Review Article

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Archives in Cancer Research
ISSN 2254-6081

2018
Vol.6 No.3:14

DOI: 10.21767/2254-6081.100180

Radiation Therapy (RT) for Diffuse Intrinsic Pontine Glioma (DIPG) in Children

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Citation: Sager O, Dincoglan F, Demiral S, Uysal B, Gamsiz H, et al. (2018) Radiation Therapy (RT) for Diffuse Intrinsic Pontine Glioma (DIPG) in Children. Arch Can Res Vol.6 No.3:14.

Abstract

Tumours of the brainstem account for approximately 10% to 15% of all central nervous system (CNS) neoplasms in children, with diffuse intrinsic pontine glioma (DIPG) being the most common type. Affected patients with DIPG are mostly children at the age of 5 to 10-years-old. While brainstem gliomas may arise in other parts of the brainstem including the midbrain and medulla oblongata with a more favourable prognosis, pontine location is very frequent with a typically aggressive disease cause leading to a limited lifespan for the affected patients. Patients with DIPG may present with cranial nerve symptoms due to compression and dysfunction of nuclei and tracts located in the pons. A wide spectrum of symptoms may occur including impaired vision and diplopia, nausea and vomiting, headache, impaired alignment of the eyes, gait disturbances, dysarthria, facial asymmetry or weakness, impaired communication with altered levels of consciousness, changes in behaviour, impaired mobility, spasticity, weakness in legs and arms. Brainstem gliomas located at the pons with diffuse and extensive infiltration are typically not amenable for complete surgical resection. In this context, radiation therapy (RT) has traditionally been the mainstay of treatment for DIPG. Optimal radiation dose and fractionation and combined modality management with RT and chemotherapy has been the focus of extensive research over several decades. Herein, we assess the utility of RT for DIPG management in light of the literature.

Keywords: Diffuse intrinsic pontine glioma (DIPG); Radiation therapy (RT); RT dose and fractionation

Received: October 01, 2018; **Accepted:** October 09, 2018; **Published:** October 14, 2018

Introduction

Brain tumours comprise approximately 20% of all childhood neoplasms [1,2]. The brainstem, including the midbrain, pons, and medulla oblongata, is a critical location for brain tumours in children which is involved in several important body functions. Tumours of the brainstem account for roughly 10% to 15% of all central nervous system (CNS) neoplasms in children, with diffuse intrinsic pontine glioma (DIPG) being the most common type [3]. Affected patients with DIPG are mostly children at the age of 5 to 10-years old [4-9]. While brainstem gliomas may arise in other parts of the brainstem including the midbrain and medulla oblongata with a more favourable prognosis, pontine location is very frequent with typical expansion and infiltration of at least half of the pons [10-16]. Vast majority of DIPG are typically high grade (World Health Organization [WHO] grade III or IV), and extensively invasive tumors following an aggressive disease course [17]. Unfortunately, the prognosis of DIPG is universally poor with a median survival of 10 months and less than 10% of affected children living beyond 2 years after diagnosis [1,7,11,18-22].

Clinical presentation and history, physical examination including thorough neurological assessment, and detailed neuroimaging with MRI are generally used in diagnosis of DIPG. Patients typically suffer from several symptoms due to aggressive disease course. Surgical intervention is substantially hampered by the critical location of DIPGs, and treatment has traditionally been instituted based on imaging findings, usually without histopathological verification [23,24]. Nevertheless, complication rates of surgery have been reduced with recent progress in neurosurgical techniques, and there has been an improvement in the understanding of the biology of DIPGs, paving the way for

developing targeted strategies although there is still room for improvement [25].

DIPG usually have unique imaging characteristics. Magnetic Resonance Imaging (MRI) is the principal imaging modality for DIPG. The DIPG lesion is typically hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI with indistinct borders, indicating the infiltrative nature of the disease [26]. Contrast enhancement is variable, and extensive infiltration and swelling of the brainstem is a common imaging characteristic. Axial and sagittal MR images of a patient with DIPG are shown in **Figures 1 and 2** respectively. Patients with DIPG may present with cranial nerve symptoms due to compression and dysfunction of nuclei and tracts located in the pons. A wide spectrum of symptoms may occur including impaired vision and diplopia, nausea and vomiting, headache, impaired alignment of the eyes, gait disturbances, dysarthria, facial asymmetry or weakness, impaired communication with altered levels of consciousness, changes in behaviour, impaired mobility, spasticity, weakness in legs and arms [1,9,11,12]. A classical triad of DIPG includes impairment of long tract leading to sensorial loss or weakness in extremities or trunk, cerebellar deficits leading to gait disturbances and impairment of coordination and balance, and cranial nerve palsies leading to facial weakness or asymmetry along with diplopia, impaired vision and impaired alignment of the eyes [27]. This wide spectrum of symptoms may lead to significant deterioration in quality-of-life of the affected patients and life-threatening consequences may occur, emphasizing the importance of vigilance for prompt patient management.

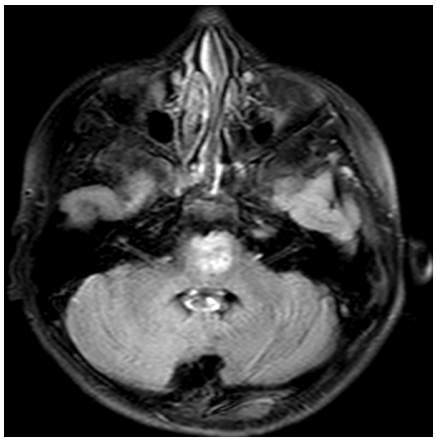

Figure 1 Axial and sagittal MR images of a patient with DIPG (Part 1).

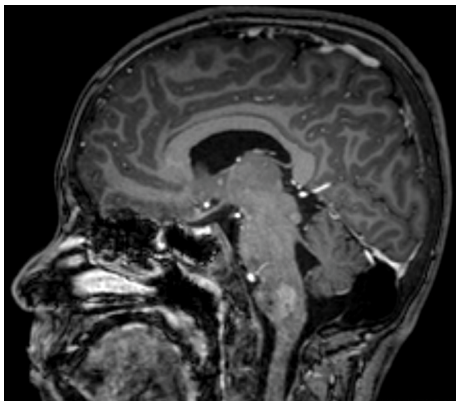

Figure 2 Axial and sagittal MR images of a patient with DIPG (Part 2).

Brainstem gliomas located at the pons with diffuse and extensive infiltration are typically not amenable for complete surgical resection. Conflicting results have been achieved so far with another important therapeutic modality, chemotherapy and biological/targeted therapies, without a striking and long-lasting benefit [1,21,28-32]. In this context, radiation therapy (RT) has traditionally been the mainstay of treatment for DIPG. Optimal radiation dose and fractionation and combined modality management with RT and chemotherapy has been the focus of extensive research over several decades. Herein, we assess the utility of RT for DIPG management in light of the literature.

Literature Review

Radiation Therapy (RT) for Diffuse Intrinsic Pontine Glioma (DIPG)

RT has a long history in DIPG management as a cornerstone treatment modality with at least transient benefit. Several trials have been conducted in an effort to optimize dose and fractionation of RT for DIPG. Conventionally fractionated RT at a dose of 54 to 60 Gy delivered with daily fractions of 1.8 to 2 Gy over approximately 6 weeks is a widely accepted dose-fractionation scheme for DIPG management [9,33,34]. Steroids are frequently used during the course of RT to alleviate symptoms of peritumoral edema, and usually stopped with dose tapering after treatment completion.

Given the relentless disease course despite RT, several strategies including hyperfractionation and dose escalation, hypofractionation, and combined modality management with RT and chemotherapy/systemic agents have been studied.

Conventionally fractionated RT

Most common and traditional dose-fractionation scheme for DIPG includes conventionally fractionated RT to a total dose of 54 to 60 Gy delivered with daily fractions of 1.8 to 2 Gy over approximately 6 weeks, with us without chemotherapy [34-55]. There have been attempts to improve outcomes of RT with integration of systemic agents before, during, or after RT. Although results of combined modality management with incorporation of systemic agents into radiotherapeutic management of DIPG has not yet been satisfactory to justify its routinization, there is ongoing extensive research on this issue without a widely accepted consensus. Despite the slow progress in terms of prolongation of survival, ongoing trials are assessing the role of single and multi-agent chemotherapy in DIPG management. Multicentre collaborative efforts are warranted to shed light on optimal DIPG management using multimodality therapy.

Hyperfractionated RT

The rationale of hyper fractionated RT is the delivery of potentially higher biologically equivalent doses of radiation without causing

excessive RT-induced toxicity. In an attempt to improve outcomes of RT for DIPG, several studies investigated the role of hyper fractionated RT for DIPG [55-71]. Hyper fractionated RT with higher radiation doses than conventionally fractionated RT was delivered as a twice-daily treatment. Total delivered dose ranged between 64 to 78 Gy in hyper fractionation trials, however, multicentre collaborative studies reported that children succumbed to their disease within 18 months of diagnosis and revealed no significant advantage of hyper fractionation over conventionally fractionated RT, which rendered hyper fractionated RT rather questionable when additional issues such as logistics, patient convenience, and the need for repeated anaesthesia in some cases are concerned.

Hypofractionated RT

While late effects of irradiation may be considered as an important concern for a mostly young patient group, there have been attempts to shorten the overall RT time for DIPG since duration of conventionally fractionated RT may be considered long particularly when the short lifespan of patients (typically limited to less than a year) is concerned. Late effects of irradiation may not be observed in the majority of patients due to their limited lifespan, and hypofractionation may be a viable radiotherapeutic strategy for prompt relief of symptoms to improve patients' quality-of-life with reduced burden on patients and families. Nevertheless, median overall survival rates in studies of hypo fractionated RT for DIPG are slightly lower, emphasizing the importance of decision making for patient selection [72-76].

Reirradiation

Although prognosis of recurrent DIPG is grim, selected patients may benefit from reirradiation [77-80]. It may be pertinent to consider focal radiation delivery with a hypo fractionated regimen for effective palliation achievement with reduced overall treatment time despite the need for optimization of RT dose and patient selection.

The use of radiosurgery in the form of Stereotactic Radiosurgery (SRS) or Stereotactic Body Radiation Therapy (SBRT) has substantially increased to treat a variety of benign and malignant conditions under stereotactic localization and image guidance for precision radiation delivery [81-98]. In this context, radiosurgery may be used for selected patients with DIPG [99,100].

Conclusion

Overall, RT remains to play a central role in DIPG management. Advances in the discipline of radiation oncology may improve the therapeutic ratio for patients with DIPG despite the need for further supporting evidence.

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