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A REVIEW ON PROTON THERAPY OF CANCER

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Abstract

Proton therapy has emerged as an advanced form of external beam radiotherapy that exploits the unique physical property of the Bragg peak to deliver high radiation doses to tumours while minimizing exit dose to surrounding normal tissues. This dosimetrist advantage is particularly relevant in paediatric cancers, central nervous system tumours, head and neck malignancies, and situations requiring re-irradiation, where reduction in late toxicities and preservation of organ function are critical. Clinical evidence demonstrates reduced acute and long-term complications, especially in children, though survival benefits over state-of-the-art photon techniques are less consistently established in adults. Modern intensity-modulated proton therapy (IMPT) enhances conformality but introduces uncertainties such as range variation and variable relative biological effectiveness, which necessitate robust treatment planning. While cost and limited accessibility remain barriers to widespread adoption, health-economic analyses suggest proton therapy may be cost-effective in select patient populations with long life expectancy or high risk of treatment-related morbidity. Emerging directions include adaptive strategies, biological optimization, and ultra-high dose-rate "FLASH" proton therapy, which show promise for further widening the therapeutic window. Overall, proton therapy represents a valuable and evolving modality in cancer management, with strongest justification in pediatric and anatomically complex tumors, and ongoing trials are expected to better define its role across common adult cancers.

Keywords: Proton Therapy, Proton Beam Therapy, Bragg Peak, Cancer Treatment.

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Introduction

In medicine, proton therapy, or proton radiotherapy, is a type of particle therapy that uses a beam of protons to irradiate diseased tissue, most often to treat cancer .The chief advantage of proton therapy over other types of external beam radiotherapy is that the dose of protons is deposited over a narrow range of depth, hence in minimal entry, exit, or scattered radiation dose to healthy nearby tissues .When evaluating whether to treat a tumor with photon or proton therapy, physicians may choose proton therapy if it is important to deliver a higher radiation dose to targeted tissues while significantly decreasing radiation to nearby organs at risk. Research on the role of radiotherapy in the management of cancer has been intensified in the last 2 decades. During the whole course of disease treatment, 60%–70% of all cancer patients need to undergo radiotherapy, mostly with photon therapy, which is delivered with linear accelerators. As the latest research and application of radiotherapeutics, heavy ion therapy especially proton therapy is well-known for its multitude of advantages over photon therapy due to its physical characteristics, known as Bragg peak. Phase II clinical trials on boron neutron capture therapy (BNCT), a binary therapeutic modality based on the nuclear capture and fission reactions that occur when the stable isotope boron-10 is irradiated with neutrons to produce high-energy alpha particles and recoiling lithium-7 nuclei, are being carried out . With low entrance dose and no exiting dose, protons deposit most energy in a certain depth which is near the end of the penetration path, known as the Bragg peak. Because of the favorable feature, lots of patients diagnosed with cancer have been treated with proton therapy for the last 30 years worldwide [1].

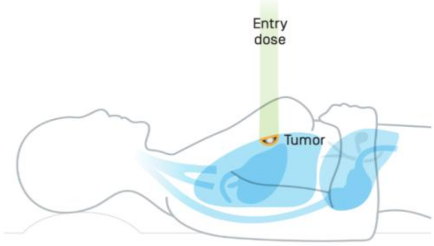

Figure 1: Image of Entry dose.

Charged particle therapy (CPT), which primarily includes proton and heavy-ion therapy, represents one of the most advanced modalities in modern radiation oncology. Unlike conventional photon-based radiotherapy, charged particles deposit their energy in tissue with a sharp peak at a specific depth known as the Bragg peak, followed by an abrupt dose fall-off beyond the target region. This unique physical property allows precise dose localization, minimizing radiation exposure to surrounding healthy tissues and critical organs while delivering higher tumoricidal doses to the malignant volume.

Since the first proposal of using fast protons for radiotherapy by R. R. Wilson in 1946, the field has evolved substantially through advances in accelerator technology, beam delivery systems, and imaging-guided treatment planning. CPT has gained clinical importance for tumours located near radiosensitive structures-such as those of the brain, spine, skull base, and in pediatric oncology-where dose conformity is essential to avoid long-term radiation toxicity.

Despite these advantages, the widespread adoption of charged particle therapy faces significant technical, biological, and economic challenges. The uncertainties in particle range, complex biological effects related to relative biological effectiveness (RBE), and the high costs associated with building and maintaining treatment facilities limit its global accessibility. Moreover, a relative scarcity of randomized clinical trials has left several questions about its comparative efficacy unanswered.

Nevertheless, ongoing research in treatment optimization, imaging integration, and biological modelling continues to enhance the precision and therapeutic potential of charged particle therapy. Protons have unique physical characteristics that allow them to deposit most of their energy at a specific depth in tissue, known as the Bragg peak. This distinct dose distribution enables clinicians to deliver high doses of radiation to the tumour target while significantly sparing normal organs and structures adjacent to it [2]. Clinically, proton therapy has shown promising outcomes in managing cancers such as pediatric tumours, head and neck cancers, prostate cancer, lung cancer, and intracranial malignancies. Its ability to reduce late radiation-induced complications, such as secondary malignancies, growth abnormalities, and organ dysfunction, has been well documented. Charged particle therapy, employing protons and heavier ions such as carbon, has emerged as a major advancement in the field of radiation oncology. Unlike conventional photon (X-ray) therapy, charged particles possess distinct physical and biological properties that enable superior dose distribution and enhanced tumour control. The key advantage lies in the Bragg peak phenomenon, where charged particles deposit most of their energy at a specific tissue depth, resulting in minimal entrance dose and virtually no exit dose beyond the target. This allows for precise tumour irradiation while effectively sparing surrounding normal tissues

The clinical application of particle beams in cancer therapy has expanded rapidly in recent decades, supported by technological progress in accelerator design, beam delivery systems, and image-guided treatment planning. Proton therapy centers have proliferated worldwide, and carbon-ion facilities have demonstrated encouraging results, especially for radioresistant and deep-seated tumours that respond poorly to conventional radiotherapy.

Despite these promising developments, the integration of charged particle therapy into mainstream oncology remains challenged by high costs, limited accessibility, and unresolved biological uncertainties. Factors such as variable relative biological effectiveness (RBE), range uncertainties due to patient anatomy and motion, and the need for rigorous clinical evidence continue to shape research and clinical practice in this field.

Overall, charged particle therapy represents a powerful and precise modality for cancer treatment, combining cutting-edge physics and radiobiology [3].

Moreover, advancements such as pencil beam scanning (PBS) and intensity-modulated proton therapy (IMPT) have further enhanced the precision and conformality of treatment delivery, enabling complex tumour shapes to be treated with minimal exposure to healthy tissues. Proton therapy has evolved as one of the most sophisticated modalities in radiation oncology, offering superior dose conformity and sparing of healthy tissues compared with conventional photon-based radiotherapy. The introduction of intensity-modulated proton therapy (IMPT) represents a significant leap forward in precision radiation delivery, utilizing pencil beam scanning (PBS) technology to shape and modulate the proton beam intensity across the tumour volume. This allows clinicians to achieve highly conformal dose distributions, reducing radiation exposure to surrounding organs-at-risk while maintaining adequate tumour coverage

The concept of intensity modulation, initially developed in photon therapy (IMRT), has been successfully adapted to proton therapy with the advent of advanced beam control and treatment planning algorithms. IMPT enables multi-field optimization, where dose distributions from multiple beam angles are calculated simultaneously to achieve optimal therapeutic outcomes. This innovation has expanded the clinical applicability of proton therapy, particularly for complex and irregularly shaped tumours located near critical anatomical structures.

Recent technological progress-including real-time imaging, adaptive planning, and motion management techniques-has further improved the accuracy and robustness of IMPT. However, several challenges persist, such as uncertainties in proton range estimation, motion-induced dose variations, and the need for more efficient computational and quality assurance methods. Moreover, continued clinical evidence is essential to validate the long-term benefits of IMPT compared with other advanced radiation modalities [4].

Aim and objective

Aim

Proton therapy in cancer is to deliver highly targeted radiation to tumours while minimizing damage to surrounding healthy tissues.

Objective:

- To deliver precise radiation doses that conforms closely to the tumor shape.
- To maximize tumour control and treatment effectiveness.
- To minimize radiation exposure and damage to surrounding healthy tissues and critical organs.
- To reduce acute and long-term side effects compared to conventional radiotherapy.
- To enable treatment of tumours located near sensitive structures that are difficult to treat with conventional radiation.
- To improve overall patient quality of life during and after treatment.

History and Development

Proton therapy is a cutting-edge form of radiation treatment that uses charged particles-protons-rather than traditional X-rays (photons) to target and destroy cancer cells. The central principle behind proton therapy is its unique depth-dose distribution, known as the Bragg peak, which allows doctors to focus radiation precisely on the tumour with minimal impact on nearby healthy tissues. This precise targeting is especially valuable when treating. The concept of using protons for medical treatment was first proposed by Robert R. Wilson in 1946.Path (Bragg peak), which could be target tumours while sparing surrounding. He recognized that protons deposit most of their energy at the end of their tissues. Proton therapy, a type of particle therapy, has its conceptual origins in the mid-20th century, largely attributed to the pioneering work of Robert R. Wilson. In his seminal 1946 paper, "Radiological Use of Fast Protons," Wilson proposed that protons could be used as a form of radiation therapy due to their unique physical properties, most notably the Bragg peak. The Bragg peak describes the phenomenon in which charged particles, such as protons, deposit the majority of their energy at a specific depth in tissue, allowing for maximum dose delivery directly to the tumour while sparing surrounding healthy tissues. This characteristic differentiated protons from conventional photon-based radiotherapy, which delivers energy along the entire path of the beam, thereby affecting both tumour and normal tissue. Wilson's insight laid the foundational principle for all subsequent research and development in proton therapy.

Following Wilson's theoretical proposal, technological and clinical advancements gradually brought proton therapy from concept to practice. In the 1950s and 1960s, physicists and medical researchers began exploring the use of cyclotrons and synchrotrons to accelerate protons to the high energies required for clinical applications. The first experimental treatments were carried out at research facilities such as the Lawrence Berkeley National Laboratory, where patients with selected cancers received proton therapy in a controlled research setting. These early clinical studies confirmed that protons could be delivered safely and precisely to deep-seated tumours, providing a clinical validation of Wilson's theoretical predictions [5]. The first clinical use of protons occurred in 1954 at the Lawrence Berkeley Laboratory (LBL) in California, primarily for neurological disorders and pituitary tumours [6]. The first clinical use of proton beams for medical treatment began in the 1950s at physics research laboratories, notably at the Lawrence Berkeley Laboratory in the United States and the Harvard Cyclotron Laboratory (HCL). These early treatments primarily targeted intracranial and ocular tumours due to the precise targeting capabilities of proton beams and the limited imaging and planning tools of the time. The development of proton therapy has been a gradual evolution from theoretical physics to sophisticated clinical practice, with key milestones shaping its current application. Following Robert R. Wilson's seminal 1946 proposal on the radiological use of fast protons, which highlighted the Bragg peak and its potential to maximize tumour dose while sparing healthy tissue, researchers began exploring practical methods for delivering proton beams to patients. While early experimental treatments in the 1950s and 1960s demonstrated feasibility, it was during the 1970s that the field began to formalize systematic treatment planning approaches, exemplified by the work of Goitein and Koehler in 1975 [7]. The 1970s and 1980s marked a significant phase in the clinical development of proton therapy, driven by advancements in imaging, such as computed tomography (CT), and improvements in treatment planning systems. These technologies allowed clinicians to more accurately map tumour geometries and adjust beam delivery accordingly. During this era, HCL became the leading center for proton therapy, treating thousands of patients and conducting studies that established clinical efficacy for ocular melanomas and skull base tumours [8].

Physical Principles of Proton Therapy

Basic principle
Energy Deposition and the Bragg Peak
Beam delivery techniques
Range and energy modulation

Basic Principle

Proton therapy is a type of external beam radiotherapy that uses charged particles (protons) instead of photons (X-rays) to deliver radiation to tumours. The unique energy deposition pattern of protons, known as the Bragg peak, allows for precise dose localization within the tumour while minimizing exposure to surrounding normal tissues [9].

Energy Deposition and the Bragg Peak

As protons travel through tissue, they lose energy gradually by ionizing atoms along their path .Beyond the Bragg peak, the dose drops rapidly to near zero-this is the key advantage over photon beams, which deposit energy exponentially throughout the tissue [10].

Beam Delivery Techniques

There are two primary beam delivery systems Passive Scattering: Uses scattering foils, collimators, and compensators to shape the beam; simpler but less flexible .Pencil Beam Scanning (PBS): Uses magnetic fields to scan a narrow proton beam spot-by-spot and layer-by-layer; allows Intensity Modulated Proton Therapy (IMPT) for precise dose shaping [11].

Range and energy modulation

The range of protons in tissue depends on their initial kinetic energy and can be precisely controlled by adjusting the accelerator's output .For example, 250 MeV protons can penetrate up to approximately 38 cm in water-equivalent material .Range modulators, degraders, and energy selection systems are used to fine-tune the beam to match the tumour's depth .Accurate CT-based treatment planning with density corrections ensures that the Bragg peak is positioned within the tumour [12].

The Bragg Peak and Dose Distribution

Bragg Peak

When protons travel through tissue, they gradually lose energy due to ionization and excitation of atoms along their path .As protons slow down, their energy loss per unit path length increases, culminating in a sharp maximum at a specific depth — known as the Bragg Peak .Beyond this point, protons come to rest, and the dose rapidly falls to nearly zero, meaning no exit dose is delivered to healthy tissues behind the tumour. Except for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radio activities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators. In his seminal 1946 paper, Robert R. Wilson first introduced the concept of using fast protons for radiotherapy, emphasizing the unique depth-dose characteristics of protons, now known as the Bragg peak. The Bragg peak describes the phenomenon in which charged particles, such as protons, deposit minimal energy while traversing tissue, with a sharp rise in energy deposition occurring near the end of their range. This results in a pronounced peak in dose at a specific depth, corresponding to the tumour location, followed by a rapid fall-off beyond the target. Unlike conventional X-rays, which gradually deposit energy along their path, protons allow for precise dose delivery that maximizes tumour irradiation while sparing surrounding healthy tissues. This property is particularly advantageous for treating tumours located near critical organs or in pediatric patients, where minimizing radiation exposure to normal tissues is crucial. Wilson's identification of the Bragg peak provided the theoretical foundation for all subsequent developments in proton therapy, including passive scattering and pencil beam scanning techniques, which aim to exploit this precise energy deposition. The Bragg peak remains the defining feature that distinguishes proton therapy from conventional photon-based radiotherapy, enabling highly conformal and targeted cancer treatment [13].

Depth–Dose Distribution

Photons (X-rays): Deliver a high entrance dose and gradually attenuate with depth — meaning normal tissues in front and behind the tumour receive significant dose .Protons: Have a low entrance dose, a sharp Bragg peak at tumour depth, and almost no exit dose — producing a superior depth–dose distribution. Current conventional radiotherapy techniques, utilizing both low and high energy photons and electrons, are highly successful in the treatment of small localized cancers. This is often accomplished with preservation of the structural and functional integrity of adjacent tis sues. However, larger tumors are less likely to be cured at doses of radiation that are still within the tolerance of adjacent normal tissues [14].

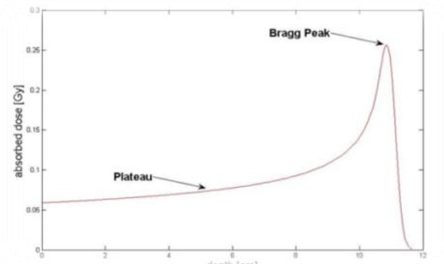

Figure 2: Image of Depth–Dose Distribution

Types of Proton Therapy Delivery

- Passive scattering
- Pencil beam scanning

Passive scattering

This traditional method spreads the narrow proton beam using physical scattering materials, such as scatter foils, before shaping the beam .The process produces a wide, homogeneous dose distribution, but offers less precision near the edges of the target compared to modern methods .Most long-term clinical data in proton therapy come from passive scattering systems [15]. In passive scattering, a physical material is placed in the beam path to scatter and hence broaden the beam; of note, as protons exit the cyclotron they travel in a narrow pencil beam. Subsequent collimation allows the lateral extent of the beam to be shaped to the target width. To cover the target's extent in depth a spread out Bragg peak (SOBP) is created with the help of a range modulating wheel. A range modulator allows generation of different proton energies and resultant Bragg peaks at varying depths such that in combination a SOBP is created [16]. Passive scattering is one of the earliest and most widely used methods for delivering proton therapy. In this technique, a narrow proton beam is broadened and shaped to cover the tumour volume using physical devices such as scatterers, collimators, and compensators. Scatterers spread the beam laterally, while custom-made collimators and compensators conform the dose to the tumor's shape in three dimensions. This method allows the treatment of complex tumour geometries while taking advantage of the Bragg peak to minimize dose beyond the target. Passive scattering is relatively simple to implement and has been used extensively in clinical practice; however, it has some limitations, including increased neutron production and less precise dose conformity compared to modern techniques like pencil beam scanning. Despite these limitations, passive scattering remains a reliable and effective approach for many proton therapy applications, particularly when robust and reproducible dose delivery is required.

Pencil Beam Scanning

This newer technique uses magnets to actively steer a thin beam ("pencil beam") of protons across the tumour .By modulating the energy and position layer by layer, the dose can be "painted" onto the tumour with vastly improved conformity and sparing of healthy tissue .Pencil beam scanning enables sophisticated treatments like intensity-modulated proton therapy (IMPT), which is analogous to IMRT in photon therapy, allowing for more complex tumour shapes and greater sparing of normal tissue [17].

Pencil beam scanning (PBS), also known as intensity-modulated proton therapy (IMPT), is an advanced method for delivering proton therapy. In this technique, the proton beam is divided into very narrow "beamlets" that are magnetically steered across the tumour in a precise, layer-by-layer fashion. Each beamlet's intensity and position are modulated to conform the dose closely to the three-dimensional shape of the tumour. Unlike passive scattering, which relies on physical devices to spread and shape the beam, pencil beam scanning allows for highly flexible and precise dose distributions with minimal exposure to surrounding healthy tissues. This method can treat complex tumour geometries, reduce neutron contamination, and enable dose painting, where different areas of the tumour receive different doses according to clinical requirements. PBS has become the preferred approach in modern proton therapy centers due to its superior dose conformity, sparing of normal tissues, and adaptability to advanced treatment planning algorithms.

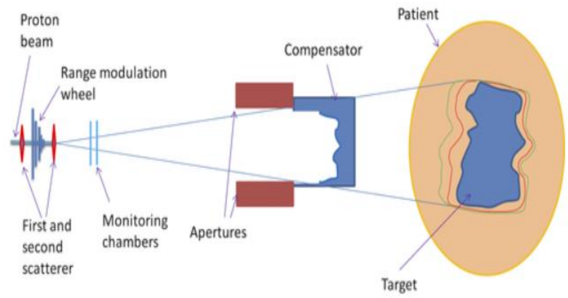

Figure 3: Image of Pencil beam scanning.

Biological Effectiveness of Protons

The biological effectiveness of protons in proton therapy is measured by Relative Biological Effectiveness (RBE), which compares the biological damage caused by protons to that caused by conventional photons (X-rays).The actual RBE for protons can vary depending on multiple factors, including tissue type, dose per fraction, linear energy transfer (LET), and biological end point. **Linear Energy Transfer (LET):** Higher LET, particularly near the Bragg peak, increases RBE.

Tissue type and cell characteristics: Different cell types and tissue densities respond differently to proton irradiation.

Dose per fraction and total dose:

Fractionation schemes can affect biological response.

Position along the proton path:

RBE tends to rise at the distal edge of the proton beam [18].

In present years, increasing numbers of reports on treatment outcome and toxicity of patients treated with protons have been published. These encompass (pediatric and adult) chordoma and chondrosarcoma of the skull-base and axial skeleton, and ependymoma and posterior fossa malignancies [19]. While this practice offers a practical solution, ongoing research supports the need for more individualized, dose- and tissue-specific RBE values, especially with advanced delivery techniques like spot-scanning and proton arc therapy. Moving beyond the reduction in integral dose, an emerging area of clinical research and the main focus of this paper is the enhanced biologic effects of proton therapy secondary to increased relative biologic effectiveness (RBE) compared with photon therapy. Clinical studies have shown data that indicates promising outcomes with particle therapy, which in turn suggests that, in addition to reducing integral dose, protons may have different biologic effects [20].

Technology and Equipment Used

The technology in proton therapy for cancer has evolved significantly to enable highly precise and effective radiation treatment .Proton therapy uses charged proton particles accelerated to high energies (70-250 MeV) that deposit most of their dose at a specific depth (Bragg peak), minimizing damage to surrounding healthy tissue compared to conventional photon radiotherapy [21].

Equipments

- ✓ Cyclotron or Synchrotron
- ✓ Beam Transport System
- ✓ Treatment Nozzle
- ✓ Delivery Systems
- ✓ Patient Positioning System
- ✓ Treatment Planning Software

Cyclotron or Synchrotron

These are the core proton accelerators. Cyclotrons spin protons at high speed to accelerate them, producing a continuous beam of fixed energy, while synchrotrons modulate magnetic fields to vary proton energy. Cyclotrons are more common due to their compactness and reliability

Beam Transport System

Magnets guide the proton beam from the accelerator to the treatment rooms through a beamline in vacuum conditions to preserve beam quality [22].

Treatment Nozzle

In the treatment room, the beam passes through the nozzle containing scanning magnets that steer the beam to the tumour. The nozzle also contains instrumentation for dose monitoring and beam positioning. The beam spot size is about 1 cm, and scanning delivers many small spots to uniformly cover the tumour volume.

Delivery Systems: Passive Scattering:

Uses scatterers, collimators, and compensators to shape the beam, an older method [23].

Pencil Beam Scanning

A modern technique that magnetically scans a narrow proton beam across the tumour with high precision, allowing intensity-modulated proton therapy (IMPT) for optimal dose conformity and sparing healthy tissue

Patient Positioning System: Robotic systems precisely position the patient to ensure accurate targeting of the proton beam every session

Treatment Planning Software

Integrates imaging modalities like CT, MRI, PET with dose calculation and optimization algorithms to create personalized treatment plans that maximize tumour irradiation while minimizing exposure to healthy tissues [24].

Figure 4: Image of Technology and equipment used.

Patient Selection and Indications

Patient Selection in Proton Therapy

Proton therapy is usually selected for patients who are most likely to benefit from its physical and clinical advantages over conventional radiation therapy, especially in reducing damage to surrounding healthy tissues. Approximately 5% to 15% of all patients receiving radiation therapy may benefit preferentially from proton therapy. Model-based selection is common for head and neck cancers, and individualized approaches are used for other types, including breast, lung, and brain cancers. Proton therapy (PBT) is high-precision radiotherapy with substantial costs, so careful patient selection is crucial to maximize clinical benefit and cost-effectiveness. Ahern (2020) emphasizes that patients should be chosen based on clinical benefit, tumour type, location, and potential to spare critical organs. Special consideration is given to paediatric patients, head and neck cancers, and tumours near radiosensitive structures, where the dosimetric advantages of protons can reduce long-term side effects.

Models for Selection

Markov modelling and other health economic models are used to simulate treatment outcomes, factoring in tumour control, normal tissue toxicity, quality of life, and long-term complications. These models allow comparison of proton therapy with conventional photon therapy, helping prioritize patients who will gain the most benefit [25].

Indications

According to the 2024–2025 guidelines, cancers with absolute indications for proton therapy include: Primary central nervous system (CNS) tumours, including malignant and benign tumours situated near critical structures like the optic nerve, brainstem, or spinal cord. Advanced (T4) or unresectable head and neck cancers. Paranasal sinus and other accessory sinus cancers, especially when involving the base of the skull. Skull-based tumours such as chordoma or chondrosarcoma.(26)

Table 1: Tumour types commonly treated.

Type of Tumour	Reason for Using Proton Therapy
Brain Tumours	Protects healthy brain tissue and critical organs.
Pediatric Tumours	Reduces long-term radiation side effects in children.

Head and Neck Cancers	Minimizes dose to spinal cord and salivary glands.
Prostate Cancer	Spares bladder and rectum from excess radiation.
Lung Cancer	Lowers radiation exposure to heart and lungs.
Liver Tumours	Protects surrounding healthy liver tissue.[27]

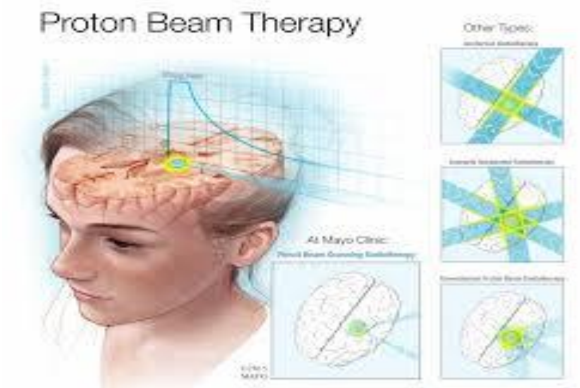

Figure 5: Image of Treatment of Brain Tumour.

Brain Tumour Treatment

Treatment planning in proton therapy of cancer:

Figure 6: Image of Treatment planning in proton therapy of cancer.

Treatment planning in proton therapy is a crucial process that ensures precise radiation delivery to the tumour while minimizing exposure to surrounding healthy tissues. The treatment plan is then evaluated using dose–volume histograms (DVHs) and 3D dose maps to ensure adequate tumour coverage and compliance with dose constraints for critical structures .Overall, treatment planning in proton therapy integrates imaging, physics, and computer optimization to deliver precise, patient-specific radiation therapy that enhances tumour control and reduces side effects [28].

Treatment Process and Patient Experience

The treatment process in proton therapy involves precise imaging, planning, and delivery of targeted proton beams to the tumour with minimal exposure to surrounding tissues, offering patients a comfortable and non-invasive experience [29].

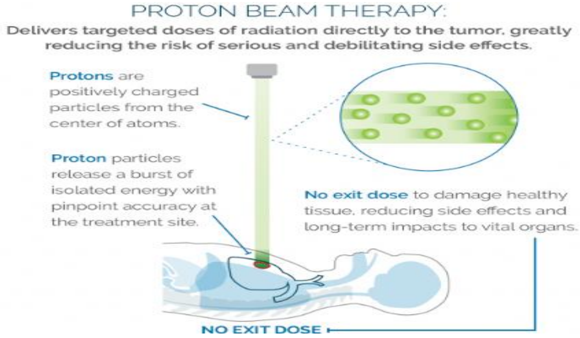

Figure 7: Image of Treatment process and patient experience.

The treatment process in proton therapy of cancer involves several precise and patient-cantered steps. It begins with an initial consultation and assessment, where oncologists evaluate medical records and imaging to determine eligibility for proton therapy. This is followed by simulation and imaging, using CT or MRI scans to map the tumour and design immobilization devices to ensure accurate positioning. Next, treatment planning is performed using advanced software to define target volumes, organs at risk, and optimal proton beam paths for precise dose delivery. Quality assurance (QA) procedures verify the accuracy of equipment and patient setup before therapy begins. During treatment delivery, patients undergo multiple sessions (fractions), each lasting about 15–30 minutes, with image-guided verification to ensure precision. After completing therapy, follow-up and monitoring are conducted to assess treatment response and manage any side effects [30].

Benefits and Advantages of Proton Therapy

1. Precise Tumour Targeting
2. Sparing Healthy Tissue
3. Reduced Side Effects
4. Effective for Pediatric Cancers
5. Option for Recurrent Tumours
6. Improved Quality of Life [31].

Proton therapy allows precise tumour targeting with minimal damage to surrounding healthy tissues, reducing side effects and the risk of secondary cancers [32]. The benefits and advantages of proton therapy in cancer treatment arise from its unique physical and biological properties. Proton therapy delivers a highly precise dose of radiation using the Bragg peak phenomenon, where protons deposit maximum energy directly at the tumour site with minimal exit dose. This allows for superior tumour targeting and sparing of surrounding healthy tissues and critical organs, reducing the risk of acute and long-term side effects compared to conventional photon therapy. It is especially beneficial for pediatric patients, as it minimizes radiation exposure to developing tissues and lowers the likelihood of secondary cancers later in life. Proton therapy also offers significant advantages in treating tumours located near sensitive structures such as the brain, spinal cord, heart, or eyes, where precision is critical. Additionally, the treatment provides better dose conformity, enabling escalation of tumour doses while maintaining safety for normal tissues. Patients often report improved quality of life due to fewer complications and faster recovery [33].

Acute and Long Time Side Effects

The acute and long-term side effects in proton therapy of cancer are generally fewer and less severe compared to conventional photon radiotherapy, due to the precise dose distribution of protons. Acute side effects may occur during or shortly after treatment and typically include mild fatigue, skin irritation, localized redness, hair loss at the treatment site, and temporary swelling. These effects are usually short-lived and subside soon after therapy completion. Long-term side effects depend on the tumour site, dose, and patient factors but are notably reduced because proton beams minimize radiation exposure to surrounding healthy tissues. Possible late effects can include fibrosis, hormonal changes, or neurocognitive effects when treating head or spine tumours, but the risk remains significantly lower than with photon therapy. In pediatric patients, proton therapy reduces the likelihood of growth abnormalities and secondary malignancies, offering major long-term benefits [34].

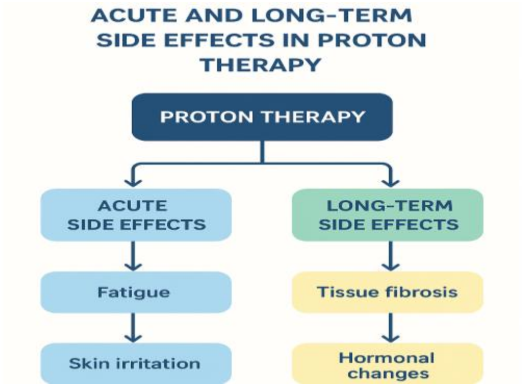

Figure 8: Image of Acute and long time side effects.

Cancer is the second leading cause of death worldwide. Around half of all cancer patients undergo some type of radiation therapy throughout the course of their treatment [35].

Clinical Outcomes and Evidences

Cancer constitutes an enormous burden on society in more and less economically developed countries alike. The occurrence of cancer is increasing because of the growth and aging of the population, as well as an increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development. Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide. Over the years, the burden has shifted to less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide .Proton beam therapy (PBT) shows promising outcomes in locally advanced pancreatic cancer, with 1- and 2-year local progression-free survival rates of 89.7% and 74.5%, respectively [36]. Global cancer statistics show that cancer is a leading cause of death, with incidence and mortality varying widely between regions due to differences in risk factors, healthcare access, and early detection. Lung, breast, colorectal, prostate, and stomach cancers are the most common and account for a large portion of cancer-related deaths.

Early diagnosis is crucial for improving survival, as localized cancers have significantly better outcomes than advanced-stage disease. Disparities in screening, treatment availability, and adherence to evidence-based protocols lead to variable outcomes across countries. Lifestyle and environmental factors, such as tobacco use, obesity, infections, and occupational exposures, strongly influence cancer risk and prognosis.

The global burden of cancer is increasing, highlighting the need for effective prevention, early detection, and equitable access to modern therapies. Epidemiological evidence guides healthcare planning, resource allocation, and clinical decision-making to improve patient outcomes worldwide. Proton therapy offers improved dose distribution compared to conventional photon radiotherapy, leading to better sparing of healthy tissues and potentially fewer side effects while maintaining effective tumour control. Although incidence rates for all cancers combined are nearly twice as high in more developed than in less developed countries in both males and females, mortality rates are only 8% to 15% higher in more developed countries. This disparity reflects regional differences in the mix of cancers, which is affected by risk factors and detection practices, and/or the availability of treatment. Risk factors associated with the leading causes of cancer death include tobacco use (lung, colorectal, stomach, and liver cancer), overweight/obesity and physical inactivity (breast and colorectal cancer), and infection (liver, stomach, and cervical cancer) [37].

Limitations and Challenges

While there is clinical evidence to support the clinical use and continued study of proton therapy, such evidence is not of sufficiently high level to convince many of the third-party payors. Nevertheless, as larger numbers of patients are being rerated with proton therapy, and with research to better understand physical, biological and immunological basis of clinical effects [38].

Limited Availability and Access: Proton therapy centers are few and costly, limiting access for many pediatric patients. Travel and financial constraints may delay or restrict treatment.

Long-term Outcomes and Data Gaps: Although early results indicate promising tumour control and reduced toxicity, long-term survival, neurocognitive outcomes, and secondary malignancy risks remain incompletely characterized due to limited follow-up.

Technical Challenges: Treatment of very young children requires immobilization, anaesthesia, and precise imaging, increasing complexity and resource requirements. Small patient size and tumour proximity to critical structures demand highly accurate planning to avoid normal tissue damage.

Integration with Chemotherapy: Timing and combination with systemic therapies, especially in infants, can be challenging and may affect overall outcomes.

Cost and Health Economics: Proton therapy is more expensive than conventional radiation, raising questions of cost-effectiveness, especially when long-term benefits are not fully quantified.

To date, the majority of clinical evidence supporting the use of proton therapy comes from small non-randomized studies. A small number of such trials have been completed and several others are currently accruing [39]. Proton radiotherapy (PRT) offers precise dose delivery and potential reduction in normal tissue toxicity in pediatric rhabdomyosarcoma. However, several limitations and challenges exist. Long-term outcome data, including survival, local control, and late toxicities, remain limited, making definitive conclusions difficult. The treatment is technically complex, requiring precise immobilization, imaging, and planning, especially for tumors near critical structures.

Small patient cohorts in clinical trials limit the statistical strength and generalizability of findings. Coordinating PRT with chemotherapy and surgery can be challenging, particularly in very young children. Additionally, PRT is expensive and available only at specialized centers, restricting access for many patients. The need for specialized infrastructure and trained personnel further complicates widespread adoption.

Overall, while proton therapy shows promise for reducing toxicity and preserving function in pediatric rhabdomyosarcoma, its limited long-term data, high cost, technical demands, and accessibility constraints remain significant challenges for clinical practice.

Firstly, high cost and limited availability are major constraints. Proton therapy centers require large and expensive infrastructure, such as cyclotrons or synchrotrons, and heavily shielded treatment rooms, making the setup and operational costs significantly higher than traditional radiotherapy facilities [40]. Consequently, accessibility remains restricted to specialized centers worldwide. Secondly, range and dose uncertainties pose technical challenges. The precision of proton beam delivery depends on accurate estimation of tissue density and stopping power, which can be affected by anatomical changes, organ motion, or setup errors. These factors may lead to under dosing of tumours or overdosing of nearby normal tissues [41]. Moreover, limited clinical evidence comparing long-term outcomes with photon therapy restricts broader adoption. While proton therapy shows theoretical and dosimetric advantages, randomized clinical trials confirming significant survival benefits in many cancers are still limited [42].

Further Directions and Research

Protons are considered to have an advantage due to their physical characteristics in that they deposit lower dose outside the target volume and that they have lower integral dose in the body as a whole. On the other hand, because of their scattering characteristics, they have a wider penumbra [43]. Their proof-of-concept study demonstrated that dynamic collimation could sharpen the edges of the proton beam, potentially allowing for higher precision in treating complex tumour geometries.

Future research directions include optimizing the DCS for clinical implementation, including integration with treatment planning systems, real-time beam control, and motion management for moving targets. Further studies are also needed to assess dosimetric advantages, potential reduction in normal tissue toxicity, and clinical outcomes compared to conventional spot-scanning techniques.

Additionally, exploring the combination of DCS with intensity-modulated proton therapy (IMPT) could further enhance treatment precision and reduce radiation exposure to adjacent critical structures. Research into automation, safety, and cost-effectiveness will be essential for widespread adoption.

Overall, innovations like dynamic collimation represent promising avenues for improving the therapeutic ratio of proton therapy, highlighting the ongoing need for technological development, preclinical validation, and clinical trials to translate these advances into routine cancer care. While a large volume of tissue away from the target may receive considerably lower dose, the dose to volumes of normal tissues immediately surrounding the target volume may be higher for protons. It is possible to reduce the penumbra of beams incident on the patient using apertures and minimizing the scanning beam spot sizes [44]. Proton therapy continues to evolve with rapid advancements in technology, clinical research, and biological understanding. Future directions aim to enhance treatment precision, accessibility, and cost-effectiveness while expanding clinical evidence for its benefits across cancer types. One key area of research is technological innovation. Developments such as pencil beam scanning (PBS), intensity-modulated proton therapy (IMPT), and adaptive proton therapy allow more conformal dose delivery and real-time adjustment for anatomical changes, improving tumour control and minimizing toxicity [45]. Integration of image-guided proton therapy (IGPT) using MRI and cone-beam CT enhances accuracy in target localization and motion management [46]. Another major direction is the exploration of biological optimization. Research on relative biological effectiveness (RBE) and the linear energy transfer (LET) of protons seeks to improve biological dose modelling, enabling better prediction of tissue responses and individualized treatment planning [47-52].

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

Both are contributed equally

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Not Applicable

Conclusion

Proton therapy has revolutionized the field of radiation oncology by offering superior dose precision and tissue sparing compared to conventional photon therapy. Its distinct physical advantage, defined by the Bragg peak, enables maximal energy deposition at the tumour site while minimizing exposure to adjacent normal tissues. This makes it particularly effective for pediatric cancers, central nervous system tumours, and malignancies near critical structures. Clinical evidence supports proton therapy's role in improving local control, reducing acute and late toxicities, and enhancing patients' quality of life. Despite these benefits, challenges persist, including high infrastructure costs, limited accessibility, and technical complexities related to dose uncertainties and motion management. Ongoing research focuses on adaptive proton therapy, intensity-modulated proton therapy (IMPT), and biological optimization to enhance treatment precision and outcomes. As technology advances and costs decrease, proton therapy is expected to become more widely available, establishing itself as a cornerstone in precision cancer radiotherapy for both adult and pediatric patients.This study has 3 important implications for future research. First, proton therapy's lower observed toxicity and its more favorable association with performance status at least raises the tantalizing possibility that the higher up-front cost of proton therapy may be offset by cost savings from reduced hospitalizations. Second, the lower observed toxicity of proton therapy offers an opportunity to explore clinical trials combining proton therapy with intensified systemic therapy and/or dose-escalated radiotherapy, which may, in turn, improve survival outcomes. The primary objective of the study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the combination, while secondary objectives included preliminary assessment of anti-tumor activity. The trial enrolled patients with locally advanced or unresectable NSCLC and carefully monitored for adverse events.

The study demonstrated that everolimus could be safely administered with thoracic radiotherapy at certain doses, with toxicities being generally manageable. Common adverse events included esophagitis, pneumonitis, fatigue, and hematologic effects, consistent with the known profiles of radiotherapy and everolimus. Dose-limiting toxicities were identified and used to recommend an appropriate dose for future Phase II studies. Although the trial was not powered to evaluate efficacy, early observations suggested potential radio sensitizing effects of everolimus, indicating that mTOR inhibition may enhance the tumoricidal effects of radiotherapy in NSCLC.

The authors concluded that this combination regimen is feasible and warrants further investigation in larger clinical trials to evaluate its therapeutic efficacy, optimize dosing schedules, and better understand the balance between toxicity and anti-tumor benefit. Future studies could explore integration with systemic therapies, biomarker-driven patient selection, and long-term outcomes. Overall, this study supports the rationale for combining targeted molecular agents with radiotherapy to potentially improve outcomes in NSCLC.

Third, in our study, older patients with more comorbid disease were more likely to receive proton therapy and experienced less toxicity; thus, proton therapy may allow older patients with more comorbidities to receive the most effective combined-modality treatments.

Reference

1. Yuan TZ. New frontiers in proton therapy: applications in cancers. Cancer Commun (Lond). 2019;39(61):61. doi:10.1186/s40880-019-0407-3. PMID: 31640788; PMCID: PMC6805548.
2. Loeffler JS, Durante M. Charged particle therapy—optimization, challenges and future directions. Nat Rev Clin Oncol. 2013;10(7):411–424.
3. Durante M, Loeffler JS. Charged particles in radiation oncology. Nat Rev Clin Oncol. 2010;7(1):37–43.
4. Togno M, et al. Advances in intensity-modulated proton therapy: Current status and future directions. Front Oncol. 2020;10:770.
5. Wilson RR. Radiological use of fast protons. Radiology. 1946;47:487–491. doi:10.1148/47.5.487.
6. Tobias CA, Lawrence JH, Born JL, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Res. 1958;18.
7. Goitein M, Koehler AM. Treatment planning for proton therapy. Int J Radiat Oncol Biol Phys. 1975;2(8):789–798.
8. Suit HD, Urie M, Goitein M, et al. Evaluation of proton beams for carcinoma therapy. Cancer. 1992;59(12):2249–2253.
9. Newhauser WD, Zhang R. The physics of proton therapy. Phys Med Biol. 2015;60(8):R155–R209. doi:10.1088/0031-9155/60/8/R155.

10. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012;57(11):R99–R117.
11. International Commission on Radiation Units and Measurements (ICRU). ICRU Report 78: Prescribing, Recording, and Reporting Proton-Beam Therapy. J ICRU. 2007.
12. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: the potential effects of calculational uncertainties. Phys Med Biol. 2014;53:1027–1042.
13. Wilson RR. Radiological use of fast protons. Radiology. 1946;47:487–491.
14. Delaney TF, Kooy HM, editors. Proton and Charged Particle Radiotherapy. Philadelphia: Lippincott Williams & Wilkins; 2008.
15. Chhabra A. Two common methods are available for the delivery of proton therapy: passive scattering and active scanning. 2016.
16. Quan EM, Liu W, Wu R, et al. Preliminary evaluation of multifield and single-field optimization for the treatment planning of spot-scanning proton therapy of head and neck cancer. Med Phys. 2013;40:081709.
17. Mohan R. Spreading and shaping can be achieved by passively-scattered proton therapy (PSPT) or using magnetic scanning of thin beamlets in optimized intensity modulated proton therapy (IMPT). 2022.
18. Lühr A, et al. Relative biological effectiveness in proton beam therapy. Phys Med Biol. 2018;63(1). PMCID: PMC5862688.
19. Chen YL, Liebsch N, Kobayashi W. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. Spine (Phila Pa 1976). 2013;38:E930–E936. doi:10.1097/BRS.0b013e318296e7d7.
20. Holtzman AL, et al. Impact of relative biologic effectiveness for proton therapy. Cancer. 2024. PMCID: PMC11171304.
21. Press RH, et al. Current status and technological advancements in proton therapy. 2024.
22. Levin WP, Kooy H, Loeffler JS, DeLaney TF. Proton beam therapy. Br J Cancer. 2005;93(8):849–854. doi:10.1038/sj.bjc.6602754. PMID: 16189526; PMCID: PMC2361650.
23. Pedroni E, Bohringer T, Coray A, et al. Initial experience of using an active beam delivery technique at PSI. Strahlenther Onkol. 1999;175 Suppl 2:18–20. PMID: 10394388.
24. Lomax A. Intensity modulation methods for proton radiotherapy. Phys Med Biol. 1999;44:185–205. PMID: 10071883.
25. Ahern V. Selecting patients for proton beam therapy. J Med Radiat Sci. 2020.
26. Zientara N, et al. A scoping review of patient selection methods for proton therapy. Radiother Oncol. 2021.
27. Levin WP, Kooy H, Loeffler JS, DeLaney TF. Proton beam therapy. Br J Cancer. 2005;93(8):849–854. doi:10.1038/sj.bjc.6602754.
28. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012;57(11):R99–R117. doi:10.1088/0031-9155/57/11/R99.
29. Smith AR. Proton therapy. Phys Med Biol. 2006;51(13):R491–R504. doi:10.1088/0031-9155/51/13/R26.
30. Smith AR. 2006; Paganetti H. 2012; Lomax AJ. 2008; Mailhot Vega RB. 2020.
31. Newhauser WD, Zhang R. The physics of proton therapy. Phys Med Biol. 2015;60:R155–R209. doi:10.1088/0031-9155/60/8/R155.
32. Newhauser WD, Zhang R. Phys Med Biol. 2015;60:R155–R209.
33. Smith AR. Proton therapy. Phys Med Biol. 2006;51:R491–R504.
34. Mailhot Vega RB, et al. Quality of life and patient-reported outcomes in proton therapy. Cancer. 2020;126(12):2636–2645.
35. International Agency for Research on Cancer. Estimated number of new cases in 2020, world, both sexes, all ages (excluding NMSC). Available from: https://gco.iarc.fr/today/online-analysis-table Accessed 6 March 2023.
36. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. CA Cancer J Clin. 2012;2015:87–108.
37. Sax Institute. Rapid review: Evidence summary on proton beam therapy. 2024.
38. Jimenez RB, Sethi R, Depauw N, et al. Proton radiation therapy for pediatric medulloblastoma and supratentorial primitive neuroectodermal tumors: outcomes for very young children treated with upfront chemotherapy. Int J Radiat Oncol Biol Phys. 2013;21:017.
39. Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. J Clin Oncol. 2014;32:3762–3770. doi:10.1200/JCO.2014.56.1548.
40. Blanchard P, et al. Proton therapy: assessment of clinical evidence. Radiother Oncol. 2016;119(2):195–201.
41. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012;57(11):R99–R117.
42. Astrahan MA. Some dosimetric aspects of proton radiotherapy. Radiat Oncol. 2008;3(1):35.
43. Hyer DE, Hill PM, Wang D, et al. A dynamic collimation system for penumbra reduction in spot-scanning proton therapy: proof of concept. Med Phys. 2014;41:091701. PMID: 25186376.
44. Hyer DE, Hill PM, Wang D, et al. Effects of spot size and spot spacing on lateral penumbra reduction

when using a dynamic collimation system for spot scanning proton therapy. Phys Med Biol. 2014;59:N187–N196. PMID: 25330783.

45. Paganetti H. Proton beam therapy. Phys Med Biol. 2016;61(15):R75–R116.
46. Verburg JM, et al. Image-guided proton therapy: advances and challenges. Br J Radiol. 2018;91(1081):20180276.
47. Paganetti H, van Luijk P. Biological considerations when comparing proton therapy with photon therapy. Semin Radiat Oncol. 2013;23(2):77–87.
48. Verma V, et al. Cancer. 2016;122(10):1483–1501.
49. Lomax AJ. Phys Med Biol. 2016;61(13):R75–R109.
50. Wong W, Yim YM, Kim A, et al. Assessment of costs associated with adverse events in patients with cancer. PLoS One. 2018;13(4):e0196007. doi:10.1371/journal.pone.0196007.
51. Deutsch E, Le Péchoux C, Faivre L, et al. Phase I trial of everolimus in combination with thoracic radiotherapy in non-small-cell lung cancer. Ann Oncol. 2015;26(6):1223–1229. doi:10.1093/annonc/mdv105.
52. Sacher AG, Le LW, Leighl NB, Coate LE. Elderly patients with advanced NSCLC in phase III clinical trials: are the elderly excluded from practice-changing trials in advanced NSCLC? J Thorac Oncol. 2013;8(3):366–368. doi:10.1097/JTO.0b013e31827e2145.