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Mini Review

Protons in Neurons: Role of Proton Beam Therapy in Pediatric Brain Tumours

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Abstract

Cancer is a major cause of childhood death, with central nervous system (CNS) neoplasms being the second most common pediatric malignancy, following hematological cancer. These CNS neoplasms often require a multimodal management in the form of surgery, chemotherapy and radiotherapy in various sequences and combinations. The last two decades have witnessed major technical advances in these treatments, thereby enabling favorable results and longer survival. However, treatment-related toxicities remain a major cause of concern, particularly for radiotherapy, after which secondary cancer, reduced function of irradiated organs, and retarded growth are significant problems. This issue is most notable in the pediatric population because of developing organs and tissues combined with longer life expectancies. Proton beam therapy (PBT) is relatively new and technically superior alternative to the often-used photon beam radiotherapy that enables equivalent and superior survival rates for pediatric tumors along with reduced risk of delayed toxicities including endocrinological disorders, neurocognitive impairment and secondary cancer. The dosimetric benefits of PBT include the absence of an exit dose beyond the Bragg peak thereby sparing normal tissue that otherwise would receive an exit dose if a photon beam were used; and this reduces the whole-body integral dose. Downsizing the devices and reducing costs remain an alarming issue in PBT. In this review article, we provide a broad overview of evolving role of PBT for treatment of pediatric CNS malignancies and the challenges involved.

Keywords: Pediatric Central Nervous System Tumors (PCNST); Proton Beam Therapy; Delayed Side-Effects; Neurocognitive Impairment

Introduction

Pediatric central nervous system tumors (PCNST) are the most common solid tumors in children, constituting the second most common pediatric cancers and a leading cause of mortality and morbidity in children worldwide. Around 25% of all cancers under 15 years of age are due to central nervous system (CNS) tumors [1,2]. About 4,300 children are diagnosed with CNS tumors annually as per the Central Brain Tumor Registry of the United States (CBTRUS); the estimated incidence of primary nonmalignant and malignant CNS tumors is 5.6 cases per 100,000 person-years for children and adolescents ≤19 years of age [3]. The estimated ten-year survival rate for all primary CNS tumors is approximately 70 percent in patients ≤19 years of age, resulting in approximately 26,000 children living in the United States with a CNS tumor. Morbidity associated with CNS tumors may be significant in terms of physical deficits as well as neuropsychological and neuroendocrine sequelae [4].

Treatment options for PCNST include radiation therapy, surgery and chemotherapy, often given in combination [5]. The last two decades have seen significant improvements in these treatment modalities, thereby enabling an overall survival and cure rates of almost 70% amongst these patients. Radiation therapy regularly has a pivotal role in treatment, and technological advancements during the past quarter of a century have dramatically improved the abi-

lity to deliver radiation in a more focused manner [6]. The use of conventional Radiotherapy however continues to be associated with clinically significant late toxicities in long-term survivors; one of the important underlying radiobiological cause being higher radiation sensitivity and lower radiation tolerance of these pediatric patients as compared to their adult counterparts [7]. These remote toxicities lead to reduced quality of life of these patients antecedent to growth and development retardation and the increased theoretical risk of secondary cancer. In PCNST survivors, over 60% report one or more radiation-related late toxicities while half of these adverse events are graded as life-threatening or severe.

Proton beam therapy (PBT) enables high conformity with the planning target volume and a reduction in dose to areas beyond the target. Owing to the unique nature of dose delivery with proton therapy a reduction of low doses to normal tissues is achievable, and is believed to allow for a decrease in long-term treatment-related side effects [8]. PBT appears to decrease the incidence and severity of late effects with the strongest evidence in PCNST that shows benefits in neurocognitive, hearing, and endocrine outcomes [9]. PBT is a form of RT that precisely delivers radiation within a defined radiation track length, with virtually no significant dose beyond the intended target. As compared to conventional RT, where larger volumes of normal surrounding tissues are irradiated, PBT is associated with lesser dose to surrounding critical normal structures, decreasing the dose to healthy tissues by a factor of 1.5 to 3.0 mainly due to the generally lower entrance dose and the complete elimination of exit dose compared to photon beams [10].

In this mini-review, we provide a broad perspective of current and emerging role of PBT for treatment of pediatric CNS malignancies. This review is based on the published scientific data from reputed indexed English journals as retrieved from pubmed, google scholar and similar platforms.

Physics and Biology of PBT

Traditionally, the therapeutic use of PBT is motivated primarily by their inverted depth-dose profile compared to photons, being characterized by the so-called Bragg peak. This limits the radiation-induced damage in nearby surrounding critical and healthy tissues. This physical property allows the treating clinicians to select multiple beams of varying energies to attain the optimum prescribed dose in the desired target volume, thereby enabling the production of Spread-Out Bragg Peak (SOBP). As a result, the eloquently located and deep-seated tumors in vicinity to Organs At Risk (OAR) can be subjected to dose-escalation along with respecting the tolerance of normal critical structures. These physical attributes of charged particle beams allow adequate treatment of pediatric patients, as they are particularly vulnerable to suffer from delayed toxicities. In addition to these physical characteristics of depth-dose distribution, PBT possesses an enhanced biological effectiveness in cell killing made possible by enhanced Linear Energy Transfer (LET) of these beams as compared to conventional X-rays. High LET values allow deposition of entire energy of these densely-ionizing radiation in the tumor-bearing area and thus enhanced, irreparable biological damage. This enhanced effect of PBT provides favourable Relative Biological Effectiveness (RBE), which is the ratio of photon and charged particle doses to attain the same biological effect [11].

Acute toxicities of PBT in children

PBT in PCNST may reduce late toxicity, but acute toxicity is not well defined. Suneja G and colleagues [12], in a retrospective review of 48 children with malignant brain tumors treated with PBT, examined acute toxicity for children with CNS malignancies treated with PBT. It was observed that the acute toxicities were generally low-grade and manageable. The most commonly observed acute toxicities were fatigue, alopecia, and dermatitis manageable with supportive care. The least common were insomnia and vomiting. This study confirmed that PBT is a well-tolerated treatment option in PCNST. In a similar study, McGovern SL., *et al*. [13] retrospectively evaluated the treatment outcomes and toxicity profiles of PBT in 31 pediatric atypical teratoid/rhabdoid tumors of the CNS. 87% of the enrolled patients were able to complete the prescribed radiation. It was seen that at an overall follow-up of 24 months for all patients, median progression-free survival and median overall survival was 20.8 months and 34.3 months respectively. Five patients developed clinical and radiological evidence of acute radiation reaction within three months post-radiation, manageable with supportive care. The authors concluded that overall survival in PCNST patients treated with PBT is promising as compared to conventional controls, but merits further research.

Delayed Neurocognitive sequelae after Radiotherapy

Deterioration of intelligence after radiotherapy is an important problem in growing children; mainly defined by the irradiation dose, volume encompassed, site of primary disease, and age of the patient while receiving radiation [14]. The late neurocognitive and psychosocial effects of treatment for PCNST represent important areas of clinical research; and negatively impact these survivors' overall health-related quality of life, educational attainment and employment rates. The neurocognitive and psychosocial outcomes in PBT survivors depend on a plethora of factors like histopathological characteristics of the tumor, tumor-induced complications, treatment techniques, individual's vulnerability and supportive mechanisms available [15]. Even the protection of a relatively small uninvolved critical normal organ, such as the cochlea and hypothalamus, in PBT can help avoid delayed hypopituitarism, neurocognitive impairment and sensory-neural hearing loss [16].

Harrabi SB., *et al*. [17] assessed dosimetric advantages of PBT over conventional radiotherapy with photons in 74 patients with low-grade glioma. Conventional three-dimensional photon and PRT plans were compared after contouring nearby critical neuronal structures and areas vulnerable to delayed risk of secondary malignancies. Target volume coverage was almost similar for the two plans in most aspects. There was a definitive reduction noted in maximal, mean, and integral doses received by critical neurologic structures and structures of neurocognitive function. This study revealed that it is feasible to spare the contralaterally located structures with PRT. The authors concluded that PRT is a highly conformal radiation technique offering superior dosimetric advantages over conventional radiotherapy by allowing significant dose reduction for OAR that are essential for neurologic function, neurocognition, and quality of life, thus demonstrating the potential of this technique for minimizing long-term sequelae.

Risk of secondary cancer

Despite the recent advances in photon-based treatment deliveries, radiation-induced secondary malignancies continue to be a major cause of morbidity and mortality among PCNST survivors. Secondary malignancy risk is affected by variables like patient's age, genetic predisposition, biological aspects, volume of tumor, location, and the dose of radiation prescribed. PBT carries a theoretical risk of relatively higher neutron scatter in tissues outside of the target volume, the overall secondary dose contribution is miniscule and the total integral dose remains significantly less with PBT as compared to photon therapy. Pencil beam scanning systems provide still greater benefits of reduced secondary dose from neutron scatter and risk of secondary cancer from PBT [18].

Mizumoto M., *et al*. [19] retrospectively evaluated the long-term benefits of PBT in 343 cancer survivors of whom 62 reported for review for 5 or more years. It was observed that the 5-year, 10-year and 20-year rates for grade 2 or higher late toxicities were 18%, 35% and 45%, respectively, while those for grade 3 or higher late toxicities were 6%, 17% and 17% respectively. There was no malignant secondary tumor noted within the field of irradiation. The authors further observed rates for all secondary tumors, malignant secondary tumors, and malignant nonhematologic secondary tumors as 8% and 16%, 5% and 13%, and 3% and 11%, cumulatively at 10 and 20 years respectively. This study confirmed that PBT has the advantage to potentially reduce the risk of late mortality and secondary cancers. Tanura M and coworkers [20] calculated the lifetime attributable risk (LAR) of radiation-induced secondary malignancies from PBT as compared to intensity-modulated radiotherapy (IMRT) in randomly sampled 242 pediatric cancer patients and found a significantly lower risk in the PBT arm.

Drawbacks and future perspectives

Proton radiotherapy remains a limited resource despite its clear potential for reducing radiation doses to normal tissues and late effects in children in comparison with photon therapy. Delivery of proton therapy requires the building of a proton center with cyclotrons or synchrotrons, which necessitates a large initial investment and specialized expertise. Because of the rising costs of cancer care, there is concern that conventional PBT centers may not be sustainable in the future. Others have argued that, because the clinical and toxicity data for PBT are incomplete compared with data for photons, it will be difficult to truly assess the cost-effectiveness of PBT. Socioeconomic factors affect the use of proton radiotherapy in children. Whether this disparity is related to differences in the referral patterns, the knowledge of treatment modalities, or the ability to travel for therapy needs to be further clarified. Improving access to proton therapy in underserved pediatric populations is essential [21]. Future directions of research and development include improvement of proton delivery techniques, quality assurance, appropriate patient selection, radiobiologic studies and cost–effectiveness analyses. There is a need to cover PBT under public and private insurance schemes. Further studies and discussions are needed to address the use of proton beam therapy with concurrent chemotherapy, and for maintaining the quality of life of patients while retaining a high cure rate [22-24].

To conclude, PBT is a highly conformal radiation technique offering superior dosimetric advantages over conventional radiotherapy by allowing significant dose reduction for OAR that are essential for neurologic function, neurocognition, and quality of life, thus demonstrating the potential of this technique for minimizing long-term sequelae.

Conflict of Interest

Nil to report.

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