Abstract

Brainstem tumors are rare pathologies, brainstem glioblastoma is even rarer. We report three pediatric patients who underwent subtotal tumor resection for brainstem tumors diagnosed as brainstem glioblastoma. The clinical courses and treatment procedures were discussed alongside a comprehensive literature review. Treatment of brainstem high-grade gliomas includes steroids, surgery, radiotherapy, and chemotherapy. However, none of these treatment modalities effectively prolongs survival time. According to literature, the median overall survival of these patients are approximately between 9 to 12 months. Glioblastoma has a poor prognosis in pediatric patients with high-grade brainstem gliomas. Radiotherapy is associated with a decreased risk of mortality at 9 months but not long-term.

Keywords: Brainstem, glioblastoma, pediatric, chemotherapy, radiotherapy

Öz

Beyin sapı tümörleri nadir görülen patolojilerdir, beyin sapı glioblastomu daha da nadirdir. Beyin sapı tümörleri için subtotal tümör rezeksiyonu uygulanın ve beyin sapı glioblastomuna tanısı alan çocuklu hastaların klinik gidislerini ve tedavi prosedürlerini, kapsamlı bir literatür taraması eşliğinde tartışmaktayız. Beyin sapında yerleşen yüksek dereceli gliomların tedavisinde steroidler, cerrahi rezeksiyon, radyoterapi ve kemoterapi bulunmaktadır. Beyin sapında yerleşen yüksek dereceli gliomların tedavisinde steroidler, cerrahi rezeksiyon, radyoterapi ve kemoterapi bulunmaktadır. Bununla birlikte, bu tedavi yöntemlerinden hiçbirinin kesin bir veri olmayıp, birçoğundan da bilimsel bir incelemesizdir. Radyoterapi, uzun vadede değil ancak ilk 9 aylık süreçte mortalite riskinde azalma ile ilişkili olarak tespit edilmiştir.

Anahtar Sözcükler: Beyin sapı, glioblastom, pediatric, kemoterapi, radyoterapi
Introduction

Central nervous system tumors are the most common type of solid cancers in the pediatric period. Averagely 10%–15% of them are located in the brainstem. Brainstem tumors are divided into four classes according to magnetic resonance imaging (MRI) scans. These include diffuse intrinsic (type I), focal (type II), dorsal exophytic (type III), and cervicomedullary (type IV). Diffuse intrinsic brainstem gliomas are the most frequent tumors among brainstem tumors. They constitute approximately 75%–80% of all brainstem tumors. Approximately 30%–40% of these gliomas are brainstem glioblastomas. Surgical excision of these tumors is almost impossible in most cases, and added to their troublesome clinical course due to brainstem compression, the prognosis of brainstem glioblastomas is very poor. In our report, we present three pediatric patients who underwent operation for brainstem tumors diagnosed as glioblastoma from histopathological examination. The clinical course and treatment modalities of this rare pathology were discussed with the backing of comprehensive literature review.

Illustrative Cases

Case 1

We admitted a 7-year-old girl to the Neurosurgery Department presenting with headache, dizziness, diplopia, and right sided muscle weakness for six days. Her neurological examination revealed right hemiparesis (muscle strength was 3/5) and lower cranial nerves dysfunction. There was no contributive medical past history. MRI revealed an expansive and cystic pontine mass of 32 × 26 × 28 mm showing peripheral contrast enhancement (Figure 1A). She underwent subtotal tumor resection via left sided suboccipital craniotomy.

Histopathological examination of the tumor revealed small, elongated bipolar atypical cells, proliferated tumor vessels, and ischemic necrosis (Figure 2). Pathological diagnosis was isocitrate dehydrogenase type 1 (IDH)-mutant high-grade glial tumor with a proliferation index of 15%–20%. Postoperative contrast enhanced cerebral MRI scans showed the decrease in tumor size (Figure 1B).

Table 1. Data of the patients with brainstem glioblastoma in the present study.

| Patient | Age / Gender | Surgery | Adjuvant treatment | POD | POD treatment | Survival | Outcome |
|---------|--------------|---------|--------------------|-----|---------------|----------|---------|
| 1       | 7 / F        | STR     | RT + TMZ-N-V        | 9 months | TMZ + BVZ + IRN | 20 months | DOD     |
| 2       | 13 / F       | STR     | RT + TMZ           | 24 months | Spinal RT + BVZ + IRN | 40 months | DOD     |
| 3*      | 14 / F       | STR     | NA                | NA | NA            | NA       | NA      |

POD: Progression of disease, F: Female, STR: Subtotal resection, RT: Radiotherapy, TMZ: Temozolomide, N: Nimotuzumab, V: Vinorelbine, BVZ: Bevacizumab, IRN: Irinotecan, NA: Not available, DOD: Dead of disease

* The patient died in three weeks after the surgery and adjuvant treatment could not be started.
Her postoperative course was uneventful and she was discharged five days after. We started temozolomide (75 mg/m²/day) with concommittant radiotherapy (RT) (total dose: 54 Gy). After completion of RT, we administered nimotuzumab (150 mg/m²/day, first and fifteenth days) and vinorelbin (25 mg/m²/day, first and fifteenth days). After two cycles of chemotherapy, right hemiparesis slightly improved, with no additional clinical findings and with partial decrease in the mass was noticed on MRI.

However, after the third cycle, we noticed deterioration in clinical findings and enlargement of the mass on MRI.

Figure 1. (A) Preoperative axial and sagittal contrast enhanced T1-weighted magnetic resonance images of patient 1 revealing an expansile and cystic pontine mass of 32x26x28 mm. The mass lesion is showing peripheral contrast enhancement. (B) Postoperative axial and sagittal contrast enhanced T1-weighted magnetic resonance images revealing the subtotal resection of the tumor and cystic cavity.
We started a protocol constituting of bevacizumab (10 mg/kg/day first and fifteenth days), irinotecan (150 mg/m²; first and fifteenth days) and temozolomide (150 mg/m²/day 1–5 days). We recorded a slight improvement in motor strength of the right upper and lower extremity. However, she finally died because of the progression of brainstem glioblastoma 20 months after the operation (Table 1). 

**Case 2**

We admitted a 13-year-old female at the Neurosurgery Department presenting with headache and left sided muscle weakness for one week. She also had left sided hemiparesis and exaggerated deep tendon reflexes on neurological examination. She had contributive medical past history. She underwent brain MRI that revealed a diffuse infiltrating pontine tumoral lesion that was heterogeneously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. There was heterogeneously diffuse contrast enhancement after gadolinium administration (Figure 3A). Then, she underwent subtotal tumor resection via right sided suboccipital craniotomy. Histopathological examination of the tumor revealed (IDH)-mutant glioblastoma. She was discharged uneventfully.

![Figure 2](image-url)

**Figure 2.** Peroperative images of patient 1 revealing: (A) the expansile pontine tumor, (B) drainage of the cystic component of the tumor, (C) resection of the solid tumor components and (D) subtotal resection cavity of the tumor. Fifth cranial nerve is intact after the tumor resection (black arrow). (E) Histopathological examination revealed small, elongated bipolar atypical cells, proliferated tumor vessels and (F) ischemic necrosis confirming the pathological diagnosis IDH-mutant type glioblastoma (H&E, 200X magnification).
Moreover, she underwent cranial RT (total dose: 54 Gy) and chemotherapy (temozolomide, 75 mg/m²/day). Following the oncological treatments, we achieved tumor regression for two years (Figure 3B). However, new tumoral formation in the fourth ventricle and spinal metastases occurred two years later (Figure 3C). We performed all spinal column RT and chemotherapy treatment as bevacimuzab (10 mg/kg/day first and fifteenth days) and irinotecan (150 mg/m² first and fifteenth days). She died because of the progression of the brainstem glioblastoma 40 months after the operation (Table 1).

Case 3

We admitted a 14-year-old girl at the hospital presenting with a progressive balance disturbance, headache, vomiting, and diplopia for two weeks. Neurological examination revealed horizontal nystagmus, cerebellar ataxia, limitation of eye abduction and neurological deficit of left cranial nerves VI and VII. Cerebellar tests were positive. Strength, sensation, and reflexes in upper and lower extremities were all normal. Brain MRI revealed a lesion in the midline brainstem that enhanced after gadolinium administration. This lesion was heterogeneously hypointense on T1-weighted images, and heterogeneously hyperintense on T2-weighted images (Figure 4). We subsequently performed a microsurgical subtotal resection of the lesion via suboccipital craniotomy. The pathological findings confirmed the diagnosis of glioblastoma. Adapted oncological treatments could not be started because of the postoperative medical condition of the patient. She died three weeks after surgery (Table 1).

Review

A thorough review of the literature revealed 19 research that have reported on clinical cases (Table 2). All of them were clinical case series with a total of 482 pediatric patients. Among the multiple articles previously written by the same authors, the most recent and comprehensive ones were included in the present review. All of the research included all kind of brainstem gliomas, not only high-grade brainstem gliomas. Patients’ data including surgery/biopsy types, histopathologic composition of tumors, adjuvant treatment modalities, median progression-free survival (PFS) and overall survival (OS) were analysed (Table 2).

Discussion

Glioblastoma is the most common and most lethal primary brain tumor in adults. However, it is rarer in childhood. Glioblastoma constitutes only 3%–7% of all pediatric central nervous system tumors. The brainstem localization of glioblastoma is uncommon. From literature, two studies presenting the pediatric glioblastoma series have found the rates to be very low. In the study by Nikitovic et al., only 20% of pediatric glioblastoma patients had brainstem glioblastoma. In the other studies, brainstem localization was in 12.5% of pediatric glioblastoma patients.

The initial symptom of brainstem glioblastoma is usually headache. Other symptoms are ataxia, dizziness, weakness, nausea-vomiting, hemiparesis, cerebellar symptoms, and symptoms related with cranial nerve deficits. In some patients, hydrocephalus can be detected due to the compression of fourth ventricle.
Figure 3. (A) Preoperative axial magnetic resonance images of patient 2 revealing a diffuse infiltrating pontine tumoral lesion that was heterogeneously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. There was heterogeneously diffuse contrast enhancement after gadolinium administration. (B) Postoperative first year axial magnetic resonance images showing tumor regression. (C) Postoperative second year axial cranial and sagittal spinal magnetic resonance images revealing new tumoral formation in the fourth ventricle and spinal metastases.
Figure 4. (A) Axial, (B) coronal and (D) sagittal contrast enhanced T1-weighted images of patient 3 showing thick irregular enhanced mass lesion located in brainstem and middle cerebral peduncula with adjacent edema and compression at fourth ventricle. (C) Axial T2-weighted image demonstrate heterogeneous hyperintense mass lesion.
Table 2. Main results of published studies about pediatric brainstem gliomas.

| Author                | Patients (n) | Surgery / Biopsy | Histopathologic composition | Adjuvant treatment | Median PFS | Median survival |
|-----------------------|--------------|------------------|-----------------------------|-------------------|------------|-----------------|
| Brosnicker et al.15, 2005 | 33           | Biopsy (3 patients), STR (1 patient) | 3 anaplastic astrocytoma, 1 GBM, 29 BNP | RT + TMZ / IRN | 8.8 months | 12 months |
| Korones et al.23, 2008 | 30           | NA               | NA                          | RT + VCR + VP-16  | 7 months   | 12 months |
| Massimino et al.25, 2008 | 62           | STR – biopsy (30 patients) | 6 grade II astrocytoma, 18 anaplastic astrocytoma, 6 GBM, 32 BNP | RT + Cisplatin + VP-16 + ifosfamide + dactinomycin | 10 months | 13 months |
| Sirachainan et al.28, 2008 | 12           | NA               | NA                          | RT + TMZ + cis-retinoic acid | 10.2 months | 13.5 months |
| Janssens et al.20, 2009 | 9            | NA               | NA                          | RT only           | 5 months   | 8.6 months |
| Jalali et al.19, 2010 | 20           | STR (8 patients) | 6 low-grade glioma, 2 high-grade glioma, 12 BNP | RT + TMZ         | 6.9 months | 9.15 months |
| Kim et al.21, 2010    | 12           | STR (1 patient)  | 1 GBM, 11 BNP               | RT + TMZ + thalidomide | 7.2 months | 12.7 months |
| Sharp et al.27, 2010  | 15           | NA               | NA                          | RT + TMZ          | 5.13 months | 9.8 months |
| Wolff et al.29, 2010  | 37           | STR (4 patients), | 4 grade II astrocytoma, 8 grade III astrocytoma, 4 GBM, 21 BNP | RT + Cisplatin + VP-16 + VCR + ifosfamide | 4.8 months | 13.6 months |
| Study            | Biopsy (patients) | Treatment | PFS       | BNP |
|------------------|-------------------|-----------|-----------|-----|
| Cohen et al. 16, 2011 | Biopsy (12 patients) | NA, NA | RT + TMZ | 6.1 months | 9.6 months |
| Kivivuori et al. 22, 2011 | STR (5 patients) | 2 grade II glioma, 3 grade III glioma, 3 BNP | RT + Topotecan + thalidomide + celecoxib + VP-16 | 11 months | 12.5 months |
| Negretti et al. 26, 2011 | Biopsy (4 patients) | 3 grade III astrocytoma, 1 GBM, 18 BNP | RT only | 5.7 months | 7.6 months |
| Bailey et al. 12, 2013 | NA (38 patients) | NA | RT + TMZ | 5.4 months | 9.5 months |
| Zaky et al. 14, 2013 | NA (6 patients) | NA | RT + TMZ + BVZ + IRN | 10.4 months | 14.6 months |
| Massimino et al. 24, 2014 | Biopsy (4 patients) | 2 grade II diffuse astrocytoma, 2 anaplastic astrocytoma, 21 BNP | RT + N + V | 8.5 months | 15 months |
| Hummel et al. 18, 2015 | NA (14 patients) | NA | RT + TMZ + BVZ + IRN | 8.2 months | 10.4 months |
| Rizzo et al. 13, 2015 | STR (5 patients) | 3 anaplastic astrocytoma, 2 GBM, 10 BNP | RT + TMZ | 7.15 months | 15.6 months |
| Fleischhack et al. 17, 2019 | NA (42 patients) | NA | RT + N | 5.8 months | 9.4 months |
| Kebudi et al. 11, 2019 | NA (24 patients) | NA | RT + N + TMZ / V | 6 months | 12 months |

PFS: Progression-free survival, BNP: Biopsy not performed, STR: Subtotal resection, GBM: Glioblastoma, RT: Radiotherapy, TMZ: Temozolomide, N: Nimotuzumab, V: Vinorelbine, BVZ: Bevacizumab, IRN: Irinotecan. NA: Not available
MRI findings are non-specific and differentiation from other lesions may be difficult. However, features such as heterogeneous signal intensity, prominent heterogeneity and multicentricity associated with a disproportionally large tumor may be useful clues in diagnosing glioblastoma in that location\textsuperscript{1,5}.

Various pathologies with an affinity for the posterior fossa parenchyma may share similar features. Neoplastic diseases (especially pontine gliomas and inflammatory demyelinating lesions) may have similar MRI features. Definitive diagnosis requires histopathological confirmation\textsuperscript{5,6,8}. Klimo et al.\textsuperscript{9} involved 11 patients (38\%) having glioblastoma in 29 pediatric patients with malignant brainstem tumors. In their cohort, histopathological diagnoses were identified by stereotactic biopsy in 10 patients, open biopsy in six patients, subtotal resection in eight patients, and gross total resection in three patients. They concluded that maximal resection has favorable effects on long-term survival\textsuperscript{9}. Puget et al.\textsuperscript{10} performed stereotactic biopsies in 130 pediatric patients with diffuse intrinsic pontine gliomas and 28 patients had grade IV tumors according to histopathologic examination. In the study cohort, only five patients had comorbidities and no mortality related to the biopsy application was reported. Thus, the median OS and PFS were 10.3 and 5.6 months, respectively\textsuperscript{10}.

The characteristic histological appearance consisted of brisk mitotic activity, nuclear polymorphism, hypercellularity, endothelial proliferation, and necrosis. The tumor corresponds to World Health Organization (WHO) grade IV. Low-grade tumors have an insidious onset and course. However, high-grade lesions have an aggressive course with rapid progression commonly resulting to death within the first year of diagnosis\textsuperscript{1,2}. Some specific molecular alterations such as activin-A receptor type 1 (ACVR1) have also been identified in pediatric brainstem gliomas\textsuperscript{11}.

Treatment of brainstem gliomas includes steroids, surgery, RT, and chemotherapy\textsuperscript{11-14}. Chemotherapy has limited effect in brainstem gliomas\textsuperscript{11-29}. Temozolomide and RT combination has been standard approach in treatment of brainstem gliomas\textsuperscript{11-16,18,21,27,28}. However, we reported equivocal results in children treated with temozolomide and RT (Table 2). Nimotuzumab (which targets epidermal growth factor receptor, EGFR) is also used in children with brainstem glioma and reported to have modest benefits on survival time\textsuperscript{11,17,25}. The protocol involving anti-vascular endothelial growth factor agents: bevacizumab with irinotecan and temozolomide was shown to be feasible and tolerable in pediatric brainstem gliomas (Table 2). However, this protocol was also reported to have limited efficacy in terms of improving survival\textsuperscript{14,18}.

According to literature, there are meta-analyses about the treatment of pediatric high-grade brainstem gliomas\textsuperscript{8,30-32}. Maxwell et al.\textsuperscript{8} used surveillance epidemiology and end results (SEER) database for the study. He enrolled 154 patients with high-grade brainstem gliomas. Median survival for the entire cohort was 10 months. Glioblastoma histology and large tumor size were significantly associated with poor survival rates. Radiation therapy was associated with a decreased risk of mortality at six and nine months but not long-term. On the contrary, extent of surgical resection did not confer any survival advantage at six months, nine months, one year, and two years\textsuperscript{8}. Lam et al.\textsuperscript{32} analyzed 124 pediatric patients with high-grade brainstem gliomas. Patients with grade III gliomas had a median survival of 13 months and those with glioblastoma had a median survival of nine months. In this cohort,
surgical resection was associated with significantly lower mortality, especially in combination with radiation therapy. Radiation therapy alone was significantly associated with decreased mortality within the first nine months after diagnosis but not with overall mortality.

In most of the patients with brainstem gliomas, we could not perform tumor sampling and histopathological examination, and these patients undergo treatment modalities as high-grade gliomas. There are not any definite rates of high-grade brainstem gliomas in the literature (Table 2). Surgeries including maximal safe resection can be performed only in patients with dorsal exophytic (type III) tumors. However, surgical resection was not associated with significantly lower mortality or good prognosis in these patients.

Conclusion

This report of three cases suggests that it is important to consider the presence of glioblastoma in the differential diagnosis of brainstem lesions. Definitive diagnosis usually requires histopathological confirmation. Accurate diagnosis of tumor type in the brainstem may lead to changes in therapeutic decisions and potentially the outcome. Treatment of brainstem high-grade gliomas includes steroids, surgery, RT, and chemotherapy. However, none of these treatment modalities really affect survival time. Median OS of these patients is approximately 9 to 12 months in the literature. Glioblastoma histology has been associated with poor prognosis in pediatric patients with high-grade brainstem gliomas. Radiation therapy has been associated with a decreased risk of mortality nine months later but not long term.

Conflict of Interest

We declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

Preparation for publication of this article is partly supported by Turkish Neurosurgical Society.

References

1. Das KK, Mehrotra A, Nair AP, et al. Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. Childs Nerv Syst. 2012;28(12):2055-62. https://doi.org/10.1007/s00381-012-1890-x
2. Kebudi R, Cakir FB. Management of diffuse pontine gliomas in children: recent developments. Pediatr Drugs. 2013;15(5):351-62. https://doi.org/10.1007/s40272-013-0033-5
3. Kebudi R, Cakir FB, Agaoglu FY, et al. Pediatric diffuse intrinsic pontine glioma patients from a single center. Childs Nerv Syst. 2013;29(4):583-8. https://doi.org/10.1007/s00381-012-1986-3
4. Veldhuijzen van Zanten SEM, Lane A, Heymans MW, et al. External validation of the diffuse intrinsic pontine glioma survival prediction model: a collaborative report from the International DIPG Registry and the SIOPEN DIPG Registry. J Neurooncol. 2017;134(1):231-40. https://doi.org/10.1007/s11060-017-2514-9
5. Mauffrey C. Paediatric brainstem gliomas: prognostic factors and management. J Clin Neurosci. 2006;13(4):431-7. https://doi.org/10.1016/j.jocn.2005.05.015
6. Nikitovic M, Stanic D, Pekmezovic T, et al. Pediatric glioblastoma: a single institution experience. Childs Nerv Syst. 2016;32(1):97-103. https://doi.org/10.1007/s00381-015-2945-6
7. Perkins SM, Rubin JB, Leonard JR, et al. Glioblastoma in children: a single-institution experience. Int J Radiat Oncol Biol Phys. 2011;80(4):1117-21. https://doi.org/10.1016/j.ijrobp.2010.03.013
8. Maxwell R, Luksik AS, Garzon-Muñdi T, et al. Population-based Study Determining Predictors of Cancer-Specific Mortality and Survival in Pediatric High-grade Brainstem Glioma. World Neurosurg. 2018;119:e1006-e1015. https://doi.org/10.1016/j.wneu.2018.08.044

9. Klimo P Jr, Nesvick CL, Broniscer A, Orr BA, Choudhri AF. Malignant brainstem tumors in children, excluding diffuse intrinsic pontine gliomas. J Neurosurg Pediatr. 2016;17(1):57-65. https://doi.org/10.3171/2015.6.PEDS15166

10. Puget S, Beccaria K, Blauwblomme T, et al. biopsy in a series of 130 pediatric diffuse intrinsic pontine gliomas. Childs Nerv Syst. 2015;31(10):1773-80. https://doi.org/10.1007/s00381-015-2832-1

11. Kebudi R, Cakir FB, Bay SB, et al. Nimotuzumab-containing regimen for pediatric diffuse intrinsic pontine gliomas: a retrospective multicenter study and review of the literature. Childs Nerv Syst. 2019;35(1):83-9. https://doi.org/10.1007/s00381-018-0001-9

12. Bailey S, Howman A, Wheatley K, et al. Diffuse intrinsic pontine glioma treated with prolonged temozolomide and radiotherapy--results of a United Kingdom phase II trial (CNS 2007 04). Eur J Cancer. 2013;49(18):3856-62. https://doi.org/10.1016/j.ejca.2013.08.006

13. Rizzo D, Scalzone M, Ruggiero A, et al. Temozolomide in the treatment of newly diagnosed diffuse brainstem glioma in children: a broken promise? J Chemother. 2015;27(2):106-10. https://doi.org/10.1179/1973947814Y.0000000028

14. Zaky W, Wellner M, Brown RJ, Blümil S, Finlay JL, Dhall G. Treatment of children with diffuse intrinsic pontine gliomas with chemoradiotherapy followed by a combination of temozolomide, irinotecan, and bevacizumab. Pediatr Hematol Oncol. 2013;30(7):623-32. https://doi.org/10.3109/08880018.2013.829895

15. Broniscer A, Iacono L, Chintagumpala M, et al. Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children: results of a multiinstitutional study (SJHG-98). Cancer. 2005;103(1):133-9. https://doi.org/10.1002/cncr.20741

16. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children’s Oncology Group. Neuro Oncol. 2011;13(4):410-6. https://doi.org/10.1093/neuono/nq2205

17. Fleischhack G, Massimino M, Warmuth-Metz M, et al. Nimotuzumab and radiotherapy for treatment of newly diagnosed diffuse intrinsic pontine glioma (DIPG): a phase III clinical study. J Neurooncol. 2019;143(1):107-13. https://doi.org/10.1007/s11060-019-03140-z

18. Hummel TR, Salloum R, Drissi R, et al. A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas. J Neurooncol. 2016;127(1):53-61. https://doi.org/10.1007/s11060-015-2008-6

19. Jalali R, Raut N, Arora B, et al. Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. Int J Radiat Oncol Biol Phys. 2010;77(1):113-8. https://doi.org/10.1016/j.ijrobp.2009.04.031

20. Janssens GO, Gidding CE, Van Lindert EJ, et al. The role of hypofractionation radiotherapy for diffuse intrinsic brainstem glioma in children: a pilot study. Int J Radiat Oncol Biol Phys. 2009;73(3):722-6. https://doi.org/10.1016/j.ijrobp.2008.05.030

21. Kim CY, Kim SK, Phi JH, et al. A prospective study of temozolomide plus thalidomide during and after radiation therapy for pediatric diffuse pontine gliomas: preliminary results of the Korean Society for Pediatric Neuro-Oncology study. J Neurooncol. 2010;100(2):193-8. https://doi.org/10.1007/s11060-010-0157-1

22. Kivivuori SM, Riikonen P, Valanne L, et al. Antiangiogenic combination therapy after local radiotherapy with toptoean radiosensitizer improved quality of life for children with inoperable brainstem gliomas. Acta Paediatr. 2011;100(1):134-8. https://doi.org/10.1111/j.1651-2227.2010.01961.x

23. Korones DN, Fisher PG, Kretschmar C, et al. Treatment of children with diffuse intrinsic brain stem glioma with radiotherapy, vincristine and oral VP-16: a Children’s Oncology Group phase II study. Pediatr Blood Cancer. 2008;50(2):227-30. https://doi.org/10.1002/pbc.21154

24. Massimino M, Biassoni V, Miceli R, et al. Results of nimotuzumab and vinorelbine, radiation and re-irradiation for diffuse pontine glioma in childhood. J Neurooncol. 2014;118(2):305-12. https://doi.org/10.1007/s11060-014-1428-z

25. Massimino M, Spreaio F, Biassoni V, et al. Diffuse pontine gliomas in children: changing strategies, changing results? A mono-institutional 20-year experience. J Neurooncol. 2008;87(3):355-61. https://doi.org/10.1007/s11060-008-9525-5

26. Negretti L, Bouchireb K, Levy-Piedbois C, et al. Hypofractionated radiotherapy in the treatment of diffuse intrinsic pontine glioma in children: a single institution’s experience. J Neurooncol. 2011;104(3):773-7. https://doi.org/10.1007/s11060-011-0542-4
27. Sharp JR, Bouffet E, Stempak D, et al. A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma. Eur J Cancer. 2010;46(18):3271-9. https://doi.org/10.1016/j.ejca.2010.06.115

28. Sirachainan N, Pakakasama S, Visudithbhan A, et al. Concurrent radiotherapy with temozolomide followed by adjuvant temozolomide and cis-retinoic acid in children with diffuse intrinsic pontine glioma. Neuro Oncol. 2008;10(4):577-82. https://doi.org/10.1215/15228517-2008-025

29. Wolff JE, Driever PH, Erdlenbruch B, et al. Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-GBM-C protocol. Cancer. 2010;116(3):705-12. https://doi.org/10.1002/cncr.24730

30. Hassan H, Pinches A, Picton SV, Phillips RS. Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis. J Neurooncol. 2017;135(1):13-20. https://doi.org/10.1007/s11060-017-2546-1

31. Khalid SI, Kelly R, Adogwa O, et al. Pediatric Brainstem Gliomas: A Retrospective Study of 180 Patients from the SEER Database. Pediatr Neurosurg. 2019;54(3):151-64. https://doi.org/10.1159/000497440

32. Lam S, Lin Y, Auffinger B, Melkonian S. Analysis of survival in pediatric high-grade brainstem gliomas: A population-based study. J Pediatr Neurosci. 2015;10(3):199-206. https://dx.doi.org/10.4103/1817-1745.165656