RESEARCH PAPER

Proton Beam Radiation Therapy (PBRT): Evidence-Based Indications, Emerging Innovations, and Future Research Priorities

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ABSTRACT
Proton therapy is a modern breakthrough in radiation oncology. It provides a more accurate alternative to conventional radiation radiotherapy with the use of photons. Proton therapy differs with the other conventional ways of radiations in that it concentrates high radiation on the tumor and the normal tissues around the tumor are not exposed to significant amounts of radiation as in the other methods. Such a strategy will minimize contact with surrounding healthy tissues. Bragg peak phenomenon renders proton therapy to have a clinical advantage. Protons also shed off the majority of their energy at a particular depth within the tumor in this process. This is because it leaves a low dose outside the target. This property enables a much safer protection of normal tissues, which reduces adverse effects of the treatment, as well as ensuring the protection of other vital organs. This review summarizes the physical principles, technological developments and clinical applications of proton therapy, with particular focus on pediatric cancers, tumors of the brain and spinal cord, head and neck malignancies, prostate cancer and ocular tumors. Evidence from clinical studies regarding tumor control, survival outcomes and toxicity profiles is discussed. Although high cost and limited availability remain challenges, continued technological innovation and expanding clinical experience are expected to enhance the role of proton therapy in contemporary cancer care.

Keywords: Bragg peak; Cancer treatment; Proton therapy; Radiation oncology; Tumor targeting.
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1. INTRODUCTION

1.1 Overview of radiation therapy in cancer

Radiation therapy is a key method in cancer treatment. It is used in nearly half of all cancer patients, either on its own or alongside surgery and chemotherapy. It works by delivering high-energy radiation that damages the DNA of cancer cells, impairing their ability to divide and survive. Because cancer cells proliferate rapidly and have limited DNA repair capacity, they are generally more sensitive to radiation than normal tissues[1]. Radiation therapy has evolved considerably from early, imprecise techniques that caused significant normal tissue damage. Advances in imaging, treatment planning, and delivery technologies have led to modern methods like three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT). These methods allow for better targeting of tumors while protecting healthy tissues.[2].

The radiation may be provided with photons, electrons, or charged particles such as protons. The most common is the use of photon-based radiotherapy. Nonetheless, this has a significant disadvantage, the inevitable exit dose subjects the healthy tissues outside the tumor to radiations[3]. As we pay more attention to accuracy and lifelong quality of life, more recent techniques are drawing attention such as the proton therapy, which can minimize the radiation dose to the surrounding tissues. The knowledge of standard

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radiotherapy is relevant to understand the increased use of proton therapy in contemporary cancer therapy[4].

1.2 Limitations of Conventional Photon Therapy

The radiation tolerance of the normal tissues typically restricts the dose escalation in photon therapy. This limitation complicates the treatment of the radioresistant or recurring tumors[5,6]. Revealing more normal tissue puts more risk of long-term side effects such as secondary cancers. Such effects are especially severe in children patients, resulting in developmental problems, neurocognitive, and organ dysfunction (Table 1)[7]. Also, high-dose conformity to irregular shaped tumors or those ones, which lie deep in the body, is still a challenge. This will lead to dose spillover to the surrounding tissues despite the better plans (Table 1)[8]. These difficulties have resulted in the creation and application of proton therapy that have superior dose distributions and protection of normal tissues.[9] (Table 1).

Table 1. Comparison Between Conventional Photon Therapy and Proton Therapy [10]

Parameter	Conventional Photon Therapy	Proton Therapy
Radiation type	X-rays (photons)	Protons (charged particles)
Energy deposition	Continuous dose along entry and exit path	Maximum dose at Bragg peak
Exit dose	Present	Minimal or absent
Dose conformity	Moderate	High
Normal tissue damage	Higher	Significantly reduced
Pediatric safety	Limited due to late toxicity	Highly favorable
Secondary malignancy risk	Higher	Lower
Cost and availability	Lower, widely available	High, limited availability

1.3. Emergence of Proton Therapy

Proton therapy has emerged as an important advancement in radiation oncology to address the limitations of conventional photon-based radiotherapy. Although the physical principles of proton interactions were established in the early twentieth century, clinical adoption was delayed by technological complexity and high costs [16]. Its main benefit is the Bragg peak. This feature allows for delivering the highest dose to the tumor while reducing exposure to nearby healthy tissues (Figure 1)[11]. Early use was confined to research facilities, but advances in accelerator technology, beam delivery, imaging, and treatment planning—particularly compact cyclotrons, synchrotrons, and pencil beam scanning—have enabled routine clinical implementation with high precision [12,13]. Proton therapy is now widely applied in pediatric cancers, CNS tumors, and head and neck malignancies, where toxicity reduction and organ preservation are critical, supported by evidence of improved clinical outcomes and quality of life [14]

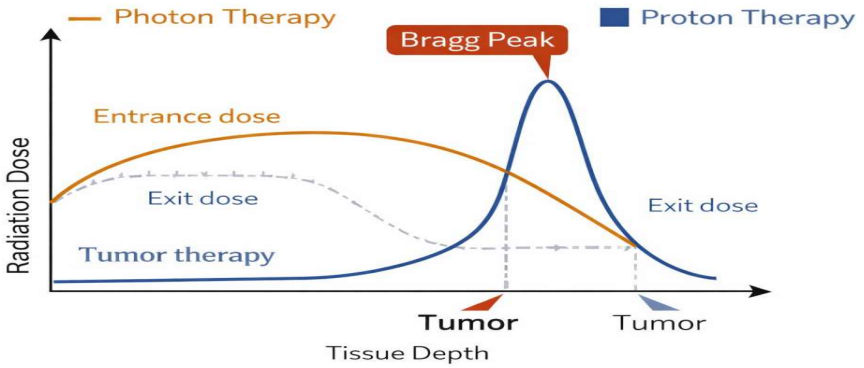

Figure 1: Dose Distribution Comparison Between Photon and Proton Therapy

2. HISTORICAL BACKGROUND OF PROTON THERAPY

2.1 Development of Particle Therapy

Particle therapy arose from early advances in nuclear physics and accelerator technology and differs from conventional X-ray radiotherapy by using charged particles, such as protons and heavy ions, to achieve superior spatial precision [15]. The finite range and characteristic energy deposition of these particles formed the basis for therapeutic use, highlighted by Robert R. Wilson's 1946 proposal of proton therapy based on the Bragg peak [16,17]. Early clinical applications in the 1950s were limited to research facilities. However, ongoing improvements in beam control, imaging, and dosimetry led to the establishment of the first hospital-based proton

therapy center at Loma Linda University Medical Center in 1990. (Table 2) [18–20]. Recent advances, including pencil beam scanning and image-guided proton therapy, have further enhanced dose conformity and normal tissue sparing, establishing proton therapy as a key modality in modern radiotherapy (Figure 2) [21].

Table 2: Historical Timeline of Proton Therapy Development [22]

Year / Period	Milestone	Significance
1919	Discovery of the proton by Ernest Rutherford	Established the proton as a fundamental nuclear particle, forming the scientific foundation for nuclear physics and enabling future applications of protons in medicine, including proton beam therapy.
1931	Ernest O. Lawrence invented the cyclotron	Enabled acceleration of charged particles, including protons, to high energies, making experimental and therapeutic use of proton beams technically feasible.
1946	Robert R. Wilson suggested using accelerated high-energy protons for medical purposes.	Introduced the concept of using the Bragg peak of protons for precise tumor irradiation, marking the theoretical birth of proton therapy in cancer treatment.
Late 1940s–1950s	Biological and radiobiological studies by Lawrence J.H., Tobias C.A. *and* Larsson B.	Provided essential biological evidence of proton beam interactions with tissues, validating the safety and therapeutic potential of proton radiation.
1954	First clinical application of proton therapy	Proton beams were used to target the pituitary gland. This aimed to reduce pituitary function in hormone-dependent breast cancer patients. It marked the first successful use of protons for therapy in humans.
1970s–1980s	Development of X-ray computed tomography (CT), large-field passive beam delivery, and 3D treatment planning systems.	Enabled accurate tumor localization, dose calculation *and* conformal dose delivery, forming the technological backbone of modern proton therapy systems.
1990	Establishment of the first hospital-based proton therapy center at Loma Linda University	Marked the transition of proton therapy from research laboratories to routine clinical practice, accelerating global clinical adoption.
1990s–Present	Rapid global expansion of proton therapy centers	Demonstrated growing clinical acceptance due to improved outcomes and reduced radiation-induced toxicity compared to conventional photon therapy.
Recent years	Introduction of spot-scanning beam technology and intensity-modulated proton therapy (IMPT)	Enabled highly precise, conformal dose delivery with superior sparing of normal tissues, making IMPT the mainstay of contemporary proton therapy.

Figure 2: History of Proton Therapy

2.2 Evolution of Proton Therapy in Clinical Practice

Proton therapy's transition from theoretical concept to established clinical modality marks a pivotal advancement in contemporary radiation oncology. First conceptualized by Robert R. Wilson in 1946, this approach leverages the distinctive Bragg peak phenomenon depositing peak radiation at a precise depth with minimal exit dose setting it apart from traditional photon irradiation[22]. Initial applications in the 1950s and 1960s were confined to research settings and primarily targeted intracranial lesions, as technological barriers impeded broader implementation[22]. Progress in beam transport and imaging technologies throughout the 1970s and 1980s facilitated effective therapy for ocular malignancies, yielding essential proof-of-concept data[23]. A landmark achievement came in 1990 with the opening of the world's inaugural hospital-based proton facility at Loma Linda University Medical Center, spurring expanded utilization for pediatric cases and central nervous system neoplasms. Subsequent innovations, including pencil beam scanning and intensity-modulated proton therapy, have further enhanced target conformity and minimized normal tissue exposure, solidifying proton therapy's role in precision radiation oncology[24].

3. PHYSICAL AND RADIOBIOLOGICAL PRINCIPLES OF PROTON THERAPY

The special properties of charged particles lead to the efficiency of proton therapy. They emit the majority of the energy at a certain depth known as the Bragg peak and then the dose rapidly decreases thus minimizing the radiation dose above the target[25]. Clinicians are able to accurately control the energy so that the Bragg peak is placed in the tumor. In the case of larger or more intricate targets, they overlap peaks to create a spread-out Bragg peak (SOBP). This method gives uniform coverage and it reduces the amount of radiation exposure greatly to the surrounding healthy tissues and can therefore be regarded as a definite alternative to conventional photon beams[26].

Modern proton therapy consists of sophisticated beam delivery techniques such as passive scattering and pencil beam scanning (PBS). Passive scattering supports simple dose modifications, whereas PBS supports the placement of the energy, which makes it possible to utilize intensity-modulated proton therapy (IMPT). This technique is very accurate and this is ideal when dealing with tumors of sensitive locations. Moreover, proton therapy will greatly lower the total dose to the healthy tissues. This has distinct advantages on children, and patients who are treated again after radiation [27].

Radiobiologically, protons are analogous to low linear energy transfer (LET) radiation such as photons, except that they exhibit a small enhancement of LET at the distal Bragg peak edge. This multiplication causes further damage of the cells[28]. Usually, proton therapy possesses the relative biological effectiveness (RBE) of approximately 1.1; nonetheless, the value varies depending on tissue characteristics, dose rate given, and the location of the beam, and it is, therefore, essential to plan proton therapy carefully and continue the research processes[29].

The damage of DNA by proton radiations takes place by direct ionization and also indirectly by generating free radicals. More intricate DNA damage, especially clustering of double-strand breaks, is observed with the higher ionization density around the Bragg peak. Cancer cells can hardly repair these injuries. This process enhances the rate at which the tumors are controlled without causing much toxicity to the adjacent healthy tissues[30].

Proton therapy increases the therapeutic index because it delivers the administered dose more precisely and has positive biological effects. This minimizes acute side effects, chronic damages, secondary cancer, and organ issues. These advantages are particularly useful in the treatment of children cancers, brain tumors and tumors around sensitive areas which are sensitive to radiation[31].

4. TECHNOLOGY AND EQUIPMENT USED IN PROTON THERAPY

Advances in technology in accelerators, beam transport systems, and planning of dosimetry have made proton therapy clinically feasible. This can be used to irradiate specific tumors without affecting normal tissues in the vicinity[32]. Cyclotrons are used to generate proton beams and offer stable, high-energy output in a small size and synchrotrons offer adjustable energies. Such characteristics facilitate modern technologies such as the intensity-modulated proton therapy[33]. It has been

demonstrated that modern delivery systems and pencil beam scanning, in particular, are more effective in 3D dose shaping and dose to adjacent tissues reduction than passive scattering delivery systems[34,35]. Meanwhile, the high-quality planning software that incorporates both multi-modality imaging and Monte Carlo simulations can deliver proton doses accurately and reliably[36].

Table 3: Comparison Between Cyclotron and Synchrotron Used in Proton Therapy [36]

Feature	Cyclotron	Synchrotron
Type of acceleration	Continuous circular acceleration at fixed energy	Cyclic acceleration with variable energy
Energy output	Fixed maximum energy (≈230–250 MeV)	Variable energy adjustable during acceleration
Energy modulation	Achieved using energy degraders	Direct energy selection without degraders
Beam delivery	Continuous beam	Pulsed beam
Size and design	Compact and mechanically simpler	Larger and more complex
Operational complexity	Easier to operate and maintain	Requires sophisticated control systems
Neutron production	Higher due to use of energy degraders	Lower, as degraders are not required
Energy efficiency	Lower (energy lost in degraders)	Higher efficiency
Suitability for PBS/IMPT	Suitable but less flexible	Highly suitable and flexible
Installation cost	Relatively lower	Higher
Clinical availability	Widely used in clinical centers	Used in advanced and research-oriented centers
Typical clinical use	Conventional proton therapy	Advanced techniques (IMPT, complex tumors)

5. COMPARISON WITH CONVENTIONAL RADIATION THERAPY

For many years, conventional photon-based radiation has been a crucial cancer treatment strategy. Proton therapy, on the other hand, has emerged as a noteworthy substitute with definite therapeutic and physical advantages. Protons exploit the Bragg peak[37], in contrast to photons, which release radiation along their entire course and expose healthy tissues to both entrance and departure dosages. This method reduces exit radiation by delivering the majority of the dosage at a particular depth within the tumor. Proton therapy is particularly helpful for malignancies that are close to important organs since it may precisely target tumors while shielding surrounding healthy tissues[38]. Dosimetrically, proton therapy offers superior dose conformity and reduced exposure to organs at risk compared with advanced photon techniques such as IMRT, benefits that are especially significant in pediatric and central nervous system cancers (Figure 3) [39].

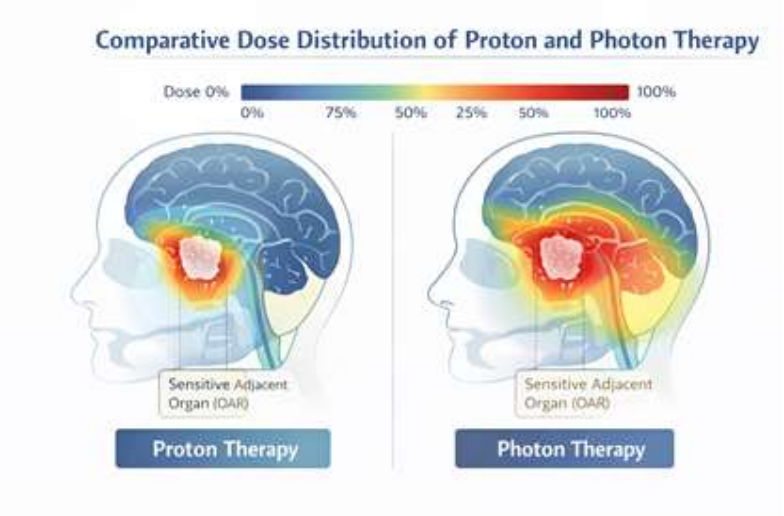

Figure 3: Comparative dose distribution of proton and photon therapy

6. CLINICAL APPLICATIONS OF PROTON THERAPY

Proton therapy delivers highly precise radiation, sparing healthy tissues, and is ideal for tumors near critical organs or when minimizing long-term side effects is essential.[40] Used for gliomas, meningiomas, medulloblastomas, ependymomas, and skull base tumors, proton therapy targets tumors near sensitive structures like the brainstem, optic nerves, cochlea, and hippocampus[41]. It enables high tumor doses while limiting healthy tissue exposure, preserving neurocognitive function and quality of life [42] In complex head and neck regions, proton therapy reduces radiation to salivary glands, spinal cord, optic system, and brainstem, lowering risks of xerostomia, dysphagia, mucositis, and long-term swallowing issues while maintaining tumor control.[43] Proton therapy delivers high doses to the prostate with minimal bladder and rectum exposure, reducing gastrointestinal and genitourinary side effects. It is valuable in dose-escalated protocols and for patients with pre-existing conditions. Children benefit from reduced exposure to developing tissues, lowering growth, cognitive, hormonal, and secondary cancer risks. Proton therapy preserves vision in uveal melanoma and protects the spinal cord in spinal tumors through steep dose fall-off. [44] As a result, proton therapy is now used across a broad spectrum of oncological indications, with its major clinical applications and associated advantages summarized in Table 4.

Table 4: Major Clinical Indications and Advantages of Proton Therapy

Cancer Type / Indication	Common Tumor Sites	Critical Organs at Risk	Key Advantages of Proton Therapy
Brain and CNS Tumors	Glioma, meningioma, medulloblastoma, skull base tumors	Brainstem, optic nerves, cochlea, hippocampus	Precise dose delivery, reduced neurocognitive toxicity, improved organ preservation
Head and Neck Cancers	Nasopharynx, oropharynx, paranasal sinus tumors	Salivary glands, spinal cord, optic structures	Reduced xerostomia, dysphagia long-term functional deficits
Prostate Cancer	Localized prostate tumors	Rectum, bladder, femoral heads	Lower gastrointestinal and genitourinary toxicity with effective dose escalation
Pediatric Malignancies	Brain tumors, sarcomas, neuroblastoma	Developing brain, endocrine organs, bones	Reduced growth impairment, fewer secondary malignancies, better long-term quality of life
Ocular Tumors	Uveal melanoma	Retina, optic nerve, lens	Vision preservation, high local control with minimal ocular damage
Spinal and Paraspinal Tumors	Chordoma, chondrosarcoma	Spinal cord, nerve roots	Steep dose gradients reduce risk of radiation-induced myelopathy

7. SAFETY, TOXICITY, AND SIDE EFFECTS

Radiation-induced toxicity remains a significant concern in cancer therapy; however, proton therapy offers a safer profile than conventional photon radiotherapy due to its precise dose delivery and minimal exit radiation [45]. Acute side effects, which occur during or shortly after treatment, commonly include fatigue, mild skin erythema, hair loss, nausea, and transient inflammation [5]. Site-specific effects such as mucositis, dysphagia, and temporary neurological symptoms may occur in head and neck or CNS treatments [46]. Compared with photon therapy, proton therapy is associated with fewer and less severe acute toxicities, largely because of reduced irradiation of surrounding normal tissues (Table 5) [49–53].

Late toxicities, including neurocognitive impairment, endocrine dysfunction, growth abnormalities, secondary malignancies, and organ-specific damage, are significantly reduced with proton therapy, particularly in pediatric patients (Table 5) [47,49–53]. Proton treatment routinely delivers lower doses to normal tissues, as shown by dosimetric tests and clinical results. As a result, there are less acute and long-term side effects and a decreased chance of developing additional malignancies[48,49–53].

Table 5: Comparison of Acute and Long-Term Toxicities: Proton vs Photon Therapy[49-53]

Toxicity Category	Proton Therapy	Photon Therapy
Acute Skin Toxicity	Mild to moderate erythema; lower incidence of severe dermatitis due to reduced exit dose	Higher incidence of erythema and moist desquamation
Fatigue	Generally mild to moderate; shorter duration	More pronounced and prolonged fatigue
Mucositis (Head & Neck)	Reduced severity and frequency due to improved tissue sparing	Higher severity and incidence
Gastrointestinal Toxicity	Lower rates of nausea, vomiting *and* diarrhea	Higher rates due to greater normal tissue exposure

Neurotoxicity (CNS Tumors)	Reduced acute neurological symptoms and cerebral edema	Increased risk of edema and neurological deficits
Long-Term Neurocognitive Effects	Significantly reduced, especially in pediatric patients	Higher risk of cognitive decline and learning deficits
Endocrine Dysfunction	Lower risk due to sparing of hypothalamic–pituitary axis	Higher incidence following cranial irradiation
Growth Abnormalities (Pediatrics)	Minimal impact on growth and development	Higher risk of growth retardation
Secondary Malignancies	Lower estimated lifetime risk due to reduced integral dose	Higher lifetime risk of radiation-induced cancers
Organ-Specific Late Toxicity	Reduced cardiopulmonary, renal *and* hepatic toxicities	Increased risk depending on irradiated volume
Overall Toxicity Profile	Favorable safety profile with improved quality-of-life outcomes	Higher cumulative toxicity burden

8. ADVANTAGES OF PROTON THERAPY

Proton therapy is superior to the conventional photon radiation due to its unique dosimetric characteristics and improved delivery modes. The concentration of maximum energy of protons in the tumor is possible due to the Bragg peak and at the same time, the areas near the tumor are exposed to the least amount of radiation possible. Tumors near sensitive organs also respond to pencil beam scanning due to the fact that it enhances conformity48. The method will remove exit dosage and limit unnecessary radiation to normal tissues. It thereby reduces the possibility of occurrence of later malignancies, acute and chronic side effects, and impairments in functions. The benefits are especially remarkable in tumours of sensitive locations and in pediatric tumours which are sensitive[54]. Ultimately, better compliance to treatment, faster recovery and the overall high quality of life are achieved due to reduced toxicity and increased tissue sparing. This holds special consideration in fostering children growth and neurodevelopment[55].

9. LIMITATIONS AND CHALLENGES

Despite the obvious clinical advantages of proton therapy, the therapy is associated with a number of difficulties, among which there are high costs, a shortage of the treatment in many countries, and complex technical specifications. It takes a lot of capital to start and operate a facility in terms of accelerator, shielding, employee competence and quality assurance. This casts doubt on whether it is economically viable involving its use over more advanced photon techniques such as IMRT[56]. There are however few proton centers with the highest being in low and middle income regions. This makes the patients have to travel long distances and exacerbates healthcare inequalities[57]. Also, it is a sensitive treatment that needs modern infrastructure, accurate immobilization, respiratory gating, and robust planning systems as it is sensitive to anatomical variations and placement errors. It relies on real time imaging and adaptive protocols in order to achieve accurate dosing[58].

10. RECENT ADVANCES AND ONGOING RESEARCH

Although it has some clinical advantages, proton therapy also has a number of critical drawbacks in terms of cost, availability, and technical issue. Table 6 and Figure 4 represent a comparison of the economic and practical aspects of proton therapy and intensity-modulated radiotherapy (IMRT).

Table 6. Comparison of Cost-Effectiveness: Proton Therapy vs IMRT [58,59,60]

Parameter	Proton Therapy	Intensity-Modulated Radiotherapy (IMRT)
Initial infrastructure cost	Very high (particle accelerator, large facility, shielding)	Moderate (linear accelerator–based setup)
Treatment delivery cost	Higher per patient	Lower per patient
Availability	Limited number of centers	Widely available globally
Dose precision	Superior due to Bragg peak and minimal exit dose	High precision but with unavoidable exit dose
Normal tissue sparing	Excellent, especially for critical organs	Good, but higher integral dose to surrounding tissues
Acute toxicity	Generally lower	Moderate
Long-term toxicity	Reduced risk, particularly secondary malignancies	Higher risk compared to proton therapy

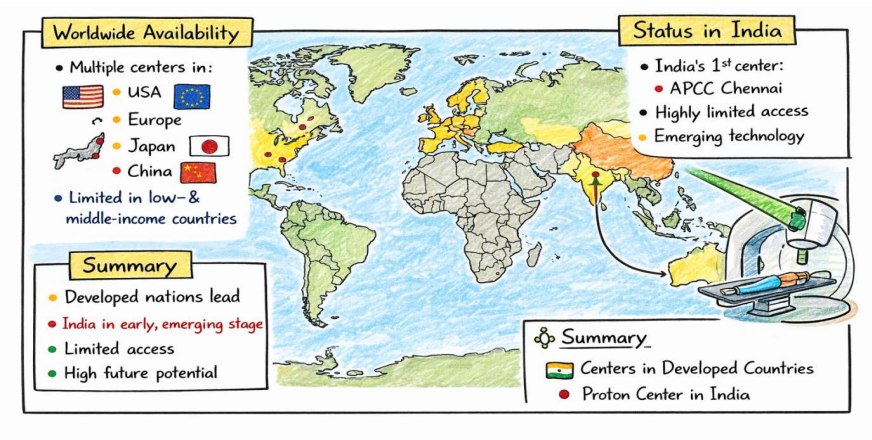

Figure 4: Global and Indian scenario of proton therapy

12. CONCLUSION

Proton therapy is an important breakthrough in radiation therapy. The special physics of the Bragg peak can be used to accurately dose the tumor with low normal tissue exposure. This review shows its increased accuracy, less toxicity to normal tissues, and increased safety, particularly in pediatric cancer and tumors that are close to sensitive organs. New methods such as pencil beam scanning, intensity-modulated proton therapy, and image-guided delivery have made it more accurate and effective in delivering treatment. As a matter of fact, proton therapy has the same tumor control rates as photon radiotherapy, and in some cases better, and significantly lower side effects in the short and long term. It preserves the quality of life, functional status, and reduces the chances of secondary cancers, which is especially crucial in patients with more chances of a longer life. This therapy is the best in cancerous diseases of children, CNS, head and neck, and those that require re-irradiation. Despite the complexity of costs and availability, the growing clinical evidence and continuous technological progress favor proton therapy as a significant and scientifically-evidence-based practice in contemporary cancer care.

Conflict of Interest: Nil

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