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Review Article

Review of dose fractionation schemes for pontine glioma irradiation

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Abstract

Brainstem tumors constitute approximately 10% to 15% of CNS neoplasms in the pediatric population, and most common of brainstem tumors is diffuse intrinsic pontine glioma (DIPG). Children with DIPG are typically diagnosed at the 5th to 10th years of their lives, with tumors being more frequently located in the pons rather than the midbrain or medulla oblongata. Symptomatology of patients may be severe and associated with compression of nuclei and tracts in the pons leading to cranial nerve dysfunctions. The wide spectrum of symptomatology may result in profound deterioration of the patients' quality of life, and management is required for symptomatic relief. Complete removal of DIPG is typically not achievable given the diffuse and infiltrating nature of the disease with significant risk of excessive toxicity associated with surgical interventions. Nevertheless, surgical biopsy may be considered as a technically feasible procedure for selected patients to allow for histopathological verification and acquisition of biological data to aid in decision making for management. Utility of chemotherapy, biological and targeted therapies is being actively investigated as a promising treatment strategy, however, there is still room for improvement for routine clinical use. Radiation therapy (RT) remains to be a principal management approach for DIPG. Herein, we provide a concise review of dose fractionation schemes for pontine glioma irradiation.

Introduction

Brain tumors in the pediatric population constitute a very frequent type of solid childhood cancers and a considerable part of all pediatric malignancies. These tumors are typically classified into supra and infratentorial with respect to their location. Another classification is based on age at diagnosis and includes congenital brain tumors, tumors of infancy period observed at younger than 1 year of age, and tumors observed in older children. Brain tumours account for about 20% of all childhood neoplasms [1-5]. Brainstem comprises a critical location for pediatric Central Nervous System (CNS) malignancies [5]. Critical parts of the brainstem include the medulla oblongata, pons, and the midbrain all of which are involved in critical functions of the human body [5].

Brainstem tumors constitute approximately 10% to 15% of CNS neoplasms in the pediatric population, and most common of brainstem tumors is Diffuse Intrinsic Pontine Glioma (DIPG) [5-7]. Children with DIPG are typically diagnosed at the 5th to 10th years of their lives, with tumors being more frequently located in the pons rather than the midbrain or medulla oblongata [5-8]. Location at the midbrain and medulla oblongata may be associated with a relatively more favorable prognosis compared to pontine location with frequent expansion and diffuse infiltration of more than half of the pons [5-10]. DIPG are typically categorized as World Health Organization (WHO) grade III or IV tumors with typically an aggressive disease course and grim prognosis [5-11]. Median Overall Survival (OS) is typically in the range of 8 to 11 months, with a low OS rate of about 30% at 1 year, and less than 10% at 2 years [11].

Diagnosis of pontine gliomas is typically based on detailed history, clinical examination and presentation findings, comprehensive neurological evaluation, and neuroimaging with Magnetic Resonance Imaging (MRI) [5]. Using the clinical and imaging findings for diagnosis has been suggested to avoid

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the considerable risk of complications associated with biopsy [12,13]. However, advances in surgery may render stereotactic and liquid biopsies to be performed for selected patients [14-16]. Histopathological verification and an improved understanding of the biology of DIPG may pave the way for development of novel treatment paradigms including immunotherapeutic strategies to combat with this dreadful disease [4,7,15-18]. The H3K27M mutation has been identified in the majority of DIPGs, and advances in epigenetic targeting of transcriptional tendencies have put forth potential molecular targets which could be further investigated [4,7,15-18].

MRI constitutes the imaging modality of choice for DIPG with unique imaging characteristics [19,20]. Conventional MRI comprises a noninvasive mode of diagnosis for DIPGs which are typically expansile and infiltrative tumors located at the pons frequently with lateral extentions to the middle cerebellar peduncles, caudally to medulla oblongata and cranially to midbrain; and MRI typically reveals a isointense or hypointense lesion on T1-weighted MRI and hyperintense lesion on T2-weighted MRI with indistinct borders consistent with the infiltrative nature of DIPGS [19,20]. Exophytic growth into the prepontine cistern may be seen in some patients and the basillar artery may also be engulfed by the lesion [20]. DIPGs may typically demonstrate mild heterogeneous enhancement or no enhancement, nevertheless, increased enhancement or ring enhancement may be suggestive of poorer prognosis [20-22].

Symptomatology of patients may be severe and associated with compression of nuclei and tracts in the pons leading to cranial nerve dysfunctions [5-8]. Headache, gait and visual disturbances, dysconjugate gaze and diplopia with abducens palsy, impaired alignment of the eyes, dysarthria, nausea and vomiting, impaired mobility and spasticity, Babinsky sign, weakness in legs and arms, facial weakness or asymmetry due to cranial nerve VII damage, behavioural alterations, impaired communication, and altered levels of consciousness may occur [5-8]. Gait, speech and coordination disturbances manifesting as *ataxia, dysarthria, and dysmetria may be suggestive of* multiple cranial neuropathies along with long tract and cerebellar signs referred to as the classical triad of DIPG [5-8,23-25]. Hydrocephalus may also be observed in a small group of affected patients due to blockade of cerebrospinal fluid flow with dorsal tumor extention [7,23,24]. The wide spectrum of symptomatology may result in profound deterioration of the patients' quality of life, and management is required for symptomatic relief. Complete removal of DIPG is typically not achievable given the diffuse and infiltrating nature of the disease with significant risk of excessive toxicity associated with surgical interventions. Nevertheless, surgical biopsy may be considered for selected patients [4,7,15-18, 26-28]. Utility of chemotherapy, biological and targeted therapies is being actively investigated as a promising treatment strategy, however, there is still room for improvement for routine clinical use [29-31]. Radiation Therapy (RT) remains to be a principal management approach for DIPG. Herein, we provide a concise review of dose fractionation schemes for pontine glioma irradiation.

Irradiation of pontine gliomas by use of conventional fractionation

Conventionally fractionated RT (CFRT) has been traditionally utilized for management of pontine gliomas with the primary goal of achieving symptomatic relief and disease control. A total RT dose of 54 to 60 Gy is delivered over approximately 6 weeks with CFRT using a daily fraction dose of 1.8 to 2 Gy [5,8,9,32-34]. Use of steroids during the RT course may aid in management of symptoms due to peritumoral edema, typically with dose tapering after treatment completion. In a systematic review by Gallitto, et al. [33], CFRT constituted the majority of definitive RT series for DIPG management. Median OS with CFRT was 12 months whereas median OS was 10.2 months for hyperfractionated RT and 7.9 months for hypofractionated RT regimens [33]. Freese et al. [34] assessed outcomes of RT and subsequent irradiation in a study group of 26 patients with DIPG. Conventional fractionation was used as the dose fractionation scheme, and patients were treated using Intensity Modulated Radiation Therapy (IMRT) [34]. Reirradiation was utilized for 3 patients with a total dose of 20 Gy delivered again with conventional fractionation [34]. The authors concluded that advances in treatment techniques could allow for retreatment of patients after definitive management with RT [34].

Irradiation of pontine gliomas by use of hyperfractionated RT

Rationale behind hyperfractionation includes delivering higher biologically equivalent doses of RT whilst avoiding treatment related adverse effects. In this context, several trials have focused on hyperfractionated RT schemes [35-42]. Mandell, et al. [42] conducted a phase III randomized controlled trial comparing hyperfractionated RT and CFRT fpr management of newly diagnosed diffuse intrinsic brainstem tumors. A total of 130 patients were enrolled, and no clear evidence of effect was observed on OS [9, 42]. Considering the absence of evidence demonstrating the superiority of hyperfractionation, it seems prudent not to opt for hyperfractionated RT regimens which also put forward additional issues including logistics, patient convenience, and potential requirements for repeated anaesthesia [5,9,33].

Irradiation of pontine gliomas by use of hypofractionated RT

Given the limited life expectancy of patients with DIPG, hypofractionated RT regimens have been considered [43-48]. Primary aim of hypofractionation is shortened overall treatment time compared to CFRT. However, no improvement in OS has been achieved with hypofractionation and even inferior outcomes have been reported [9,33,43-48]. In the systemic review by Gallitto *et al.* [33], mean median OS for hypofractionated RT series was 7.9 months with a mean 1-year OS rate of 28.8%. Nevertheless, hypofractionated RT regimens may offer decreased treatment burden on patients and their families. In this context, selected patients may be considered for hypofractionated RT regimens despite need for further supporting evidence [49].

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Reirradiation of pontine gliomas

Despite the poor prognosis of DIPG with limited survival durations, reirradiation may be considered [34]. Reirradiation schemes may include CFRT as well as radiosurgical applications [34,50-52]. Comprehensive studies addressed the utility of reirradiation for DIPG [53-58]. Janssens, et al. analyzed the benefit and toxicity of reirradiation at first progression of DIPG [56]. They treated 31 children aged 2-16 years with DIPG at first progression with a reirradiation dose of 19.8 – 30 Gy [56]. Median overall survival was 13.7 months for patients receiving reirradiation, and the authors concluded that majority of DIPG patients responding to upfront RT may benefit from reirradiation with acceptable toxicity [56]. Massimino, et al. assessed the results of nimotuzumab and vinorelbine, RT and reirradiation for diffuse pontine glioma in childhood [57]. Twenty five patients were enrolled, and 11 out of 16 patients with local relapse received reirradiation to a dose of 19.8 Gy delivered over 11 days [57]. Median progression free survival was 8.5 months and median overall survival was 15 months [57]. The authors concluded that the treatment strategy should be further investigated in view of the interesting results [57]. Wolff et al. reported their experience on treatment of recurrent DIPG including reirradiation as part of management in 7 patients out of the total 31 patients [58]. The authors concluded that reirradiation should be tested in a prospective clinical study in view of the encouraging response rates [58].

Recent years have witnessed significant advances in radiation oncology with widespread adoption of contemporary RT strategies including Image Guided Radiation Therapy (IGRT), Intensity Modulated Radiation Therapy (IMRT), and Adaptive Radiation Therapy [59-65]. Radiosurgery in the form of Stereotactic Radiosurgery (SRS), Stereotactic Body Radiation Therapy (SBRT) and Hypofractionated Stereotactic Radiation Therapy (HFSRT) may be used for focused irradiation of several CNS disorders as well as several other tumors throughout the human body [66-100]. Rationale of radiosurgery includes highly focused delivery of high and ablative RT doses to well defined targets with optimal normal tissue sparing with stereotactic localization, robust immobilization, and steep dose gradients around the target. Nevertheless, there is relatively limited experience with this relatively newer radiotherapeutic strategy.

Conclusions and future perspectives

RT plays a major role in management of pontine gliomas. Given the limited life expectancy of patients with DIPG, RT may be utilized for achieving at least a transient stabilization of disease and improvement in symptoms and quality of life. Improved understanding of the biology of DIPG may allow for utilization of targeted therapies to achieve an improved therapeutic ratio for pontine gliomas.

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