

## Radiotherapy in the management of diffuse intrinsic pontine glioma- Three clinical cases with literature review

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### Abstract

Diffuse intrinsic pontine glioma (DIPG) is an aggressive primary pediatric brain tumor. Typical DIPG was defined radiographically as a poorly defined tumor with mass effect occupying  $\geq 75\%$  of the pontine axial diameter that was hypointense on T1-weighted MR images and hyperintense on T2-weighted images. We present three children with DIPG after radiotherapy (RT) in order to expand the knowledge of this aggressive brain tumor and to emphasize the main role of the radiation method in its treatment. Our observations from the realized RT are that despite highly risky tumor localization, conventional and hypofractionated RT are well tolerated, without acute neurological toxicity and allow second irradiation /re-irradiation, due to local tumor progression. The atypical MRI image of the pontine tumors requires a stereotaxic biopsy or spectroscopic MRI. With a biopsy or MRI data on undifferentiated malignant tumor such as glioblastoma and medulloblastoma, radiation strategy is much more accurately assessed, as well as the need for craniospinal RT.

**Keywords:** Diffuse intrinsic pontine glioma; childhood; MR images; radiotherapy; re-irradiation.

### Introduction

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary brain tumor in children with a median age at diagnosis of 6 to 7 years [1-5]. Findings on MRI include an intrinsic, centrally located tumor involving  $>50\%$  to  $66\%$  of the pons with hypointensity on T1 images and hyperintensity on T2 images with indistinct tumor margins and engulfment of the basilar artery, and absence of cystic or exophytic components [6-9]. Children diagnosed with DIPG have a less than 10% 2-year survival rate [10]. Complete surgical resection of DIPG is hindered by the location and infiltrative nature of the tumor [11,12]. The mainstay of treatment for DIPG is conventional fractionated radiotherapy (RT) [13]. We present our observations in three children with DIPG after RT in order to expand the knowledge of this aggressive brain tumor and to emphasize the main role of the radiation method in its treatment.

### Clinical case №1

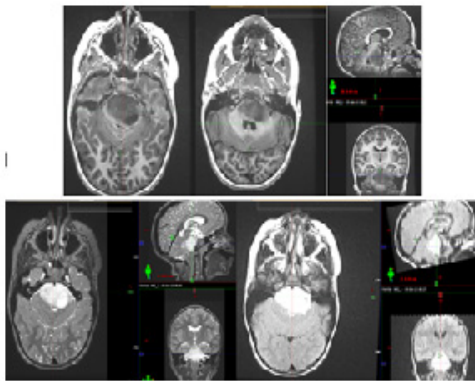
We present a 6- year- old boy. Since December 2019, he had been complaining about episodic morning nausea and vomiting. January 2020 additional symptoms include dizziness, accompanied by constant nausea and headache. Parents notice that the left eye of the child diverts to the right and prefers to sleep on his right side, while on the left side receives dizziness.

After pediatric consultation and brain MRI, a brain stem tumor was found. MRI / January 2020 - Supratentorial bilateral brain parenchyma has a normal structure and signal intensity. The ventricular system has a normal location, shape and size. Subarachnoid spaces and basal cisterns are not dilated. Basal nuclei- without pathological changes. Pons is deformed and enlarged, with a homogeneous structure diffusely engaged by an infiltrative tumor, without MR data on diffusion restriction after intravenous contrast matter administration. The tumor is with hypointensity on T1 images and hyperintensity on T2 images with indistinct tumor margins engaging the left medium cerebellar peduncle and flums slightly in the direction of the left pontocerebellar angle. Small brain with normal structure and signal intensity. Selar- and paraselar structures-intact. Orbits and orbital contents - normal MR image. Conclusion- MR images of the changes described as diffuse pontine glioma (DPG) (Figure 1).

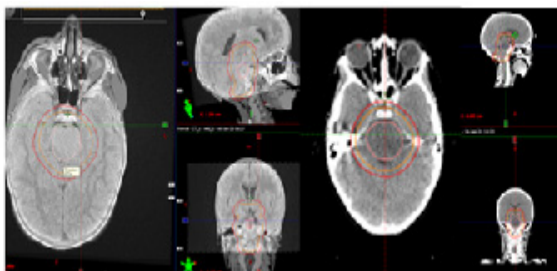
After consultation with experienced neurosurgeons, it is considered to be diffuse infiltrative glioma in the pontine brainstem, which is inoperable and due to high risk no biopsy was required. Oncology commission has assessed, that the only healing opportunity is to conduct a definitive radiotherapy (RT). In February 2020, an intensity modulated radiotherapy (IMRT) in the brain stem tumor with a 1.5 cm insurance zone,

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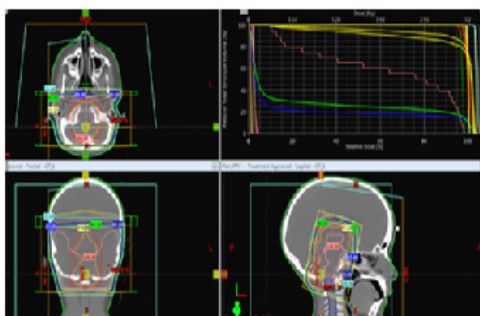
by twenty eight fractions with daily doses (DD) 1,8 Gy up to total dose (TD) 50,4 Gy was performed (**Figure 2, Figure 3**). The child endured RT very well, without acute neurological effects. After 6 months, his condition worsened with nausea and vomiting as a result of tumor progression. The severe general condition does not allow the performance re-irradiation in the tumor progression.



**Figure 1:** Brain MRI/ January 2020 - An infiltrate pontine tumor with hypointensity on T1 images and hyperintensity on T2 images with indistinct margins, engages the left medium cerebellar peduncle and flums slightly in the direction of the left pontocerebellar angle.



**Figure 2:** Contouring the target volumes GTV, CTV and PTV after fusion/overlay of the planning CT with the diagnostic MRI.

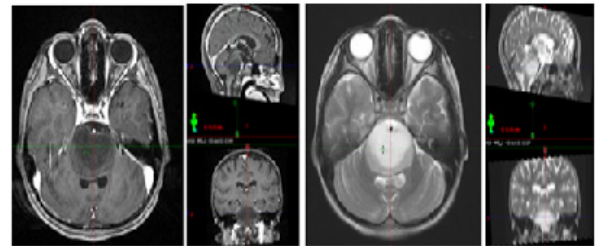


**Figure 3:** Intensity modulated radiotherapy (IMRT) in the brain stem tumor with a 1.5 cm insurance zone, by twenty eight fractions with daily doses (DD) 1,8 Gy up to total dose (TD) 50,4 Gy. The histogram presents the distribution of radiation doses in the critical adjacent normal tissues and in target volume.

### Clinical case №2

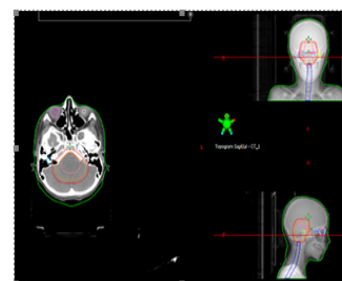
We present a 6-year-old girl. In April 2021, the parents noticed speech and equilibrium difficulty, followed by subsequent headache and episodic vomiting. On May 2021, brain MRI was conducted, which visualized an infiltrative intraaxial lesion in the pontine brainstem, whose engaged structures were blended and deformed. Tumor data engaging pons and brainstem measures 44x33x34mm with hypointensity on T1

FLAIR and T2 FLAIR images and hyperintensity on T2 FSE images. The lesion demonstrates perifocal edema reaching the mesencephalon with deformation of the pontine contours, eradicating the peripontine cistern and highly narrowing the perimesencephalic cistern. The fourth cerebral ventricle has compression based on perifocal edema. A lightweight dilatation of both lateral ventricular and third cerebral ventricle without data on transependymal liquor resorption is recorded (**Figure 4**).

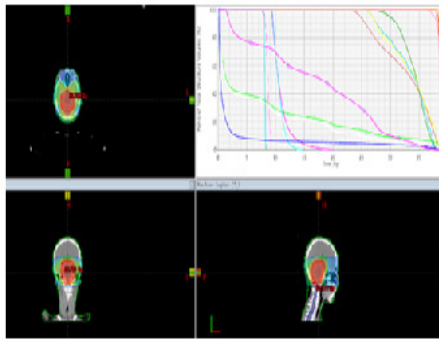


**Figure 4:** Brain MRI/ May 2021 - Tumor data engaging pons and brain stem measures 44x33x34mm with hypointensity on T1 FLAIR and T2 FLAIR images and hyperintensity on T2 FSE images. The lesion demonstrates perifocal edema reaching the mesencephalon with deformation of the pontine contours, eradicating the peripontine cistern and highly narrowing the perimesencephalic cistern. The fourth cerebral ventricle has compression based on perifocal edema.

After consultation with experienced neurosurgeons, it is considered to be diffuse infiltrative glioma in the pontine brainstem, which is inoperable and due to high risk no biopsy is required. Oncology commission has assessed, that the only healing opportunity is to conduct a definitive radiotherapy (RT). In June / 2021, a 3 D conformal radiotherapy (3D CRT ) in the brain stem tumor with a 1.5 cm insurance zone, by three fractions gradually rising daily doses (DD) 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to total dose (TD) 33 Gy was conducted. The sum of total tumor dose is 38.6 Gy, corresponding to a biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy. The child endured RT very well, without acute neurological effects and no changes in laboratory performance. **Figure 5** and **Figure 6** present tumor volume contouring for reparation of forthcoming RT and 3D CRT with dose tumor distribution and dose in adjacent normal brain structures.

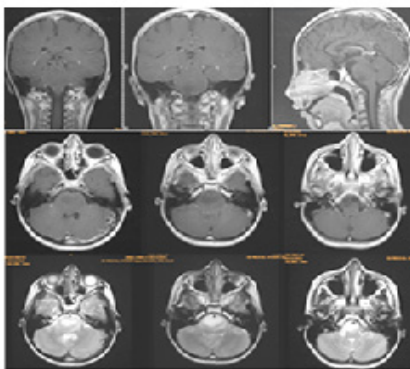


**Figure 5:** 3D conformal radiotherapy (3D CRT) planning raying by contouring of the brainstem tumor volume and the adjacent normal tissues and organs.

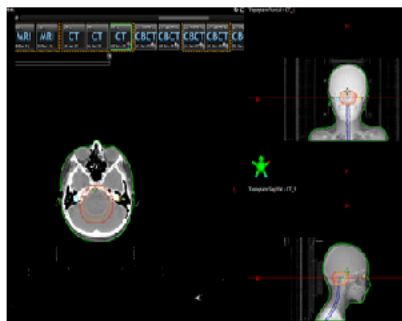


**Figure 6:** 3D CRT in the brainstem tumor by three fractions gradually rising DD 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2Gy/ equieffective dose (EQD2) 46.71 Gy. The histogram presents the distribution of radiation doses in the critical adjacent normal tissues and in target volume.

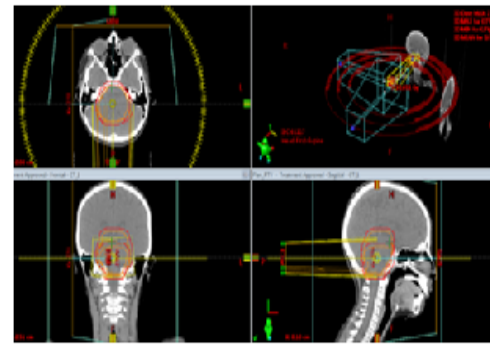
After 8 months of completion of RT, on the brain MRT, a local tumor progression was established. MRI reported increased tumor size as well as increased edema in the left pontine area without new supra- and infra tentorial lesions (Figure 7). Due to the lack of other alternative therapeutic methods, after a literary review, a re-irradiation was conducted. It was again IMRT by VMAT technique in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up to TD 20 Gy (Figure 8, Figure 9). The child endured RT very well, without acute neurological effects and no changes in laboratory performance.



**Figure 7:** Brain MRI/ December 2021 MR data for increased tumor size as well as increased edema in the left pontine area without new supra- and infratentorial lesions. Local tumor progression after 3D Conformal Radiotherapy with DD 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2Gy/ equieffective dose (EQD2) 46.71Gy.

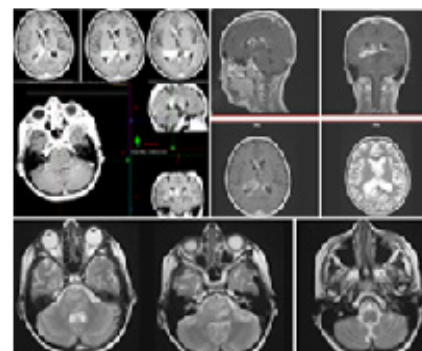


**Figure 8:** Intensity modulated radiotherapy planning raying by contouring of the brainstem tumor volume and adjacent normal tissues and organs.



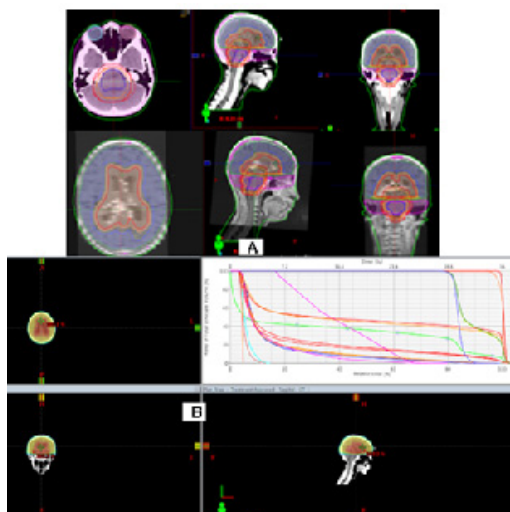
**Figure 9:** Intensity modulated RT (IMRT)/ re-irradiation with VMAT technique in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up to TD 20 Gy. The histogram presents the distribution of radiation doses in the critical adjacent normal tissues and in target volume.

Two months after the re-irradiation, MRI visualizes metastases on the walls of the two lateral brain ventricles (Figure 10). The child had episodes of vomiting without a headache, which necessitated RT at the third stage in the entire brain without a twice irradiated primary pontine tumor with simultaneous boost in the brain ventricles (Figure 11A). IMRT was planned with DD 1.5 Gy up to TD 30Gy in the supratentorial brain parenchyma with simultaneous brain ventricles boost with DD 1,8 Gy up to TD 36Gy (Figure 11B). After 6 radiation fractions (10,8 Gy in brain ventricles), the child began to vomit, which imposed brain CT without contrast and RT interruption. Brain CT-Infiltrative hypodense lesions are medically located with infiltration of the posterior third of the two lateral ventricles, third ventricle and corpus calosum. Data on hypodense zones in the thalamus more pronounced on the left and in the basal nuclei. Data on hydrocephalus and dilated cisterns. Small calcifications in the fields described above in the ventricles. The pontine tumor has heterogeneous density is iso- and hypodense with a maximum diameter of 41mm (Figure 12A). The CT proved hydrocephalus, which was treated with anti-inflammatory and anti-edematous medications. After three months, the child died as a result of hydrocephalus (Figure 12 B).

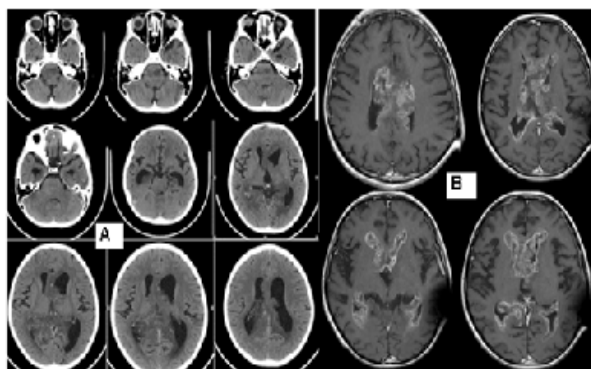


**Figure 10:** MRI/ March 2022- Metastases on the walls of brain ventricles with hyperintensity on T1+ GD and T2 FSE images. The pontine tumor with hypointensity on T1 FLAIR and T2 FLAIR images and hyperintensity on T2 FSE images.





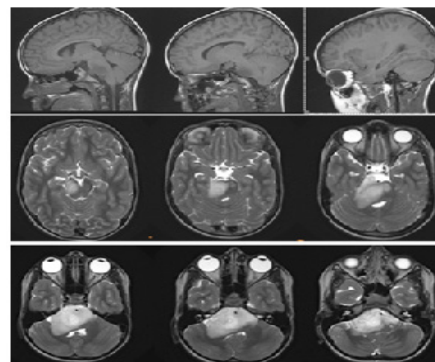
**Figure 11:** A/ Contouring and fusion of the three targeted volumes (both of the previous tumor irradiation) as a preparation for RT of supratentorial brain parenchyma with lateral ventricles; B / IMRT with DD 1.5 Gy up to TD 30Gy in the supratentorial brain parenchyma with simultaneous brain ventricles boost with DD 1,8 Gy up to TD36Gy.



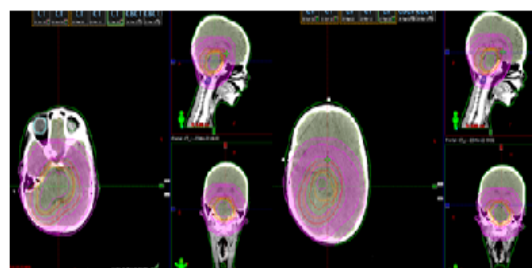
**Figure 12:** A/Brain CT without intravenous contrast- CT data on hydrocephalus; B/MRI data on metastatic cells accumulated on the walls of brain ventricles.

### Clinical case № 3

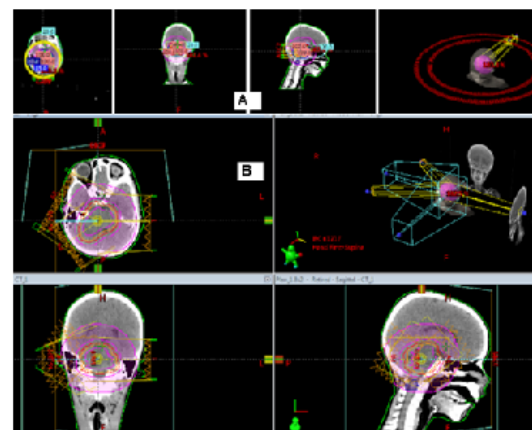
We present a 7- year- old boy. On the occasion of headaches, episodes of vomiting, dizziness and double vision, a CT and MRI of the brain with tumor data in the posterior cranial fossa (PCF) was carried out. MRI/ March 2022- The infratentorial right half of the mesencephalome, pons, the right cerebellar peduncle and the medulla oblongata are engaged by the irregular intraaxial zone of pathologically altered signal intensity. The finding has a heterogeneous structure, with a predominantly hyperintense signal of T2 and FLAIR images and hypointense T1 signal. The finding infiltrates the fourth ventricle and spreads extraaxially by stenating the right half of the prepontine cistern and the two pontocerebellar angles. After intravenous administration of contrast matter, no increase in the signal intensity of the formation was reported. Among the described lesion, the artery basilaris is monitored, which is mildly stensed. No data on internal and external hydrocephalus (**Figure 13**). After consultation with experienced neurosurgeons, it is considered to be diffuse infiltrative glioma in the pontine brainstem, which is inoperable and due to high risk no biopsy is required. Oncology commission has assessed, that the only healing opportunity is to conduct a definitive radiotherapy. In April 2022, an intensity modulated radiotherapy (IMRT) by the VMAT method in the brain stem tumor with a 1.5 cm insurance zone with daily doses (DD) 1,8 Gy up to total dose (TD) 54 Gy was performed (**Figure 14**, **Figure 15**). The child endured RT very well, without acute neurological effects.



**Figure 13:** MRT/ March 2022- The infratentorial right half of the mesencephalome, pons, the right cerebellar peduncle and the medulla oblongata are engaged by the irregular intraaxial zone of pathologically altered signal intensity. The lesion has a heterogeneous structure, with a predominantly high signal on T2 and FLAIR images and hypointense T1 signal.



**Figure 14:** IMRT planning raying by contouring of the brainstem tumor volume and the adjacent normal tissues and organs.



**Figure 15:** Intensity modulated radiotherapy by the VMAT method of the stages first A/ in the large target volume with DD 1.8 Gy up to TD 39.6 Gy and second as B/ an overdose/ boost of the GTV up to TD 54 Gy.

### Discussion

Children with DIPG are typically diagnosed at the 5th to 10th year of their life, with tumors being more frequently located in the pons rather than the midbrain or medulla oblongata [14-16]. Most of the remaining 80% of tumours are diffuse brainstem gliomas (DBG) [11]; usually a fibrillary (World Health Organization (WHO) grade 2) or malignant (WHO grade 3 or 4) astrocytoma with typically an aggressive disease course and grim prognosis [3,17-19]. DBGs are the most aggressive subgroup of brainstem tumours, and typically occur in the pons (part of the brainstem) [20]. MRI constitutes the imaging modality of choice for DIPG with unique imaging characteristics [21,22]. Although the imaging criteria used to define a classical or 'typical' DIPG (tDIPG) vary to some extent, and there are inconsistencies in the interpretation of the images [23], the general consensus radiographic features of tDIPG include a T1-hypointense and T2-hyperintense tumor involving at least 50% of the axial pontine diameter [24-26]. Typical DIPG was

defined radiographically as a poorly defined tumor with mass effect occupying  $\geq 75\%$  of the axial pontine diameter that was hypointense on T1-weighted MR images and hyperintense on T2-weighted images [27]. DIPGs may typically demonstrate mild heterogeneous enhancement or no enhancement, nevertheless, increased enhancement or ring enhancement may be suggestive of poorer prognosis [28-30]. In many centers in the United States, biopsy is reserved for patients with a clinical diagnosis of 'atypical' DIPG (aDIPG), i.e., pontine tumors in which the above imaging features are absent or incomplete [31]. In the three clinical cases presented, the classical MRI criteria meet in the first and third clinical case (Figure 1, Figure 13), but the second accounts for hypointensity on T1 FLAIR and T2 FLAIR images and hyperintensity on T2 FSE images (Figure 4). This atypical MR image and the subsequent clinical disease development is the basis for such pontine tumors without the possibility of biopsy, to be extremely careful. Because of the vitally important brainstem functions, the brain tumors localized there are extremely difficult to treat, especially with the application of the radiation method, which can cause a sudden stopping of respiratory and cardiac activity. Surgery of DIPG to relieve hydrocephalus, is not indicated, because the typical appearances on MRI are characteristic and reduction in tumor size only adds to the child's worsened overall condition [32]. There is currently no indication for image guided stereotactic brain biopsy in children with a short history and typical MR appearances, because it currently will not alter management strategy [33]. During the past three decades, numerous clinical trials have been conducted in newly diagnosed DIPG patients including RT with or without chemotherapy, targeted agents and immunological approaches. None of these trials have demonstrated a clear improvement in median overall or progression-free survival (PFS) [34].

Radiotherapy remains the gold-standard treatment for diffuse intrinsic pontine gliomas (DIPG); by contrast, chemotherapy has not shown any benefit [35]. Several studies have concluded that conventional external-beam RT up to TD 54 Gy in 30 fractions in 6 weeks was the treatment mainstay [36-42] with median time to progression and overall survival of 6 and 9 months [8,41,43]. In the clinical cases presented with the MP image corresponding to classic DIPG, we conducted a conventional fractionated IMRT with DD 1.8 Gy up to TD 50.4-54 Gy (Figure 2, Figure 3, Figure 14, Figure 15). As a general principle, the treatment volume of the radiation field should encompass all the site(s) of disease with a defined margin to allow for non-imageable tumour spread into adjacent brain (1 cm for low grade and 2 cm for high grade tumours) [44]. To increase the overall and disease-free survival, other dose fractionation modes such as hyperfractionated and hypofractionated RT was applied [45,46]. Given the limited life expectancy of patients with DIPG, hypofractionated RT regimens have been considered [35,47-51]. Hypofractionated RT has potential radiobiological advantages over standard conventional fractionated therapy in newly diagnosed glioblastoma multiforme [52]. Some institutions have employed hypofractionated RT to decrease the length of therapy in an effort to reduce the patient's burden, with clinically similar levels of disease control reported [35,51,53-55]. Hypofractionated RT is well tolerated with the advantage of decreasing the treatment burden on children and their families [45], with nearly comparable results to conventional fractionation, though not fulfilling the non-inferiority assumption [55,56]. In hy-

po-fractionated schemes a total dose of 45 Gy is delivered in daily fractions of 3 to 5.5 Gy over three weeks [35]. Due to the shorter healing period of the hypofractionated RT, we considered to realize it after gradually rising daily doses due to critical neurological structures localized on the brainstem (Figure 5, Figure 6). Despite the poor prognosis of DIPG with limited survival durations, re-irradiation may be considered. With advances in treatment techniques, it is feasible to re-irradiate select patients with progressive disease [15]. Re-irradiation (Re-RT) can safely be delivered for progressive DIPG. Utility analysis suggests that a schemes of 24 Gy in 12 fractions are preferred [57]. 25 patients were enrolled, and 11 out of 16 patients with local relapse received Re-RT to a dose of 19.8 Gy delivered over 11 days [58]. The majority of patients with DIPG, responding to upfront RT, do benefit of Re-RT with acceptable tolerability [59]. Based on the attempt of the above-mentioned authors, in the presented clinical case with tumor progression after 8 months of the hypofractional RT (Figure 7), we decided to carry out a re-irradiation in brainstem target volume with a 0.2 cm insurance zone with DD 2 Gy up to TD 20 Gy (Figure 8, Figure 9). Despite our concerns about the tolerability of this re-irradiation, the child experienced it very well without acute side neurological toxicity. After two months, in the pontine tumor with an atypical MRI image, we observe the development of liquid metastases on the lateral cerebral ventricle walls, despite the hypofractionated RT, followed by re-irradiation (Figure 10). Such a find is rarely observed and most likely corresponds to glioblastoma in childhood, which is very rare. Another histological possibility is that it is a pontine meduloblastoma, in which if a biopsy was performed, primary RT should include the entire craniospinal axis. The conclusion of this clinical case is that the atypical MRI image of the pontine tumors requires a stereotaxic biopsy or spectroscopic MRI.

## Conclusion

Diffuse intrinsic pontine glioma (DIPG) is an aggressive primary pediatric brain tumor. Radiotherapy plays a major role in management of pontine gliomas. Our observations from the realized RT are that despite highly risky tumor localization, conventional and hypofractionated RT are well tolerated, without acute neurological toxicity and allows second irradiation /re-irradiation, due to local tumor progression. The atypical MRI image of the pontine tumors requires a stereotaxic biopsy or spectroscopic MRI. With a biopsy or MRI data on undifferentiated malignant tumor such as glioblastoma and meduloblastoma, radiation strategy is much more accurately assessed, as well as the need for craniospinal RT.

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