Vignan's Journal of Biotechnology and Pharmacy

https://doi.org/10.

REVIEW ARTICLE

A Review on Proton Therapy for Brain Tumors

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Received: 24-06-2024, Accepted: 18-02-2025, Published: 22-04-2025

Abstract

A brain tumor is a collection of neoplasms, each with its own unique biology, prognosis, and treatment. Some tumors, such as meningiomas and lymphomas, do not originate from brain tissue and are more accurately classified as "intracranial neoplasms." Primary brain tumors include more than 100 distinct types, each with its own set of presentations, treatments, and outcomes. Among those affected, 59% are adult females and 41% are adult males, while 3.9% of children aged 0-14 years are diagnosed with brain tumors. Proton therapy has been used for many years to treat a variety of cancers, including brain tumors. This type of radiation therapy uses protons instead of X-rays, delivering radiation more precisely to the targeted brain area, which results in fewer side effects. As a result, proton therapy is emerging as a promising treatment option for cancer. Some proton treatments use a machine called a gantry, which provides dosimetric advantages over photon radiation therapy due to the steep dose fall at depth, characterized by the Bragg peak. In this article, we will explore brain tumors, their statistics, pharmacological actions, clinical trials, and the use of proton therapy in treating adult and pediatric brain tumors, skull base tumors, and the associated side effects.

Keyword: Brain tumors, Bragg peak, Gantry, Proton therapy, Skull base tumors

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Introduction

Brain Tumors: A brain tumor is a group of neoplasms, each with its own distinct biology, prognosis, and treatment. Some of these tumors, such as meningiomas and lymphomas, do not originate from brain tissue and are more accurately referred to as "intracranial neoplasms." Around 2% of central nervous system (CNS) tumors are malignant. Compared to other types of cancer, brain tumors can have long-lasting and life-altering effects on a patient's physical, cognitive, and physiological well-being (Brain Tumor Facts. National Brain Tumor Society).

Gender	Percentage
Female	59%
Male	41%
Children	3.9%

Type of brain tumor	Percentage
Benign	72%
Malignant	28%

Statistics

Primary brain tumors are more than 100 distinct types and each of which has its own spectrum of presentations, treatments and outcomes. (Brain tumor facts, National brain tumor society)

In America

Population	Category of brain tumor
1 million Americans	Living with brain tumors.
94,390 Americans	Will receive primary brain tumor diagnosis in 2023.
18,990 Americans	Will die from malignant brain tumor in 2023.

Types of brain tumors in children

Types of brain tumors	Percentage
Pilocytic astrocytomas	18.7%
Other gliomas	15.3%
Embryonal tumors	12.2%
Medulloblastomas	68.3%
Atypical teratoid /rhabdoid tumors	17.2%

In India: Around 2% of Central Nervous System (CNS) tumors are malignant. In India, the incidence of CNS tumors ranges from 5 to 10 per 100,000 people. Astrocytomas are the most common type of primary tumor, accounting for 38.7%, with the majority being high-grade gliomas (59.9%) (Dasgupta et al., 2016)

Proton therapy

Proton therapy is a form of radiation therapy that uses protons rather than X-rays. It provides a painless method for treating certain cancers and is emerging as a promising new treatment option. Because it can more precisely target the tumor, it minimizes damage to surrounding tissues, resulting in fewer side effects compared to other forms of radiation therapy. (Proton therapy approved by the Cancer.Net Editorial Board) Because of their remarkable physical properties, without exit dose this therapy is appropriate for these brain tumors. There will be diminution of neurocognitive toxicity and quality of life will be increased particularly in children because of the decrease of the brain integral dose. (Weber et al., 2020)

Figure 1: Proton Therapy

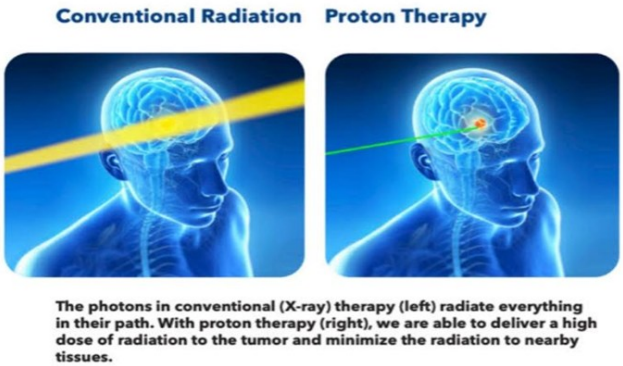


Figure 2: Conventional radiation vs Proton therapy

In the management of Central Nervous System tumors and to optimize the tumor local control radiotherapy is an important treatment modality. In dose escalation paradigm and /or for dose sparing of critical structures / organs at risk the particles can be used because of optimal dose confirmation which is provided by the latter modality and it can be applied to those CNS tumors that are radio resistant such as skull base chordoma and chondrosarcoma or non benign tumors and also in patients with favorable prognosis like in patients with benign or low grade brain tumors (Angelis, 2001).

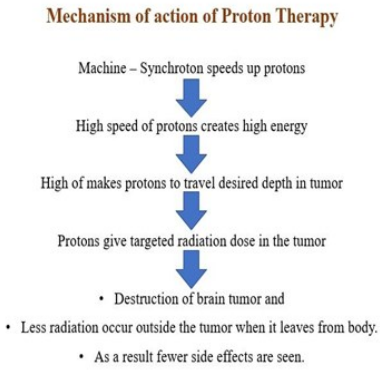
Proton beam therapy for brain tumors

In proton therapy, dose distribution is characterized by a well-defined maximum range, which depends on the initial energy, and a sharply defined Bragg peak where the dose is primarily deposited. The dosimetric advantages of proton therapy over

photon therapy are widely recognized, though these benefits can vary significantly from case to case and are largely dependent on tumor location. Adeberg et al. assessed the relative benefits of proton therapy for five common brain tumor locations, suggesting that parietal tumors tend to benefit the most in terms of brain sparing. Tamura et al. used in silico modeling to estimate that the lifetime risk of secondary cancer after craniospinal irradiation (CSI) is reduced with proton therapy compared to photon therapy. Preliminary evidence also indicates that the dosimetric advantages of proton therapy may translate into clinical benefits, such as a reduction in neurocognitive disabilities and an improvement in quality of life. (Weber et al., 2020)

Pharmacological Action

Like other forms of radiation therapy, proton therapy works by delivering radiation to treat brain tumors, but it uses protons instead of X-rays. Protons are positively charged particles that, at high energy levels, can destroy cancer cells. Proton therapy may also be combined with other treatments, such as X-ray radiation, surgery, chemotherapy, or immunotherapy. A synchrotron, also known as a cyclotron, is a machine that accelerates the protons to high energy, enabling them to travel through the body to the desired depth. Once at the target site, the protons deliver a focused dose of radiation directly to the tumor. Compared to conventional radiation therapy, proton therapy results in less radiation exposure outside the tumor, which is why it tends to cause fewer side effects. Protons deposit a minimal entrance dose as they enter the body, and their penetration depth is determined by their kinetic energy—higher energy protons penetrate deeper. Once they reach the target, they deliver the dose and stop, eliminating the exit dose. (Foote et al., 2012)



Gantry: A gantry is a large machine found in some proton therapy treatment rooms. It rotates around the patient, delivering treatment from the best possible angles to target the tumor. Gantries can be very large, sometimes reaching the height of three stories. As the gantry moves, it positions the machine's nozzle correctly, allowing protons to be directed toward the tumor. Once the patient is properly positioned, the treatment team, located outside the treatment room, controls the delivery of proton therapy using remote controls. Through audiovisual equipment inside the room, the team can see and hear the patient throughout the procedure. The protons travel through the machine and are guided by magnets to the tumor site. It's crucial that the patient stays still during treatment to ensure the tumor remains within the focused proton beam. (Foote et al., 2012).

Clinical trials which established the proton therapy role for the management of brain tumors

To justify the additional costs associated with proton therapy, particularly for brain and non-CNS tumors, high-quality data is essential in the era of evidence-based medicine. A model-driven validation approach, enriched with an experimental arm outside the traditional randomized controlled trial (RCT) paradigm, can facilitate the clinical validation of proton therapy. This approach will generate the best data to provide scientifically sound evidence on how to select patients for proton therapy. For a range of malignancies, including CNS tumors, combining these trials will help optimize the therapeutic balance for value-based cancer management. However, caution is needed, as depending on the study endpoint—such as late toxicity, including radiation-induced tumors—adverse events may emerge after a long interval following proton therapy. Subjects with previous radiation to the head and neck or brain, very extensive lesions which have been described as gliomatosis cerebri are excluded from majority of the studies.

Several databases, including clinicaltrials.gov, CTSU/NRG, EORTC, and PTCOG, were queried, leading to the identification of 43 prospective brain tumor trials activated between 1996 and 2019. Trials that had already evaluated target agents, immune checkpoint inhibitors, or hypoxic-target agents combined with radiation therapy (including protons) were excluded. Of the included trials, 23 (53%) focused on adults, and 12 (30%) focused on pediatric patients, while 3 studies (7%) were for children, adolescents, and

young adults. The most common brain tumors studied were chordoma or chondrosarcoma (7 trials, 16%), meningioma (6 trials, 14%), and low-grade glioma (6 trials, 14%). However, the majority of studies were either not accruing participants (17 trials, 39%) or were still in the activation process (2 trials, 5%). Five studies (12%) had been closed, and 3 studies (7%) had an unknown status.

Other trials

Methods: Thomas E. Merchant and colleagues at St. Jude Children's Research Hospital (Memphis, TN, USA) and the University of Florida Health Proton Therapy Institute (Jacksonville, FL, USA) conducted a single-arm Phase 2 study in patients with craniopharyngioma. The study included subjects aged 0-21 years at the time of enrollment who had not previously undergone radiotherapy or intracystic therapies. These eligible patients were treated with passively scattered proton beams, delivering a dose of 54 Gy (relative biological effect), with a 0.5 cm clinical target volume margin.

Findings: 94 patients were enrolled and treated with surgery and proton therapy between Aug 22, 2011 and Jan 19, 2016.

Gender	Number and percentage
Female	49 (52%)
Male	45 (48%)

Race	Number and percentage
White	62 (66%)
Black	16 (17%)
Asian	2 (2%)
Other races	14 (15%)

Median Age: 9.39 years

As of data cutoff (Feb 2, 2022) – Median follow up was 7.52 years

No death occurred at 3 years.

After 5 years

Adverse effects	Number and Percentage
Necrosis	2 (2%)
Severe vasculopathy	4 (4%)
Permanent neurological conditions	3 (3%)
Decline in vision from normal to abnormal	4(7%) of 54 patients with normal vision at baseline

Most common grade 3-4 adverse events

Adverse Events	Percentage
Headache	6%
Seizures	5%
Vascular disorders	6%

Interpretation: When compared to photon therapy proton therapy showed improved cognitive outcomes. Children and adolescents have high tumor control rate and low severe complications rate when they are treated with limited surgery and postoperative proton therapy for craniopharyngioma. The outcomes which were achieved with this treatment represent a new benchmark to which other regimens can be compared. (Merchant et al.,2023)

Proton therapy for adult brain tumors

Patient with benign and low grade brain tumors might show some clinical benefit from proton therapy. A substantial number of low grade glioma (LGG) patients are long term survivors. Plan comparative studies have shown the proton therapy potential to decrease radiation dose that are delivered to OARs. A study that applied an escalated boost with protons to a total dose upto 90 Gy (RBE) lead to the improvement in tumor control rate and median survival time. In low grade benign tumors some of the meningiomas can also be considered. The choice of treatment for the symptomatic or progressive meningioma is the total surgical resection. For all kinds of meningiomas surgery is not suitable and radiation therapy is therefore often indicated. Meningiomas of large and complex shaped are located close to brainstem, optical nerve, pituitary gland and cochlea however may present a challenge in therapy and for this the protons may provide possibilities of dose esclation

for non benign meningiomas. In a number of countries including Switzerland, Germany, Sweden and USA eight retrospective studies delivering proton therapy were conducted and the sample size ranged from 39 to 170 participants. Four studies included Grade 1-3 meningioma, two studies included Grade 1 -2 and one Grade one meningioma only. In two studies patients with Grade 2-3 meningioma received combination of photons and carbon ions whereas patients with Grade 1 received only proton therapy. Local control rates of five years for low risk meningioma were better (94-100 %) when compared with meningioma of high risk (49-88%) and in four studies was found that tumor grading was found to be of prognostic significance in univariate analysis. The toxicity induced by proton therapy was moderate and the rate was 3.6-12.8% Grade greater than or equal to 3 late effects (Weber et al., 2020).

Due to steep fall of dose at depth which is characterized by Bragg peak the proton beam therapy (PBT) offers dosimetric advantages over photon radiation therapy. Tumor control, late toxicity and quality of life in adults with primary brain tumors are evaluated in number of studies (Stross et al., 2020). Reduction in doses for the left temporal lobe and normal brain tissue translated into lower estimated probabilities of impairment in specific neurocognitive test scores after proton therapy. There was reduction in probability of impairment in COWAT (letter S) test from 6.8% to 5.4% when the mean dose was reduced from 1490 to 1092 cGy in EQD2 to the left temporal lobe ($P<0.001$). Similar results were seen the normal brain the dose was reduced from 750 to 451 cGy in EQD2; $P<.001$), the impairment probability in the WAIS-IV coding test was reduced from 5% to 4.1%. When compared with photon therapy the proton therapy (PT) is able to reduce the dose to normal brain structure and also there was reduction in the average mean dose to most of the analyzed structures (Petruccelli et al., 2023).

Proton Therapy for Pediatric Brain Tumors

Cancer affects more than 380,000 children aged 0-19 years globally each year, making it the leading cause of childhood deaths in high-income countries (HICs). The toxicity resulting from treatments in patients with primary brain cancers often leads to significant morbidity for childhood cancer survivors (CCS). When compared to standard photon therapy, proton therapy has shown its ability to more precisely target tumors, sparing surrounding normal tissues, including critical organs-at-risk (OARs). This precision has made proton therapy a widely accepted radiation modality for treating various childhood malignancies. The advantages of proton therapy for brain tumor irradiation include better sparing of healthy brain tissue and other OARs, such as the cochlea, pituitary gland, hippocampus, optic structures, and brainstem. Additionally, proton therapy allows for excellent sparing of organs anterior to the vertebral bodies, such as the spinal cord, using posterior proton field arrangements (Weber et al., 2020).

Pediatric brain tumors for which proton is used most commonly are

- Craniopharyngiomas
- Ependymomas
- Germ cell tumors,
- Low grade gliomas
- Meduloblastomas and
- Atypical teratoid / rhabdoid tumors (ATRT)

The likelihood of late CNS toxicity is reduced when protons are used to treat children with brain tumors, as the integral dose to the brain is minimized—particularly in very young patients with tumors such as ATRTs, ependymomas, or medulloblastomas. Multimodal treatment, combining surgery, chemotherapy, and radiotherapy, is essential for managing pediatric CNS malignancies, and advances in these treatments have led to more favorable outcomes and longer survival rates. Among pediatric solid tumors, brain tumors are the most common. Proton therapy is classified as low linear energy transfer (LET) radiation and has a similar relative biological effectiveness (RBE) to photon therapy, typically considered to be 1.1. Proton beams feature the Bragg peak, which delivers the dose to the tumor volume while spreading out (spread-out Bragg peak or SOBP). The energy before and after the peak is almost zero, meaning that the dose to normal tissue surrounding the tumor is significantly reduced compared to photon radiotherapy. This property is particularly beneficial for pediatric tumors located near critical normal tissues that should be avoided during irradiation. Merchant et al. suggested that proton therapy consistently reduces low and intermediate-dose areas (0-40 Gy). Organs like the cochlea and hypothalamus, which are relatively small and critical

but not adjacent to the primary tumor volume, can be preserved. This preservation may result in better intelligence retention, endocrine function, and hearing (Mizumoto et al., 2017).

Proton Therapy for Skull base tumors

The incidence of skull base chondrosarcomas (SbChs) and chordomas (SbC) is less than 1 per million, making them very rare tumors. These tumors are typically located near critical organs-at-risk (OARs) and are considered radioresistant, including but not limited to the optic apparatus, brainstem, pituitary gland, and cochlea. Management of SbChs and SbCs typically involves cytoreductive surgery followed by postoperative radiotherapy. However, when evaluating the benefits of proton therapy for skull base tumors, it's important to note that these tumors are rare, and most published studies come from single institutions, with only a few exceptions. Conventional radiotherapy delivering a median dose of 50 Gy has shown a 5-year progression-free survival (PFS) rate of 17% and a 5-year local control (LC) rate of 23% in two proton series involving 17 and 48 patients with SbC and extracranial chordomas. While conventional radiotherapy may provide valuable palliation for these challenging patients, it rarely leads to a cure for chordomas (Weber et al., 2017).

Recent proton therapy studies for skull base tumors (chordoma and chondrosarcoma) in adult patients

By histology for skull base tumors the role of proton therapy is variable. The proton therapy can shield more effectively the remaining normal brain parenchyma for skull base benign tumors such as pituitary adenomas, Craniopharyngiomas and benign meningiomas in a manner that can lower secondary malignancy induced by radiation and potentially cognitive effects (Noel & Gondi. 2016). Without combining other radiotherapies proton therapy itself showed favorable local control and increased survival and the incidence of radiation induced toxicities are low which manifests promising clinical benefits (Nie et al., 2022).

Author (Ref)	Year	Tumor type	Patients	Mean Dose (GyRBE)	Mean FU (months)	Proton Therapy Only	PBS only	Outcome	Positive prognostic factors LC (p<0.05)
Youn et. al	2018	Chordoma	34	69.6	42.8	Yes	Yes	5yLC: 87.3% 5yOS :92.9%	Skull base vs cervical
Fung. et. al	2018	Chordoma	106	(68.4-73.8)	61.0	No	No	5yLC : 88.6%	Tumor volume <25 cc
Demizu et. al	2017	Chordoma and ChSa	68	70	52.6	Yes	Yes	5yLC : 71.1% 5yOS :75.3%	Female gender
Weber et. al	2016	Chordoma and ChSa	222	72.5	50.0	Yes	Yes	7yLC :70.9% 7yLC :93.6% 7yOS :81.7%	Non competitive BS GTV ChSa vs chordoma

Side Effects

The treatment is painless and after the treatment the patient may experience fatigue.

Other side effects include problems on affected skin: Redness, Irritation, Swelling, Dryness Blistering and peeling (Foote et al., 2012).

Conclusion

There are more than 100 distinct types of primary brain tumors, and compared to other cancers, brain tumors have the potential to cause lasting, life-altering physical, cognitive, and physiological impacts on a patient's life. Among the various treatment options, radiotherapy plays a crucial role in optimizing tumor control for Central Nervous System (CNS) tumors. However, radiotherapy is associated with both acute and late adverse effects. Proton therapy is emerging as a promising treatment option, offering dosimetric advantages over photon therapy. It has the ability to better separate uninvolved normal tissues, including critical organs-at-risk (OARs), by directly targeting brain tumors, leading to fewer side effects. However, more studies are needed to assess the full efficacy of proton therapy in treating brain tumors. We hope that in the future, proton therapy will become more widely developed for brain tumor treatment, reducing the risk of adverse effects and bringing us closer to a cancer-free world.

Disclosure

Ethics approval and Consent of the participants

Not Applicable

Consent for publication

Not applicable

Competing Interest

Nil

Consent for publication

Nil

Funding

Nil

Author's Contribution

All authors are equally contributed to this work.

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