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Exceptional Tumor Regression in Diffuse Intrinsic Pontine Glioma Post-Radiotherapy: A Case Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 13-year-old
Final Diagnosis: Diffuse intrinsic pontine glioma
Symptoms: Ataxia • cranial nerve palsy
Clinical Procedure: —
Specialty: Neurology • Oncology • Radiology

Objective: Unusual clinical course

Background: Diffuse intrinsic pontine glioma represent approximately 10% to 20% of all pediatric central nervous system tumors. Classic brain stem symptoms are cranial nerve deficits, long tract signs, ataxia, alone or in combination. Focal radiotherapy has been the standard of care in patients with diffuse intrinsic pontine gliomas with minimum response. Here, we present an unusual case with excellent tumor regression with radiotherapy and good clinical outcome.

Case Report: A 13-year-old girl presented with headache and imbalance during walking for the past 2-3 months, along with a deviation of the right eye in the last month. Brain magnetic resonance imaging (MRI) suggested a well-defined solid cystic altered-signal-intensity lesion involving the pons and medulla, causing its expansion up to the midbrain on the left side. The lesion was 4.6×3.7×3.6 cm. We applied the intensity-modulated radiotherapy technique (IMRT) using a 6-MV photon beam with the conventional dose fractionation of 54 Gy in 30 fractions (1.8 Gy/fraction). Three months later, MRI brain with spectroscopy and perfusion showed evidence of non-enhancing, altered-signal-intensity lesion in the pons and medulla, measuring 1.9×2.2×2.4 cm.

Conclusions: Early detection of symptoms of DIPG in a young patient along with effective radiological investigation with valid tumor board decision as definitive radiotherapy as a sole therapeutic treatment option and with robust radiotherapy planning resulted in an excellent response, with 80% reduction in gross tumor volume (GTV) as seen in pre-radiotherapy (RT) and post-RT MRI images.

Keywords: Diffuse Intrinsic Pontine Glioma • Diffusion Magnetic Resonance Imaging • Radiotherapy • Radiotherapy Planning, Computer-Assisted

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/944869

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Introdcution

Brain stem tumors account for about 10-20% of all pediatric central nervous system tumors. Most of these tumors are diffuse and infiltrating lesions of the pons, known as diffuse intrinsic pontine gliomas. Typical signs and symptoms are observed in children with diffuse intrinsic pontine gliomas, which is secondary to the tumor's location and infiltrative nature. Classic brain stem symptoms such as cranial nerve deficits, long tract signs, ataxia, or a combination of the 3 are often present in these patients [1].

These tumors are diagnosed on the basis of imaging characteristics alone, in which MRI scan shows an intrinsic lesion based within the pons, which usually exerts a mass effect on adjacent structures such as the fourth ventricle and basilar artery. The tumors are usually hypointense on T1-weighted sequences and hyperintense on T2 and fluid-attenuated inversion recovery sequences, and rarely show significant contrast enhancement at diagnosis. There are few recognized prognostic factors in patients with diffuse intrinsic pontine glioma. The 2 described prognostic factors include: time between onset of symptoms and diagnosis, and the presence or absence of significant neurological symptoms. Patients with NF-1-harboring lesions and symptoms that are otherwise compatible with diffuse intrinsic pontine glioma often have a more indolent clinical course and better outcomes.

The prognosis of DIPG is poor, with a median survival of less than 1 year and a 2-year overall survival rate of less than 10% [2].

Focal radiotherapy has been the standard of care in patients with diffuse intrinsic pontine glioma; in conjunction with focal irradiation, a variety of experimental chemotherapeutic and biologic agents have been investigated. In newly diagnosed patients, fractionated local irradiation has shown improvement in symptoms in approximately 75% of patients, but the overall survival remains disappointing.

Case Report

A 13-year-old girl with menarche presented at the Radiation Oncology Outpatient Department (OPD), walking with support, with headache and imbalance during walking for the past 2-3 months, along with a deviation of right eye in the last 1 month. She was apparently well 3 months ago when she noticed gradual onset of imbalance on her right side, not associated with any past history of trauma to the lower limbs or eyes. This was not associated with cough with expectoration or evening rise of temperature. She had no history of falling or head injury, and she had no ENT bleeding, vomiting, or any history of loss of consciousness or seizure. Then, she started noticing double vision along with gradual diminution of vision. Her visual acuity was 6/6 in bilateral eyes and her field of vision was within normal limits. She was consulted at her local hospital, where she received hematinics, multivitamin supplements, and other conservative management, but her symptoms were not relieved, so she visited our tertiary care hospital.

On general examination, her condition was good but she was not able to perform her routine activities independently and had difficulty in running and kept falling. She had diplopia, and there was no pallor, icterus, or swollen lymph nodes. There were no rashes or spots on her face, armpits, groin, or under the breasts, and there were no café au lait spots. On pelvic examination, pubic hairs were present and the sexual organs were developed within normal limits. On systemic examination, the cardiovascular system was normal, with S1 and S2 heard, with no murmur. On respiratory examination, air entry was equal on both side, and there were no adventitious sounds heard. The abdominal examination revealed a soft abdomen, with no hepatosplenomegaly. There was no tenderness in any quadrants of the abdomen, and there was no guarding or rigidity. On central nervous system examination, her higher motor functions were intact, with no slurring of speech. Her attention span was normal. Cerebellar ataxia was present, with swaying on the right side during walking. On cranial nerve examination, cranial nerve VI appeared to be affected by lateral rectus muscle palsy, but the others were within normal limits. Hyperreflexia was present, but no signs of muscle wasting were found. There were no sensory deficits and no motor deficits,with power 5/5 in bilateral upper and lower limbs. On cerebellar examination, dysdiadochokinesia was absent and there were no dysmetria. Her bowel and bladder functions were normal, with no deficits.

Laboratory investigations were performed, including complete blood count, kidney function, and liver function test. Her hemoglobin was borderline low, at 9.2 gm%. Her creatinine was 1.0 mg/dl. Results of other tests were within normal limits. Magnetic resonance imaging (MRI) brain showed a well-defined solid cystic altered-signal-intensity lesion involving the pons and medulla, causing expansion, with minimal adjacent vasogenic edema extending up to the midbrain on the left side. Lesion measured 4.6×3.7×3.6 cm. The solid component appeared iso- to hyperintense on T1 and T2WI, no restriction on DWI, and no blooming on SWI, showing minimal post-contrast enhancement. There was also peripheral enhancement of cystic component of the mass (**Figures 1, 2**). A mass effect is noted in the form of effacement of the fourth ventricle and anterior displacement of the basilar artery, causing its partial encasement (less than 180 degrees). There were no signs of hydrocephalus. Spinal MRI was not done.

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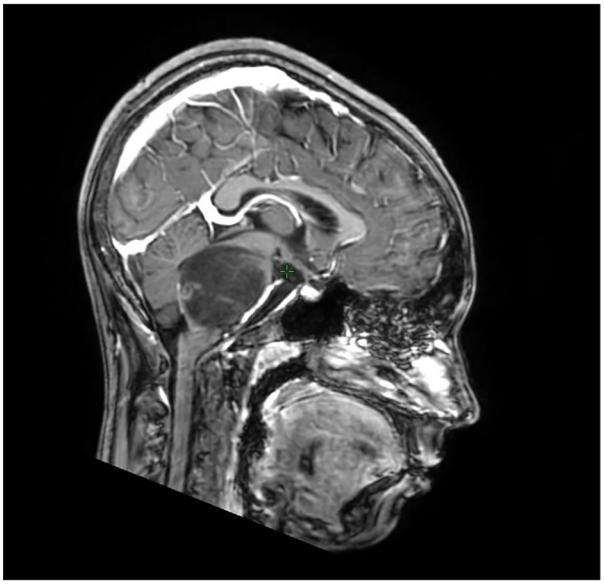

Figure 1. Pre-treatment index MRI brain in sagittal view, showing well-defined solid cystic signal intensity lesion at pons and medulla.

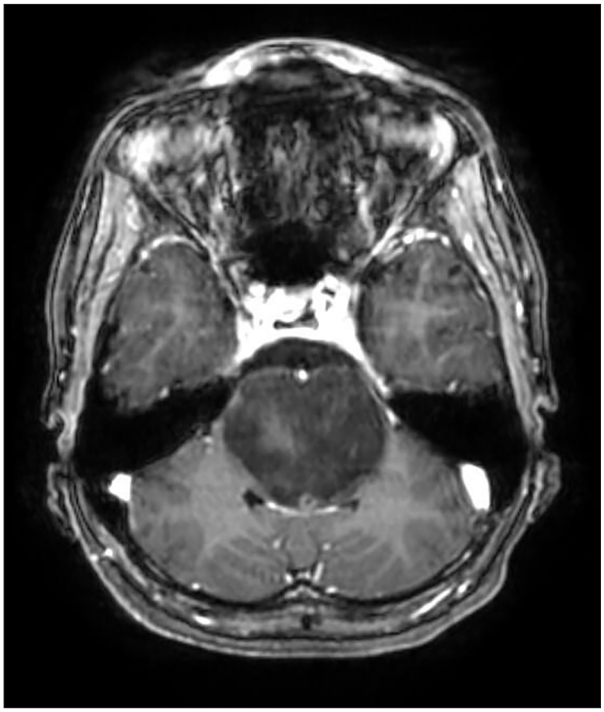

Figure 2. Pre-treatment index MRI brain in axial view, showing solid cystic component with peripheral enhancement causing mass effect on surrounding tissue.

The possibility of a pontine primitive neuroectodermal tumor was excluded as there was no leptomeningeal spread noted and also there was no taurine peak. Also, there were no winding or bending arteries present. Even though the disease surrounds the basilar arteries, there is no widening of the vessels, which means vascular malformations are unlikely. The possibility of hemangioblastoma is also excluded because there are no mural nodules, although there is slight enhancement of the cystic wall. Therefore, the final diagnosis might be either Diffuse Intrinsic Pontine Glioma or, less likely, Pilocytic Astrocytoma.

Tumor Board discussion involved input from Neurosurgery, as the location of lesion is at vital position, with possible severe neurological complications during biopsy and surgery. The patient was scheduled for definitive radiation therapy and sent to the Radiation Oncology Department. Her guardian received an explanation of the current disease status, prognosis, pros and cons of radiotherapy, and possible short- and long-term adverse effects.

Pre-radiotherapy consent was signed. The patient was placed in head-first supine position with arms by the side. A neck rest was used for neck stabilization with a clamp. A 2.5-mm non-contrast CT scan was done from the vertex to mandible. A planning MRI was executed for the patient following a protocol specifying 2 mm thick axial images without gaps between slices. This imaging has been registered with the planning CT scan, and the process of contouring was carried out. A singular gross tumor volume (GTV) was delineated with the assistance of T1-weighted contrast-enhanced (T1C), T2-weighted (T2W), and FLAIR imaging sequences. For the Clinical Target Volume (CTV), a 3 mm margin was added. The planning target volume (PTV) was defined by extending a 5 mm margin outward from the GTV. This was done alongside the contouring of critical organs at risk which included the brain minus PTV, spinal cord, hippocampus, pituitary gland, bilateral optic nerves as well as the chiasm, and the cochleas. Special attention was given to the pituitary, bilateral hippocampi, and spinal cord to keep radiation exposure as low as reasonably achievable (ALARA).

Given the target and organ delineation, the patient was treated with IMRT techniques using a 6-MV photon beam with the conventional dose fractionation of 54 Gy in 30 fractions (1.8Gy/fx). The Eclipse version 16.1 (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system was used via 7 field arrangements confining to the PTV. Treatment planning was done considering ALARA principle for all organs at risk while maximizing the radiation dose to treatment volume. The doses were calculated using the anisotropic analytical algorithm. The Dmax and D95% were 106.9% and 97.35% of planning target volume, respectively (**Figures 3, 4**). The doses received by various organs were less than the maximum permissible dose: Lenses Dmax <7 Gy, Eye Dmax <40 Gy, Optic Nerve Dmax <55 Gy, Optic Chiasm Dmax <50 Gy, Cochlea Dmean <40 Gy, Pituitary Dmean <40 Gy, and the spinal cord Dmax <40 Gy (**Figure 5**). Before the delivery of treatment, a patient-specific quality assurance (QA) plan was generated and executed, which passed the gamma analysis by 97.4% with 3% dose tolerance and 3 mm distance to agreement.

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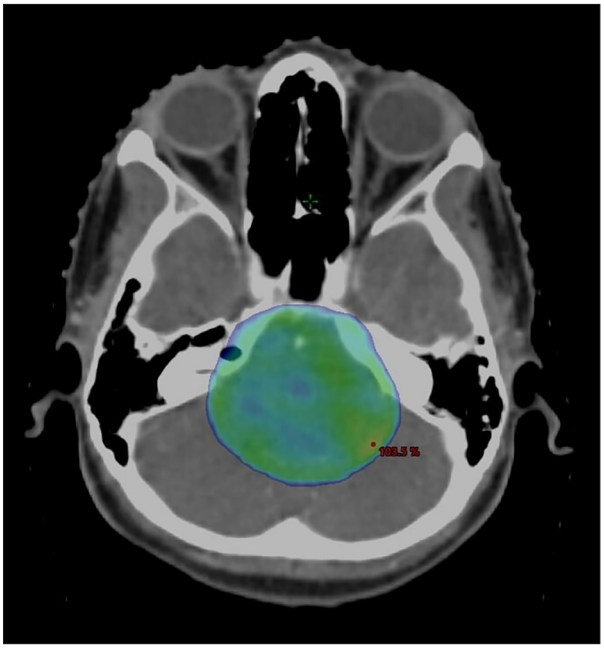

Figure 3. Dose distribution of the 95% dose into the PTV. The shaded blue-green area on the axial image shows dose coverage of 95% as planned in the treatment planning system.

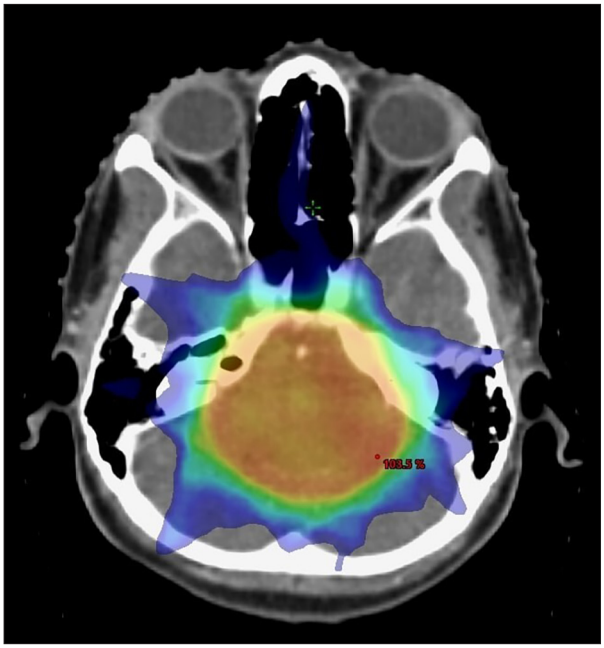

Figure 4. Dose distribution of the 50% spill around the PTV. The spill dose area on the axial planning CT image on surrounding normal tissue of cerebellum, cerebrum, cochlea, and optic nerve.

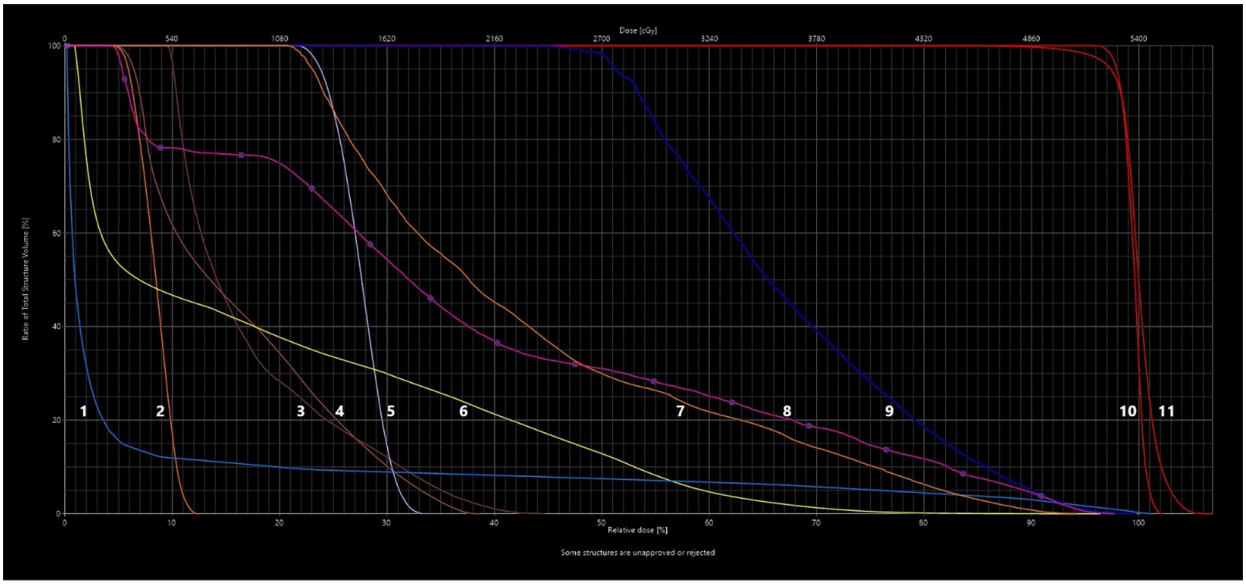

Figure 5. Dose-volume histogram (DVH) for organ at risk (OAR). All ALARA criteria were met: 1 – spinal cord' 2 – left eye' 3 – left optic nerve' 4 – right eye' 5 – right optic nerve' 6 – rest brain' 7 – left hippocampus' 8 – right hippocampus' 9 – optic chiasm' 10 – GTV' 11 – PTV.

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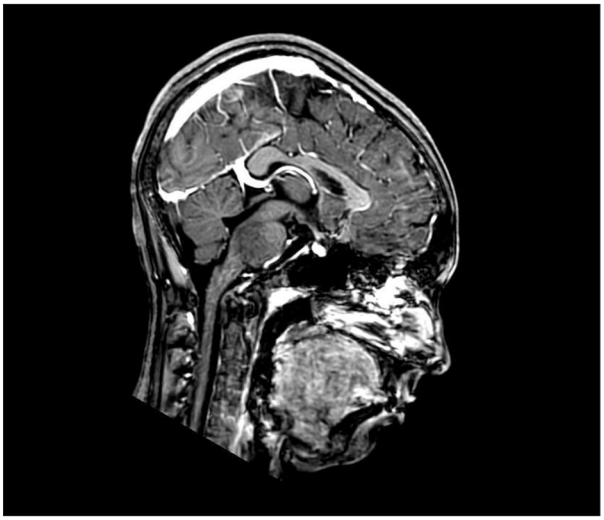

Figure 6. MRI brain in sagittal view 3 months after treatment, showing minimum T1 hypointense altered-signal-intensity lesion at the pons and medulla, with excellent response to radiotherapy.

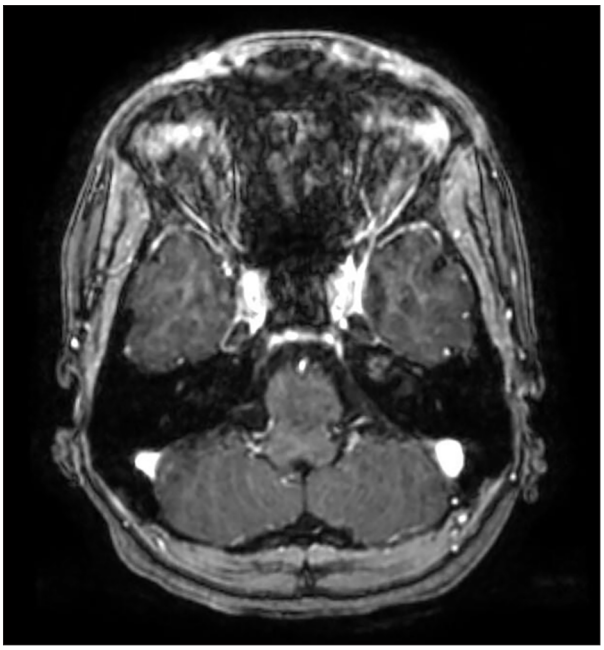

Figure 7. MRI Brain in axial view 3 months after treatment, showing minimum peripheral enhancement at the pons, indicating good response to therapy.

The treatment was administered with daily 3D image-guided on-board imaging kV, along with weekly assessment for toxicities. The treatment lasted 6, weeks without undue gaps. No major skin or central nervous system toxicities were observed during the treatment. The patient was followed up clinically after 2 weeks for assessment of acute toxicities.

No acute toxicity was observed with respect to neurological symptoms and skin. Post-radiotherapy clinical assessment was done after 3 months, showing excellent clinical improvement in gait and nerve VI palsy (diplopia was resolved). Post-radiotherapy MRI brain with spectroscopy and perfusion 3 months later showed a non-enhancing, altered-signal-intensity lesion in the pons and medulla, measuring 1.9×2.2×2.4 cm (it was previously 4.6×3.7×3.6 cm) appearing hypointense on T1 and hyperintense on T2W, no restrictions on DWI, with corresponding high signal on ADC, and no blooming on SWI. MR spectroscopy showed increased choline peak with reduced NAA in regions of interest (**Figures 6, 7**). There was a significant reduction in tumor size. According to the RECIST criteria 1.1, there was partial response to definitive radiotherapy. The next clinical follow-up was scheduled in 3 months with ophthalmic evaluation and hormonal assessment.

Discussion

Brain tumors comprise about 20% of all neoplasms in children. Pontine glioma is the most fatal central nervous system glioma in children, with median survival of 16-24 months. Low-grade astrocytoma comprises of 15-20% of pontine gliomas, and the remaining 80% are diffuse type. The median age at onset of DIPG is 6-7 years [3]. The most common presentation of a brainstem glioma, particularly one arising in the pons, involves diffuse enlargement of the affected structure. Patients typically report experiencing symptoms for a relatively short duration, with the median being about 1 month. These symptoms often include morning headaches, difficulties in walking or maintaining balance, slurred speech, and a combination of weakness and numbness in both limbs and signs that include cranial neuropalsy, long tract signs (hyperreflexia, a Babinski sign, and weakness), and cerebellar signs (ataxia, dysmetria, or dysarthria). Our patient, had slow, progressive development of ataxia and double vision, which started 3 months ago. Cranial nerve impairment is often present, with multiple, unilateral, or bilateral cranial nerve deficits, particularly cranial nerves VI and VII paresis. Our patient had palsy of cranial nerve VI, which presented as double vision. The tumor covered the basilar artery, and had many axial or exophytic extensions to the midbrain, cerebral peduncles, cerebellum, or medulla. Hydrocephalus and metastatic disease from diffuse tumors of the pons are rare [4]. In contrast, patients with a focal brainstem tumor have a more insidious presentation, with a long history of localizing signs, such as isolated cranial nerve deficit and contralateral hemiparesis. Elevated intracranial pressure is uncommon and is associated with poor prognosis. These tumors sometimes involve the medulla or the midbrain, and may cause emesis and failure to grow. Tumors arising in the tectal region cause increased intracranial pressure and hydrocephalus due to obstruction of the aqueduct of Sylvius [5]. In

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our patient, MRI did not show hydrocephalus or any clinical signs of increased ICT like severe headache, vomiting, or sudden onset of blurred vision.

The longer duration of symptoms (mean 6 weeks), absence of raised ICT and seizures, and good performance score in our patient suggested a good prognosis and progression-free survival. Use of dexamethasone before and during radiotherapy treatment is a negative prognostic factor, as it affects the blood–brain barrier. Our patient, although symptomatic, did not have symptoms of high intracranial tension, so dexamethasone was not started, which provides good prognosis and promising impact on patient's future outcome with respect to overall survival (OS) and disease-free survival (DFS). Various imaging modalities are available for brainstem glioma diagnosis, but high-quality MRI is the criterion standard in clinical management to localize the lesion, differentiate focal from diffuse nature, exclude other diagnoses, and guide tissue biopsy. A focal tumor is typically well-marginated and enhances with contrast, and occupies more than 50% of the axial diameter of the pons [6]. MRI brain in our case showed a diffuse tumor lesion that was poorly marginated, had inhomogeneous enhancement, and occupied more than 50% of the axial diameter of the pons, engulfing the basilar artery (GTVp: 35.1 cm^3). Contrast enhancement is found inconsistently in both malignant gliomas and low-grade tumors and thus is not a reliable prognostic indicator. MRI spine is sometimes used for assessment of spinal dissemination, but was not used in our patient due to resource limitations and absence of aggressive symptoms.

Leach has provided the largest registry, with 400 cases, of MR imaging features in DIPG, showing a correlation between imaging characteristics in DIPG and overall survival, and showed that tumor extension beyond the pons, larger tumor size at diagnosis, contrast enhancement, necrosis, presence of diffusion restriction, and distant disease at diagnosis are associated with poorer overall survival [7]. In our patient, imaging features like slight extension of the tumor in the midbrain indicated a poor prognosis, but imaging with minimum contrast enhancement and no diffusion restriction suggested a good prognosis and overall good response.

A multicenter study by Kim et al assessed various prognostic factors associated in DIPG. They assessed data on overall survival of 162 patients with DIPG evaluated after radiotherapy, and found that poor performance status, age <10 years, and post-radiotherapy necrosis were independently associated with poor OS in multivariate analysis [8]. Our patient was over 10 years old and the post-radiotherapy MRI scan suggested no necrosis, which both predict a good prognosis.

The standard dose fractionation used for DIPG is 54-60 Gy in 30 fractions using conventional fractionation of 1.8-2.0 Gy/fraction. A systematic review by Gallitto et al on the role of radiotherapy provided insights into the role of hypofractionation and hyperfractionation radiotherapy in DIPG.

Hypofractionation in DIPG:
A phase III randomized controlled trial by Mohamed S. Zaghloul et al from Children's Cancer Hospital, Egypt evaluated the role of hypofractionation (39 Gy/13 fractions in 2.6 weeks) versus conventional fractionation (54 Gy/30 fractions in 6 weeks) in which 72 patients with newly diagnosed DIPG were randomized to hypofractionation and conventional fractionation arms. They concluded that hypofractionated radiotherapy imposes less burden on patients and their relatives, with comparable overall survival and 1-year progression-free survival [9].

Hyperfractionation in DIPG:
The largest study, CCG-9882, emphasizing the role of hyperfractionation in DIPG, by Packer et al, in which 66 patients with DIPG were treated with a total dose of 78 Gy, 1 Gy per fraction, twice daily with a separation of minimum of 4 hours and a maximum of 8 hours, for 5 days a week. Results showed interim response to treatment in 20 of 58 (34%) evaluable patients, with 8 (14%) patients showing a more than 50% reduction in tumor dimension, but these results do not reflect improvement in terms of progression-free survival (PFS) and OS [10].

Hypofractionation is evidently a better option than conventional fractionation for advanced-stage patients. Initial results indicate that hypofractionation is well-tolerated, decreases the treatment time, and limits acute reactions in patients and emotional burden to their families. Hypofractionated regimens are observed to be statistically comparable to conventional RT with regard to OS, in recent prospective randomized controlled studies. On the other hand, hyperfractionation brings greater risk of early toxicities and are suggested to be avoided for cases other than clinical trial settings. The MRI brain after radiation therapy has been evaluated and discussed in various papers. The study by Smith et al from the Department of Radiology, Hospital of the University of Pennsylvania, USA evaluated 34 patients with DIPG and showed disease reduction, tumor progression before worsening of symptoms, post-treatment cyst formation, and hemorrhage. The ideal time for post-radiotherapy response MRI is 4-10 months [11]. The role of early post-radiation MRI scans in children with DIPG has been assessed by Ko et al, who found no significant difference in dimensions of tumor between 2 and 6-8 weeks [12].

Conclusions

Robust radiotherapy treatment with respect to contouring, planning, and treatment delivery can be used informatively by junior radiation oncologists, medical physicists, and radiotherapy technologists. The presented case showed excellent

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response of >80% reduction in GTV volume in pre-RT and post-RT MRI images, suggesting definitive radiotherapy is the ultimate treatment option for DIPG patients, supported by very good clinical improvement when there is proper assessment, management, planning, and treatment delivery. Also, this text summarizes the rough idea of brainstem glioma cases in the Indian population and offers a general overview of how to manage this condition. If a patient has symptoms for a longer time, shows no signs of diffusion restriction on DWI in MRI scans after radiotherapy, has minimal tumor contrast enhancement, and experiences significant clinical improvement following treatment, these can be seen as good prognostic signs for recovery, as supported by earlier research and studies. The literature also suggests regular clinical and imaging follow-up for early recurrence/progression detection and subsequent intervention. Telephone follow-up of our patient showed good symptomatic clinical improvement. Proton therapy for diffuse intrinsic pontine glioma is an emerging approach that requires further research.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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