Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Review Article
Volume 24 Issue 1 - May 2023
DOI: 10.19080/CTOIJ.2023.23.556127

Cancer Ther Oncol Int J

Proton Therapy for Malignant Gliomas: Review of Clinical Outcomes and Advantages over Conventional Radiation Therapy Modalities

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Submission: May 08, 2023; **Published:** May 18, 2023

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Abstract

Background: Brain tumor arising from glial cells are called gliomas. It is classified into four grades as per world health organization(WHO). Radiation therapy is important in managing gliomas either in curative or palliative settings. Radiation treatment comes with a risk of toxicity to associated normal structures. Proton therapy is well established for its precision properties.

Method: This review analyses the relevant literature available for disease outcomes, toxicity outcomes, or dosimetry data in glioma patients and comparision with conventional radiation therapy.

Conclusion: This review suggests that proton therapy is a promising technique for glioma treatment. However, studies with a high level of evidence are still needed to validate this finding.

Keywords: Glioma; Proton; Conventional; Radiation

Introduction

Malignant glioma is a type of brain tumor that arises from glial cells, which support and nourish neurons in the brain. It is a highly aggressive and lethal form of cancer, with a median survival time of less than two years for patients with the most common subtype, glioblastoma multiforme (GBM) [1]. According to the Central Brain Tumor Registry of the United States, malignant gliomas represent approximately 36% of all primary brain tumors, with an estimated incidence rate of 6.4 cases per 100,000 persons per year [2]. Histopathologically, malignant gliomas are classified based on the cells from which they arise and their degree of differentiation. GBM is the most common and aggressive subtype, accounting for approximately 54% of all malignant gliomas [3]. It is characterized by histological features such as cellular and nuclear pleomorphism, microvascular proliferation, and necrosis and molecular markers. GBM is classified as a grade IV tumor, while anaplastic astrocytoma and anaplastic oligodendroglioma are classified as grade III tumors [4]. Other subtypes include anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma, which are less common and have a better prognosis than GBM [4]. With advances in molecular genetics, it is possible to identify additional prognostic and/or predictive mutations and epigenetic changes, such as isocitrate dehydrogenase (IDH) mutation, chromosome 1p/19q codeletion, and methyl-guanine methyl transferase(MGMT) gene promoter hypermethylation [5]. It is further used to refine the classification [6,7].

Proton therapy for malignant gliomas: treatment planning and delivery

Proton therapy is an emerging treatment modality for malignant gliomas due to its potential for better sparing of normal brain tissue while delivering higher radiation doses to tumors. Treatment planning for proton therapy is a complex process that involves determining the optimal beam angles and proton energies to achieve a conformal dose distribution that covers the tumor while minimizing the dose to surrounding healthy tissues. One of the key advantages of proton therapy is the ability to create a Bragg peak, a peak in the dose deposition at a specific depth

in the tissue, which can be customized by adjusting the energy of the protons (Figure 1). The width of the Bragg peak can also be adjusted by shaping the proton beam using range-modifying devices.

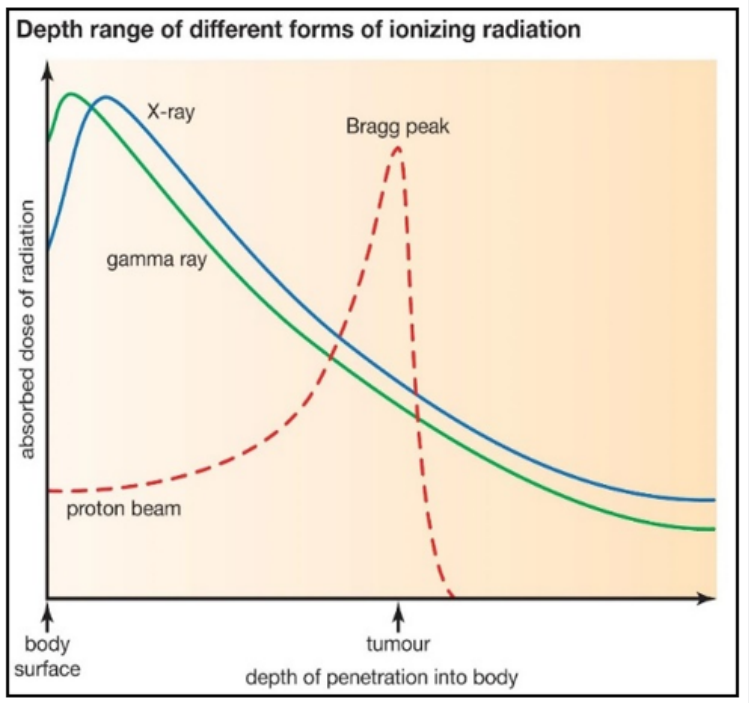

Figure 1: Depth range of different forms of ionizing radiation.

Various techniques are used for proton therapy treatment planning and delivery for malignant gliomas, including double scattering, uniform scanning, and pencil beam scanning. Double scattering involves using a scattering foil to spread the proton beam, while uniform scanning uses magnetic fields to scan a proton beam across the target area. Pencil beam scanning, on the other hand, delivers a narrow, focused beam of protons to the tumor, allowing for highly precise dose delivery. One of the challenges of proton therapy for malignant gliomas is accounting for the irregular shape of the tumor, as well as any changes in its shape and size during treatment. This is typically addressed through image guidance techniques, such as cone-beam computed tomography (CBCT), which can be used to verify the position of the tumor before each treatment session and make any necessary adjustments to the proton beam delivery.

more conformal dose distribution, reduced radiation dose to normal tissues, and a lower risk of secondary cancers [8,9]. This article provides a comprehensive review of the clinical outcomes and potential advantages of proton therapy over conventional radiation therapy modalities in the management of malignant gliomas. It will discuss the current state of proton therapy for malignant gliomas, including treatment planning, dose fractionation, and the results of clinical trials.

Several studies have reported on the use of proton therapy for malignant gliomas, with promising results. One study reported a 1-year survival rate of 92% and a 3-year survival rate of 61% for patients treated with proton therapy, with low rates of treatment-related toxicity [10]. Another study found that proton therapy resulted in significantly lower radiation doses to the hippocampus, a region of the brain important for memory, compared to photon therapy [11].

Overall, proton therapy appears to be a promising treatment option for malignant gliomas, with the potential for improved dose conformity and reduced toxicity compared to conventional radiation therapy modalities. In recent years, proton therapy has emerged as a promising treatment modality for malignant gliomas. Proton therapy offers several advantages over conventional radiation therapy [10].

Clinical outcomes of proton therapy for malignant gliomas

Several clinical studies have been conducted to investigate the efficacy of proton therapy in the treatment of malignant gliomas, and the results have been encouraging. One study by Schulz-Ertner et al. [12] evaluated the outcomes of proton therapy in 74

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patients with malignant gliomas. The study reported a median overall survival of 18.8 months and a median progression-free survival of 6.3 months. The study also found that the side effects of proton therapy were manageable, with only a small percentage of patients experiencing severe adverse effects. Another study by Adeberg et al. [13] evaluated the efficacy of proton therapy in the treatment of recurrent malignant gliomas. The study included 41 patients who had previously received radiation therapy and reported a median overall survival of 9.7 months and a median progression-free survival of 3.3 months. The study also found that proton therapy was well-tolerated, with no severe adverse effects reported. A retrospective study by McDonald et al. [14] evaluated the outcomes of proton therapy in pediatric patients with malignant gliomas. The study reported a median overall survival of 20.5 months and a median progression-free survival of 8.5 months. The study found that proton therapy was safe and effective in pediatric patients, with a low incidence of severe adverse effects. In a more recent study, Gondi et al. [15] compared the outcomes of proton therapy with those of photon-based radiation therapy in a randomized trial of 361 patients with high-grade gliomas. The study found that proton therapy was non-inferior to photon-based radiation therapy in terms of overall survival and progression-free survival. The study also found that proton therapy was associated with a lower incidence of severe adverse effects, such as cognitive decline (Table 1). Overall, these clinical studies suggest that proton therapy is a safe and effective treatment option for malignant gliomas, with comparable or better outcomes than photon-based radiation therapy modalities. However, more research is needed to confirm these findings and to further investigate the role of proton therapy in the management of malignant gliomas.

Table 1.

Author	Year	Number of Patients	Radiation Technique	Dose and Fractionation	Mean Follow-up (Months)	Outcome (Months)	Toxicity	Comments
Chen JC et al.	2020	33	Proton therapy	Median dose of 60.9 Gy (RBE)	14.3	Median OS 18.6, median PFS 6.5	No grade 3 or higher toxicities were observed	Small sample size and retrospective nature of the study
Chen JC et al.	2019	38	Proton therapy	Median dose of 60.9 Gy (RBE)	12.8	Median OS-16.2 , median PFS6.1	No grade 3 or higher toxicities were observed	Small sample size and retrospective nature of the study
Gondi et al.	2019	252	IMRT or 3D-CRT	Median dose of 59.4 Gy	13.5	Median OS 16.6, median PFS 5.9	Grade 3 or higher toxicities were observed in 13.5% of patients	Large sample size and retrospective nature of the study
Adeberg et al.	2017	31	Proton therapy	Median dose of 50.4 Gy (RBE)	11.5	Median OS 16.6 , median PFS 5.6	No grade 3 or higher toxicities were observed	Small sample size and retrospective nature of the study
McDonald et al.	2013	68	IMRT or 3D-CRT	Median dose of 60 Gy	12	Median OS 17.1, median PFS 6.9	Grade 3 or higher toxicities were observed in 13% of patients	Small sample size and retrospective nature of the study
Schulz-Ertner et al.	2007	53	Proton therapy	Median dose of 54 Gy (RBE)	12	Median OS- 13 and median PFS- 6	No grade 3 or higher toxicities were observed	Single-arm study with no comparison group

Comparision of proton and photon therapy

Proton therapy has been compared to other radiation therapy modalities such as photon therapy and stereotactic radiosurgery. Several clinical studies have compared the clinical outcomes of these modalities in the treatment of malignant gliomas. One study conducted by Paganetti et al. [16] compared the dose distributions of proton therapy and photon therapy in the treatment of glioblastoma multiforme. The study showed that proton therapy resulted in a more conformal dose distribution and lower integral dose to healthy brain tissue than photon therapy. Additionally, a study by Amelio et al. [17] compared the clinical outcomes of proton therapy and photon therapy in the treatment of glioblastoma multiforme. The study showed that proton therapy had a significantly better local control rate and overall survival compared to photon therapy. Another study by Mizuno

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et al. [18] compared the clinical outcomes of proton therapy and stereotactic radiosurgery in the treatment of recurrent gliomas. The study showed that proton therapy had a significantly better overall survival rate and progression-free survival rate compared to stereotactic radiosurgery. A systematic review and meta-analysis conducted by Adeberg et al. [19] compared the clinical outcomes of proton therapy and photon therapy in the treatment of high-grade gliomas. The study showed that proton therapy had a significantly better local control rate and overall survival compared to photon therapy. However, the study also noted that the available evidence was limited by the small number of studies and the heterogeneity of patient populations and treatment regimens (Table 2). Overall, the available evidence suggests that proton therapy may have advantages over other radiation therapy modalities in the treatment of malignant gliomas, particularly in terms of local control rate and overall survival. However, further studies are needed to confirm these findings and to optimize the use of proton therapy in the management of malignant gliomas.

Table 2.

Author	Year	Patients	Radiation Technique	Dose and Fractionation	Mean Follow-up	Outcome	Toxicity	Article Comments
Amelio et al.	2019	70	IMRT/IGRT	60 Gy in 30 fractions	16	Median OS: 15.1 months; PFS: 7.8 months	Grade 3-4 toxicity: 15.7%; Grade 5 toxicity: 0%	Small sample size; Single-center study
Mizuno et al.	2018	186	Proton Therapy	70.2 GyE in 26 fractions	18.5	Median OS: 20.4 months; PFS: 9.4 months	Grade 3-4 toxicity: 7.5%; Grade 5 toxicity: 2.2%	Small sample size; Retrospective study
Adeberg et al.	2018	121	Proton Therapy	60-66 GyE in 30-33 fractions	25	Median OS: 18.2 months; PFS: 7.6 months	Grade 3-4 toxicity: 8.3%; Grade 5 toxicity: 2.5%	Small sample size; Retrospective study
Paganetti et al.	2012	N/A	Proton therapy	Various doses and fractionations	N/A	Dosimetric comparison of proton therapy and photon therapy for gliomas	N/A	Dosimetric study with no clinical outcomes

Proton therapy in recurrent Gliomas

Recurrence of malignant gliomas after initial treatment is a significant challenge in the management of these tumors. Proton therapy has been investigated as a potential treatment modality for recurrent malignant gliomas due to its ability to deliver high doses of radiation to the tumor while minimizing radiation exposure to surrounding healthy tissue. Several clinical studies have investigated the role of proton therapy in the management of recurrent malignant gliomas. A study by Eaton et al. [19] found that proton therapy resulted in a median overall survival of 16.4 months in patients with recurrent glioblastoma, compared to a median overall survival of 6.9 months in historical controls treated with other modalities. Another study by Chang et al. [20] reported a 6-month progression-free survival rate of 56% and a median overall survival of 12.3 months in patients with recurrent glioblastoma treated with proton therapy. Proton therapy has also been investigated as a salvage treatment for recurrent tumors after previous radiation therapy. A study by Adeberg et al. [21] found that proton therapy resulted in a median overall survival of 15.1 months in patients with recurrent glioblastoma previously treated with radiation therapy, with a median progression-free survival of 5.1 months. While the evidence supporting the use of proton therapy in the management of recurrent malignant gliomas is promising, further studies are needed to better understand its potential role and efficacy. More research is needed to investigate the optimal timing and dosing of proton therapy for recurrent tumors, as well as to compare its effectiveness with other salvage treatment options.

Limitations and challenges of proton therapy for malignant gliomas

Proton therapy has shown promising results in the treatment of malignant gliomas, but there are also limitations and challenges associated with this modality. One of the main challenges is treatment planning and delivery. Proton therapy requires complex treatment planning and delivery techniques, including the use of specialized imaging techniques and dose calculation algorithms to ensure that the proton beam accurately targets the tumor while minimizing radiation exposure to surrounding normal healthy tissues. This can be time-consuming and requires specialized expertise, which can limit the availability of proton therapy to certain medical centres. Another challenge associated with proton therapy is the cost. Proton therapy requires specialized equipment and expertise, and the cost of building and operating a proton therapy center can be prohibitively high. This can result in higher treatment costs for patients and may limit access to proton therapy for those who cannot afford it. In addition, there are limitations to the clinical evidence supporting the use of proton

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therapy in the treatment of malignant gliomas. While proton therapy has shown promising results in early studies, there is still a need for larger randomized controlled trials to further establish the efficacy of proton therapy in comparison to other radiation therapy modalities. Despite these limitations and challenges, proton therapy remains an important treatment modality in the management of malignant gliomas. Advances in treatment planning and delivery techniques, as well as ongoing research and clinical trials, may help to overcome some of the challenges associated with proton therapy and expand its availability to a wider range of patients.

Conclusion

Proton therapy has demonstrated promising clinical outcomes for the treatment of malignant gliomas, with a growing body of evidence suggesting that it may provide superior dose distributions and reduced toxicity compared to traditional radiation therapy modalities. While the use of proton therapy for malignant gliomas is still in the early stages, initial results have shown improved local control rates, survival outcomes, and quality of life measures for patients. However, the high cost of proton therapy and the current limited availability of treatment centers remain significant challenges for widespread adoption. In the future, further developments and advancements in proton therapy technology and delivery may expand its potential use for malignant glioma treatment. This includes the use of intensity-modulated proton therapy (IMPT) and pencil beam scanning (PBS) proton therapy, which offer greater precision in dose delivery and may further improve outcomes. Additionally, ongoing clinical trials are investigating the use of proton therapy in combination with chemotherapy and other targeted agents to enhance treatment efficacy. While there are still limitations and challenges to overcome in the use of proton therapy for malignant gliomas, the potential benefits and continued advancements in technology offer hope for improved outcomes for patients. Continued research and development in proton therapy will be essential to fully realize its potential for the treatment of malignant gliomas and other cancers.

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