho Lee

Seoul National University College of Medicine

Youngkyong Kim

Kyung Hee University Hospital

Do Hoon Lim

Samsung Medical Center Department of Radiation Oncology

Shin-Hyung Park

Kyungpook National University

Seung Do Ahn

Asan Medical Center

In Ah Kim

Seoul National University Bundang Hospital

Jung Ho Im

CHA Bundang Medical Center

Jae Wook Chung

Chonnam National University Medical School

Joo-Young Kim

National Cancer Center

Il Han Kim

Seoul National University College of Medicine

Chang-Ok Suh

CHA Bundang Medical Center

Hong In Yoon (✉ YHI0225@yuhs.ac)

Yonsei Cancer Center <https://orcid.org/0000-0002-2106-6856>

Keywords: diffuse intrinsic pontine glioma, radiotherapy, prognostic factors, pediatric brain tumor

Posted Date: November 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1070562/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Cancer Research and Treatment on March 4th, 2022. See the published version at <https://doi.org/10.4143/crt.2021.1514>.

Abstract

Purpose

This multicenter retrospective study aimed to investigate prognostic factors for survival, encompassing clinical and radiologic features and treatments, in newly diagnosed diffuse intrinsic pontine glioma (DIPG) patients treated with radiotherapy.

Methods

Patients <30 years of age who underwent radiotherapy as an initial treatment for DIPG between 2000 and 2018 were included; patients who did not undergo an MRI at diagnosis and those with pathologically diagnosed grade I glioma were excluded. We examined medical records of 162 patients collected from 10 participating centers in Korea. The patients' clinical and radiological variables, molecular and histopathologic data, and treatment response were evaluated to identify the prognosticators for DIPG and estimate survival outcomes.

Results

The median follow-up period was 10.8 months (interquartile range, 7.5–18.1). The 1- and 2-year overall survival (OS) rates were 53.5% and 19.0%, respectively, with a median OS of 13.1 months. Long term survival rate (≥ 2 years) was 16.7%, and median OS was 43.6 months. Age (<10 years), poor performance status, treatment before 2010, and post-radiotherapy necrosis were independent prognostic factors related to poor OS in the multivariate analysis. In patients with increased post-radiotherapy necrosis, the median OS was 13.3 months for bevacizumab group and 11.4 months for no-bevacizumab group ($P = 0.138$).

Conclusion

Therapeutic strategy for DIPG has remained unchanged over time, and its prognosis remains poor. Our findings suggest that appropriate efforts are needed to reduce the occurrence of post-radiotherapy necrosis. Further well-designed clinical trials are recommended to improve the poor prognosis observed in DIPG patients.

Introduction

Diffuse intrinsic pontine glioma (DIPG) accounts for 10–20% of all childhood brain tumors, and has a poor prognosis with a median overall survival (OS) of less than 12 months [1–3]. Approximately 10% of pediatric patients with DIPG survive for 2 years or more after their diagnosis [4]. Based on recent advances in molecular profiling, the World Health Organization (WHO) defined a new pathologic entity,

'diffuse midline glioma, H3K27M-mutant' [5]. The pathologic diagnosis of this new variant is defined by the presence of a somatic mutation at position K27 in one of several histone-encoding genes. DIPG cases with H3K27M mutation, which account for approximately 80% of clinically recognized DIPGs, have a significantly worse prognosis than those without H3K27M mutation [6]; however, to date there is no known treatment for such cases in clinical practice.

Owing to the anatomical complexity and critical functions of the brainstem, surgical resection is rarely performed and pathologic diagnosis via biopsy is also very limited. Radiotherapy remains the standard of care, which only delays the progression of disease for some months [7]. However, radiotherapy techniques, such as optimal target volume, radiotherapy modality, and dose schemes, are not well established. To improve prognosis, the additive use of chemotherapy with radiotherapy was investigated by several studies, which reported conflicting results [8, 9]. Bevacizumab, an anti-vascular endothelial growth factor antibody, was investigated as a novel therapeutic agent, but has not been proven to be effective in children with DIPG. Despite the tremendous development of medical technologies over decades, DIPG remains under-researched due to the rarity of the tumor, unproven pathology, and absence of effective therapeutic option.

This multicenter retrospective study aimed to examine the clinical practice in Korea and investigate the prognostic factors associated with survival in children newly diagnosed with DIPG who were treated with radiotherapy.

Materials And Methods

Study population

The medical records of patients with newly diagnosed DIPG who were treated with radiotherapy between January 2000 and December 2018 at 10 participating centers were retrospectively reviewed based on the Korean Radiation Oncology Group (KROG) 20-01 protocol. This study was approved by KROG and the institutional review boards of each participating center, according to the ethical standards of the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective study design.

Patients under 30 years of age and who had undergone gadolinium-enhanced magnetic resonance imaging (MRI) at diagnosis, with radiologic features consistent with DIPG, were included in the study. DIPG was diagnosed when MRI showed a T1-hypo (or iso) intense and T2-hyperintense lesion involving at least 50% of the pons. Patients with focal brainstem glioma, dorsally exophytic tumor, and extrinsic tumors secondarily invading the pons were excluded. Moreover, patients who were pathologically diagnosed with a WHO grade 1 glioma or non-glioma histology and those whose follow-up data could not be obtained were also excluded. All cases were required to be treated with radiotherapy. Histological diagnosis through stereotactic biopsy or resection was not essential as DIPG was routinely diagnosed based on the radiologic characteristics.

Clinical and radiologic variables

Clinical data, including age, sex, Karnofsky/Lansky (if patient's age was < 16 years) performance status, symptoms, and duration of symptoms was obtained from the patients' medical records. The symptoms were stratified under three categories: cranial nerve palsy, cerebellar signs (nystagmus, dysarthria, dysmetria, or ataxia), and pyramidal tract signs (mono-, hemi-, or quadriparesis; hyperreflexia; or positive Babinski sign). Histopathologic data were obtained for those who underwent biopsy or surgical resection. Information of molecular markers, including O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, IDH1 mutation, p53, Ki-67, and 1p19q co-deletion, were collected if the data were available.

Radiologic findings of the tumor were reviewed by neuroradiologists from each institution based on the MRI acquired at diagnosis. We obtained information of extrapontine extension, enhancement, infiltrative margin, cystic/necrotic feature, hydrocephalus, and leptomeningeal seeding from the MRI data. Leptomeningeal dissemination was evaluated if whole spine MRI data were available.

Treatment data regarding radiotherapy (modality, dose, and target volume), chemotherapy regimen, and the use of bevacizumab for radiation necrosis were also collected. Gross tumor volume (GTV) was defined as a T1-hypo (or iso) intense and T2-hyperintense lesion. Clinical target volume (CTV) was defined as GTV +0–2 cm margin, and planning target volume (PTV) was defined as CTV+ margin within 1 cm, according to the institutional policy.

Response evaluation

Treatment response was assessed in two ways: by a radiologic assessment using follow-up MR images, and by the clinical improvement of symptoms and signs. Images acquired within 2 months after completion of radiotherapy were used for response evaluation. Treatment response was evaluated using T2-weighted images according to the Response Assessment in Pediatric Neuro-Oncology criteria and classified as follows [10]: complete response (CR; no evidence of disease), partial response (PR; $\geq 25\%$ decrease in the two-dimensional [2D] products of the maximum perpendicular diameters), stable disease (SD; $< 25\%$ reduction or increase in 2D products of the maximum perpendicular diameters), and progressive disease (PD; $\geq 25\%$ increase in the 2D products of the maximum perpendicular diameters or any new sites of disease). Clinical symptomatic response was divided into three categories (improved, not-changed, and aggravated) based on the changes in the clinical symptoms and signs which were available based on the electronic medical records.

Statistical analysis

The date of diagnosis was based on the date the first MRI showing the DIPG features was performed, regardless of the pathologic diagnosis. OS was calculated from the date of diagnosis to the date of death or that of last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to that of brain MRI showing progression of disease or that of death. Independent sample t-tests were used to compare continuous variables, such as baseline characteristics, between the two groups. Pearson's Chi square test or Fisher's exact test, as appropriate, were used to compare categorical variables. The

Kaplan–Meier method with log-rank test and Cox regression were used to analyze survival outcomes. Stepwise Cox proportional hazards regression was used to perform a multivariable analysis on prognostic factors for OS (inclusion criteria $P < 0.05$). All statistical tests were two-tailed with significance level of $P < 0.05$. The data were analyzed using IBM SPSS software version 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Patients and treatments characteristics

A total of 162 patients from 10 tertiary academic institutions were analyzed in this study. The median patient age was 7 years (interquartile range [IQR], 5.0–12.3 years) and only three patients were aged less than 3 years. Symptoms related to cranial nerve palsy and cerebellar signs were observed in 63.6% and 66.7% of the patients, respectively. In contrast, pyramidal signs were less frequently observed (32.1%). The median duration of symptoms was 4 weeks (IQR; 2–8 weeks). Histological diagnosis was established in 44 patients through biopsy or surgical resection. Most of the patients (90.9%) had a confirmed diagnosis of grade 3 glioma or higher. Eighteen patients were diagnosed with diffuse midline glioma, H3K27M-mutant, which corresponded to 85.7% of the patients who were histologically diagnosed after 2016. Information on molecular biomarkers was available in a very limited number of patients. MGMT data was available for 17 patients, among whom only one patient had MGMT methylation. Additionally, *IDH1* mutation and 1p19q co-deletion were observed in 3 out of 28 patients and 1 out of 15 patients, respectively, for whom the data were available (Table 1).

Table 1
Clinical and radiologic information

	No. of patients	%
Age (years)		
Mean (SD)	10.0 (7.0)	
Median (IQR)	7.0 (5.0-12.3)	
Sex		
Male	89	54.9
Female	73	45.1
Lansky/Karnofsky performance status		
Median (IQR)	70 (60-80)	
< 80	89	54.9
≥ 80	72	44.5
Unknown	1	0.6
Symptoms		
Cerebral nerve palsy	103	63.6
Cerebellar signs	108	66.7
Pyramidal signs	52	32.1
Symptom duration, median (IQR), weeks	4.0 (2.0-8.0)	
Pathologic confirmation		
No	118	72.8
Biopsy only	30	18.5
Surgical resection	14	8.7
Histopathology		
Diffuse midline glioma, H3K27M-mutant	18	11.1
Glioblastoma	8	4.9
Anaplastic astrocytoma	14	8.6
Diffuse astrocytoma	4	2.4

Abbreviations: MRI=magnetic resonance image, IQR= interquartile range

	No. of patients	%
MRI features		
Extrapontine extension	124	76.5
Enhancement	103	63.6
Infiltrative margin	94	58.0
Cyst or necrosis	61	37.7
Hydrocephalus	23	14.2
Abbreviations: MRI=magnetic resonance image, IQR= interquartile range		

Intensity-modulated radiotherapy was used in 69 patients (42.6%), followed by 3D conformal radiotherapy in 63 (38.9%), proton therapy in 22 (13.6%), and 2D radiotherapy in 8 patients (4.9%). The median dose of radiotherapy was 54 Gy (range, 30–62.5 Gy; IQR, 54–54 Gy). CTV was defined as GTV + less than 1 cm margin for 67 (41.3%) and GTV + 1-2 cm margin in 68 patients (42%). PTV was defined as CTV + 3 mm margin in most of the patients. Concurrent chemotherapy was administered in 84 patients (51.9%) using with temozolomide (TMZ) (48.1%) and other regimens (3.8%), which consisted of vincristine, etoposide or BCNU. Adjuvant chemotherapy was performed in 70 patients (43.2%) using TMZ (59/70 patients) and other regimens (11 patients), which consisted of thalidomide, vincristine, ACNU or BCNU. Among patients who progressed after radiotherapy, 49 patients (35.3%) underwent salvage treatment. Of these patients, 45 underwent chemotherapy alone, 2 underwent re-radiotherapy with chemotherapy, and 2 underwent surgery (Table 2).

Table 2
Treatment information

	No. of patients	%
RT modality		
2D-RT	8	4.9
3D-CRT	63	38.9
IMRT	69	42.6
Proton	22	13.6
CTV volume		
GTV without margin	15	9.9
GTV + margin < 1 cm	67	41.4
GTV + margin 1-2 cm	68	42
GTV + margin $\geq$ 2 cm	2	1.2
RT dose (Gy), Median (IQR)		
GTV	54 (54-54)	
CTV	52.2 (46-54)	
Concurrent chemotherapy		
No	78	48.1
Yes	84	51.9
Adjuvant chemotherapy		
No	92	56.8
Yes	70	43.2
Salvage treatment		
No	84	51.9
Chemotherapy only	45	27.8
Re-RT + chemotherapy	2	1.2
Surgery	1	0.6
Surgery + chemotherapy	1	0.6

Abbreviations: RT=radiotherapy; 2D=2-dimensional; 3D=3-dimensional; IMRT=intensity-modulated radiotherapy; CTV= clinical target volume; GTV=gross tumor volume; Gy=gray; IQR=interquartile range

	No. of patients	%
Unknown	29	17.9
Abbreviations: RT=radiotherapy; 2D=2-dimensional; 3D=3-dimensional; IMRT=intensity-modulated radiotherapy; CTV= clinical target volume; GTV=gross tumor volume; Gy=gray; IQR=interquartile range		

Clinical outcomes

The median follow-up period was 10.8 months (IQR, 7.5-18.1). The 1-year and 2-year PFS were 26.3% and 8.4%, respectively, and the median PFS was 7.7 months (95% CI, 6.9-8.5 months). The 1-year and 2-year OS were 53.5% and 19.0%, respectively, and the median OS was 13.1 months (95% CI, 11.7-14.5 months). OS improved significantly over time as shown in Figure 1C. Median OS was 11.4, 13.5, and 17.6 months for patients treated before 2010, 2010-2015, and after 2015, respectively. Statistically significant difference in OS was found between patients treated before 2010 and 2010-2015 ($P = 0.041$), and between patients treated before 2010 and after 2015 ($P = 0.011$). Additionally, the 2-yr OS rates of patients who were treated before and after 2010 were 10.2% and 23.2%, respectively ($P = 0.008$).

There were 27 long-term survivors (16.7%) who survived more than 24 months, and their median OS was 43.6 months (95% CI, 24.3-62.9). When we compared the patient characteristics between short- and long-term survivors (Supplementary table 1), long-term survivors were more likely to be age ≥ 10 years (51.9% vs. 31.9% for short-term survivors; $P = 0.047$). Long-term survivors presented with higher rates of extrapontine extension (92.6% vs. 73.3% for short-term survivors; $P = 0.035$) and lower rates of cyst/necrosis (18.5% vs. 41.5%; $P = 0.025$). In addition, salvage treatment was performed in more than twice the number of patients in the long-term survivors compared to the short-term survivors (65% vs. 31.5% for short-term survivors; $P = 0.005$).

Treatment response after radiotherapy was CR in 4, PR in 72, SD in 49, and PD in 35 patients. The overall response rate to radiotherapy was 47.5%. Symptomatic improvement was observed in 87 patients (53.7%); however, no change in symptoms was observed in 33 patients (20.4%), and worsening of symptoms was observed in 29 patients (17.9%). Most of the failures were local (infield intracranial) failures in 110 patients (67.9%), followed by outfield intracranial failures in 22 (13.6%) and extracranial seedings in 4 patients (2.5%).

Prognostic factors

We performed univariate and multivariate analysis to investigate the prognostic factors related to OS, including clinical features, radiologic findings, and treatments (Table 3). Younger age (< 10 years), poor performance status at diagnosis, no extrapontine extension, cystic or necrotic feature, treatment decades before 2010, and post-radiotherapy necrosis were significantly related to a worse survival outcome in univariate analysis (Table 3; Figure 1). The 1-year OS was 44.3% for patients who had increased necrosis after radiotherapy and 63.9% for those who had no change or decreased necrosis (Figure 1D; $P = 0.003$).

On multivariate analysis, younger age (< 10 years), poor performance status, treatment decades before 2010, and post-radiotherapy necrosis were found to be independent prognostic factors related to poor OS.

Table 3
Prognostic factors for overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (< 10 years vs. ≥ 10 years)	0.593	0.41-0.85	0.004	0.662	0.46-0.76	0.029
Sex (male vs. female)	1.158	0.83-1.62	0.395			
Karnofsky/Lansky PS (< 80 vs. ≥ 80)	0.705	0.50-0.99	0.043	0.684	0.48-0.97	0.032
Extrapontine extension (no vs. yes)	0.599	0.40-0.89	0.011	0.707	0.47-1.07	0.104
Tumor margin (well vs. infiltrative)	0.976	0.70-1.37	0.887			
Tumor enhancement (no vs. yes)	1.113	0.78-1.58	0.552			
Cyst or necrosis (no vs. yes)	1.413	1.01-1.99	0.048	1.308	0.90-1.89	0.155
Hydrocephalus (no vs. yes)	1.259	0.79-2.01	0.333			
Surgery (no vs. yes)	0.716	0.47-1.09	0.121			
Treatment decades (~2010 vs. 2010~)	0.628	0.44-0.89	0.009	0.578	0.40-0.84	0.004
RT modality (3D-CRT vs. IMRT)	0.927	0.64-1.33	0.683			
RT modality (proton vs. IMRT)	1.668	0.93-3.00	0.088			
Post-RT necrosis (other vs. increased)	1.713	1.20-2.44	0.003	1.499	1.03-2.19	0.035
Concurrent chemotherapy (no vs. yes)	1.199	0.86-1.68	0.292			
Adjuvant chemotherapy (no vs. yes)	0.966	0.69-1.36	0.842			
Abbreviations: HR=hazard ratio; CI=confidence interval; PS=performance status; RT=radiotherapy; 3D-CRT=3-dimensional conformal radiotherapy; IMRT=intensity-modulated radiotherapy						

With regard to the post-radiotherapy necrosis, we further analyzed whether the use of bevacizumab had an effect on the prognosis. Bevacizumab was administered in 23 out of 150 patients whose data were available. The patients who received bevacizumab showed a longer median survival of 18.3 months compared to those who did not (12 months), although it was not statistically significant ($P = 0.386$). Then, we divided the patients into two groups according to the post-radiotherapy necrosis (increased vs. decreased/absent). Among those who had increased post-radiotherapy necrosis, the median OS was 13.3 months for patients who used bevacizumab and 11.4 months for those who did not use bevacizumab ($P = 0.138$; Figure 2A). For patients with no or decreased post-radiotherapy necrosis, the median OS was 17.6 months for patients who used bevacizumab and 18.1 months for those who did not use bevacizumab ($P = 0.318$; Figure 2B).

We investigated whether any specific radiation factors, including target volume, prescribed dose, and radiotherapy techniques, had an effect on the OS. Radiotherapy techniques showed no significant effect on OS after adjusting other clinical factors. With regard to the radiotherapy dose, we could not perform a meaningful analysis as the prescribed dose was homogenously 54 Gy in most of the patients during the study period. For the CTV volume, the pattern of failure was not significantly different according to the CTV margin, since most of the failures were infield progression ($P = 0.160$) (Table 4).

Table 4
Failure rates according to the CTV volume

CTV volume				
	GTV+ no margin	GTV+ <1cm	GTV+1-2cm	GTV+ >2cm
Site of progression	N (%)	N (%)	N (%)	N (%)
Infield intracranial failure	11 (78.6)	41 (75.9)	49 (86)	2 (100)
Outfield intracranial failure	3 (21.4)	9 (16.7)	8 (14.0)	0 (0.0)
Extracranial failure	0 (0.0)	4 (7.4)	0 (0.0)	0 (0.0)
Abbreviations: CTV=clinical target volume; GTV=gross tumor volume				

Discussion

In this study, we investigated the clinical outcomes and prognostic factors, including clinical, radiologic, and pathologic factors in patients under 30 years of age who received radiotherapy for DIPG in Korea. As reported in previous literature [11], the number of brainstem glioma patients per institute was limited due to its rarity. Thus, we designed this multicenter study including 10 tertiary academic institutions for about 20 years. In our study, we found that the median survival time was 13 months and the percentage of long-term survivors was 16.7%, which was similar to other previously reported results [3, 8, 12].

As with previous studies, age ≥ 10 years and good performance status at diagnosis were confirmed as prognostic factors in our study [1, 3]. Furthermore, salvage treatment performed in these patients resulted in better prognosis. Notably, the recently treated patients had significantly better survival than those treated before the year of 2010, even after adjusting for the other clinicopathological factors, imaging features, and treatments. As the pattern of practice and the dose of radiotherapy for DIPG remained unchanged throughout the study period, the improvement in survival may be driven by the evolution of general management for patients and the active intervention for the problem that the patients encountered, probably due to an improved socio-economic condition with good medical insurance reimbursement. Using Surveillance, Epidemiology and End Results (SEER) data, Brandel et al. reported that the survival of grade 3 oligodendroglioma patients improved over time even after adjusting treatment. They also suggested that the survival improvement may be owing to the evolving patterns of medical management [13].

Historically, biopsy has not been recommended for diagnosis, and surgical resection was hindered by the location and infiltrative nature of the tumor. This trend was reconfirmed through a recent survey from the European Society for Pediatric Oncology (SIOPE) brain tumor group [14]. Recent advances in the stereotactic surgery of the brain have enabled us to obtain tissue for genomic analyses, and genetic studies are being conducted accordingly. It was found that the H3K27M mutation exist in approximately 80% of DIPGs [6, 15], and a new disease entity “diffuse midline glioma, H3K27M-mutant” has been incorporated in the 2016 WHO classification of central nervous system tumors [5]. However, genetic or histologic findings have not yet led to a meaningful therapeutic change in the real practice [16]. In our study, biopsy was performed in 18.5% of patients, and surgical resection was done only in 8.7% of patients. Moreover, molecular parameters were obtained only from a very limited number of patients, so it was impossible to conduct further analysis on the molecular parameters. Therefore, many studies regarding the prediction of the prognosis of patients with DIPG were based on imaging findings, which may be applied easily in the actual clinical environment [17–19].

We also investigated the MRI features associated with OS in this study. In the univariate analysis, extrapontine extension of tumor, cystic/necrotic feature, and post-radiotherapy necrosis were prognostic factors related to OS; of which, only post-radiotherapy necrosis was a significant prognostic imaging feature for survival in the multivariate analysis. Recently published report of 357 patients from the international DIPG registry showed that tumor extension beyond pons, enhancement, and tumor necrosis were poor prognostic imaging features related to OS in univariate analysis, but no imaging feature was significant in multivariate analysis [18]. Extrapontine extension was a poor prognostic factor for OS in their study, while it was associated with good prognosis in our study. Interpreting this result, we hypothesized that the rapid growth of tumor was related with the development of symptoms before the development of extrapontine extension, whereas less aggressive tumors were likely diagnosed late with extrapontine extension due to its late onset of symptoms. Additionally, we observed that patients with extrapontine extension had less cystic or necrotic features than those without (32.3% vs. 54.1%, $P = 0.016$), which may suggest more indolent features of tumors with extrapontine extension. Nonetheless,

considering that it was not statistically significant when adjusting patient's demographics and treatments, further studies investigating MRI features are needed.

Despite the efficacy of bevacizumab in adult glioblastoma, little is known about its efficacy in pediatric patients with newly diagnosed or recurrent DIPG [20–22]. The multinational collaborator study by Hoffman et al. reported that the use of bevacizumab at diagnosis showed greater odds of long-term survival in multivariable logistic regression [1]. Recently, Crotty et al. reported a single-center experience of a 3-drug maintenance regimen of TMZ, irinotecan, and bevacizumab following radiotherapy, which showed prolonged survival in patients with DIPG compared to historical single-agent TMZ [22]. In our study, bevacizumab was used in 23 patients. The OS was better in patients treated with bevacizumab than in those who were not. When patients were divided according to the post-radiotherapy necrosis, we found that the difference in survival was more pronounced in patients with post-radiotherapy necrosis than in those without, although it was not significant. In light of these results, given the small number of patients of our study, we may suggest that the use of bevacizumab in pediatric DIPG patients could be beneficial, especially in patients with increased post-radiotherapy necrosis. Further well-designed trials are needed to determine the potential efficacy of bevacizumab in pediatric DIPG patients.

All patients included in this study underwent radiotherapy as their initial treatment, so we intended to analyze whether the radiation dose and target volume had an effect on the prognosis. However, it was difficult to analyze the effect of the radiotherapy dose on survival because most patients received a relatively homogenous dose of radiation (median 54 Gy) despite the data collected by several clinicians from multiple institutions covering a relatively long period of 19 years. Considering that most failures were infield progression, and the pattern of failures were not affected by the radiotherapy volume, we suggest that a large margin of 1 cm or more to the target volume may not be beneficial. Similar results from 97 patients were reported by Tinkle et al. [23]. They also concluded that no apparent survival or tumor-control benefit was achieved by extending the CTV margins beyond 1 cm.

Several studies have been conducted on neoadjuvant, concurrent, and adjuvant chemotherapy in addition to radiotherapy to improve the prognosis of DIPG patients [24–26]. A phase II study evaluating the efficacy of chemoradiotherapy with TMZ followed by adjuvant TMZ conducted by the Children's Oncology Group showed a disappointing result [9]. In their study, the 1-year event-free survival (EFS) rate was 14%, which failed to achieve a higher rate than the historical baseline of 21.9% observed in CCG-9941. Although these disappointing results on TMZ have been reported by several prospective studies, we found that concurrent or adjuvant use of TMZ was still carried out in our practice depending on the clinician's discretion. This suggests that there are still no applicable drugs that are significantly effective to DIPG patients. In our study, we also could not find any beneficial effect of TMZ as a concurrent or adjuvant therapy after radiotherapy.

Our study had limitations. First, there was an unavoidable bias due to its retrospective nature. Considering the low incidence of DIPG, it is nearly impossible to recruit a large number of patients in the prospective setting. To minimize the bias from the retrospective design, we strictly applied a detailed

eligibility criteria and tried to include a homogenous patient group. Second, the sample size was relatively small despite pooling patients treated at 10 tertiary institutions over a period of 19 years. However, because there was no significant change in the treatment policy and radiotherapy dose during the study period, the attributable bias might be minimal. Third, there was very limited information on molecular findings to proceed with the analysis. We thought that it reflected the actual clinical situation where pathologic confirmation was not usually performed unless in a trial setting.

In conclusion, radiotherapy, as a mainstay of treatment for pediatric DIPG, was performed without significant change in specifics such as dose scheme and target volume. The prognosis of DIPG patients was poor despite slight improvement in survival over time. As radiation necrosis was a prognostic factor related to OS, efforts are needed to reduce occurrence of post-radiotherapy necrosis. Furthermore, the use of bevacizumab for radiation necrosis may be helpful in some patients. Future prospective studies to elucidate its role will be warranted.

Declarations

Acknowledgments: None.

Conflict of interest: None

Funding statement: None

Data availability: All data generated or analysed during this study are included in this published article (and its supplementary information files).

Author contributions

All authors contributed to the study conception and design. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conceptualization: Chang-Ok Suh, Hong In Yoon

Methodology: Hyun Ju Kim, Joo Ho Lee, Youngkyong Kim, Do Hoon Lim, Shin-Hyung Park, Seung Do Ahn, In Ah Kim, Jung Ho Im, Jae Wook Chung, Il Han Kim

Formal analysis and investigation: Hyun Ju Kim, Chang-Ok Suh, Hong In Yoon, Joo-Young Kim

Writing - original draft preparation: Hyun Ju Kim

Writing - review and editing: Hong In Yoon, Chang-Ok Suh, Joo-Young Kim

Supervision: Hong In Yoon, Chang-Ok Suh

References

1. Hoffman LM, van Veldhuijzen SEM, Colditz N et al (2018) Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries. *J Clin Oncol* 36:1963–1972
2. Jackson S, Patay Z, Howarth R et al (2013) Clinico-radiologic characteristics of long-term survivors of diffuse intrinsic pontine glioma. *J Neurooncol* 114:339–344
3. Jansen MH, van Veldhuijzen SE, Sanchez Aliaga E et al (2015) Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria. *Neuro Oncol* 17:160–166
4. Hargrave D, Bartels U, Bouffet E (2006) Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol* 7:241–248
5. Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 131:803–820
6. Wu G, Broniscer A, McEachron TA et al (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet* 44:251–253
7. Langmoen IA, Lundar T, Storm-Mathisen I et al (1991) Management of pediatric pontine gliomas. *Childs Nerv Syst* 7:13–15
8. Wagner S, Warmuth-Metz M, Emser A et al (2006) Treatment options in childhood pontine gliomas. *J Neurooncol* 79:281–287
9. Cohen KJ, Heideman RL, Zhou T et al (2011) Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. *Neurooncology* 13:410–416
10. Cooney TM, Cohen KJ, Guimaraes CV et al (2020) Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Lancet Oncol* 21:e330–e336
11. El-Khouly FE, van Veldhuijzen SEM, Santa-Maria Lopez V et al (2019) Diagnostics and treatment of diffuse intrinsic pontine glioma: where do we stand? *J Neurooncol* 145:177–184
12. Hassan H, Pinches A, Picton SV, Phillips RS (2017) Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis. *J Neurooncol* 135:13–20
13. Brandel MG, Alattar AA, Hirshman BR et al (2017) Survival trends of oligodendroglial tumor patients and associated clinical practice patterns: a SEER-based analysis. *J Neurooncol* 133:173–181
14. Tejada S, Aquilina K, Goodden J et al (2020) Biopsy in diffuse pontine gliomas: expert neurosurgeon opinion-a survey from the SIOPE brain tumor group. *Childs Nerv Syst* 36:705–711
15. Schwartzentruber J, Korshunov A, Liu XY et al (2012) Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* 482:226–231

16. La Morales A, Hashizume R, Kieran MW (2015) Future Clinical Trials in DIPG: Bringing Epigenetics to the Clinic. *Front Oncol* 5:148
17. Tam LT, Yeom KW, Wright JN et al (2021) MRI-based radiomics for prognosis of pediatric diffuse intrinsic pontine glioma: an international study. *Neuro-oncology advances* 3:vdab042–vdab042
18. Leach JL, Roebker J, Schafer A et al (2020) MR imaging features of diffuse intrinsic pontine glioma and relationship to overall survival: report from the International DIPG Registry. *Neurooncology* 22:1647–1657
19. Szychoł E, Youssef A, Ganeshan B et al (2021) Predicting outcome in childhood diffuse midline gliomas using magnetic resonance imaging based texture analysis. *J Neuroradiol* 48:243–247
20. Hummel TR, Salloum R, Drissi R et al (2016) A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas. *J Neurooncol* 127:53–61
21. Gururangan S, Fangusaro J, Poussaint TY et al (2014) Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas—a Pediatric Brain Tumor Consortium study. *Neuro Oncol* 16:310–317
22. Crotty EE, Leary SES, Geyer JR et al (2020) Children with DIPG and high-grade glioma treated with temozolomide, irinotecan, and bevacizumab: the Seattle Children's Hospital experience. *J Neurooncol* 148:607–617
23. Tinkle CL, Simone B, Chiang J et al (2020) Defining Optimal Target Volumes of Conformal Radiation Therapy for Diffuse Intrinsic Pontine Glioma. *International Journal of Radiation Oncology* Biology* Physics* 106:838–847
24. Broniscer A, Iacono L, Chintagumpala M et al (2005) Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children. *Cancer* 103:133–139
25. Jalali R, Raut N, Arora B et al (2010) Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. *International Journal of Radiation Oncology* Biology* Physics* 77:113–118
26. Chassot A, Canale S, Varlet P et al (2012) Radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. *J Neurooncol* 106:399–407

Figures

Fig. 1

Figure 1

Kaplan-Meier curves representing overall survival (OS) based on (A) patient age (years), (B) performance status, (C) treatment period, and (E) post-radiotherapy necrosis.

Fig. 2

Figure 2

Overall survival (OS) rates according to the use of bevacizumab in (A) Post-radiotherapy necrosis increased group and (B) Post-radiotherapy necrosis no or decreased group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SUPPLEMENTARYTABLE1.docx](#)