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Proton Beam Therapy on Pediatric Cancer: A Review

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ABSTRACT: Proton beam therapy (PBT) is an advanced radiation modality that offers significant benefits in pediatric oncology, particularly in reducing radiation-induced toxicities and secondary malignancies. Unlike conventional photon-based therapies such as intensity-modulated X-ray therapy (IMXT) and volumetric-modulated arc therapy (VMAT), PBT utilizes the Bragg peak to deliver radiation precisely to tumors while sparing surrounding healthy tissues. This advantage is crucial in children, where long-term survivorship is a major concern. Studies show that PBT lowers the lifetime attributable risk (LAR) of secondary cancers by up to 50% in whole central nervous system (CNS) treatments and significantly reduces organ-at-risk (OAR) exposure, particularly in the brain, spinal cord, and optic structures. Despite challenges such as high costs, limited accessibility, and technical complexities, growing clinical and dosimetric evidence demonstrates that PBT is superior to conventional radiotherapy, providing safer and more effective treatment for pediatric cancer patients.

KEYWORDS: Biomedical and Health Sciences, Physical Medicine, Pediatric Cancer Oncology, Proton Beam Therapy, Secondary Cancer Prevention.

Introduction

Cancer is one of the leading causes of death among children worldwide, with approximately 400,000 new cases diagnosed annually.[1] Unlike adult cancers, which often result from long-term environmental exposures and accumulations of genetic mutations, pediatric cancers arise due to developmental disruptions, making them biologically distinct and often highly aggressive.[2] Common types include leukemia, brain tumors, lymphomas, and sarcomas, which typically require surgery, chemotherapy, and radiation.[3] Advances in treatment have raised survival rates to over 80% in many high-income countries, but they also bring long-term risks.[4] Children's developing tissues are highly sensitive to radiation, increasing the likelihood of chronic health issues, cognitive impairment, and secondary cancers.[5] These concerns highlight the need for safer treatments — an area where PBT is gaining attention due to its ability to reduce radiation-induced damage.[6]

Radiation therapy has been a cornerstone in cancer treatment for over a century, offering a targeted method of destroying malignant cells through DNA damage. By inducing breaks in cellular DNA, radiation disrupts the ability of cancer cells to proliferate, leading to tumor shrinkage and eradication.[7] However, while radiation therapy is highly effective, normal tissues in the treatment field are also exposed to radiation. This is particularly concerning in pediatric patients, whose rapidly dividing cells are more susceptible to radiation-induced damage, increasing the risk of both acute and long-term toxicities.[3] Children who receive radiation therapy are at a higher risk of developing secondary cancers later in life because of radiation exposure to healthy tissues.[5] This has led to significant efforts to refine radiation delivery techniques to improve targeting accuracy while reducing exposure to surrounding normal structures.[3]

Radiation therapy can be broadly categorized into two main types: external beam radiation therapy (EBRT) and internal radiation therapy, or brachytherapy.[2] EBRT is the most commonly used form, delivering high-energy radiation from an external source to the tumor site, while brachytherapy involves placing radioactive material directly within or near the tumor to provide localized radiation exposure.[6] Within EBRT, there are two primary subtypes: photon therapy and proton therapy. Photon therapy, which includes X-rays and gamma rays, has been the traditional standard for radiation treatment. It works by delivering energy that ionizes atoms in the target tissue, leading to DNA damage and cell death.[7] However, a major limitation of photon therapy is that it deposits energy continuously along its entire path, making both healthy tissues before and beyond the tumor receive radiation exposure.[4] This increases the likelihood of side effects and long-term complications, particularly for pediatric patients.[8] Advanced photon-based techniques, such as intensity-modulated radiation therapy (IMRT), including Intensity-modulated X-ray Therapy (IMXT), and volumetric-modulated arc therapy (VMAT), have improved dose conformity to some extent, but they still exhibit the fundamental limitation of exit dose beyond the tumor.[9]

Then, Three-Dimensional Conformal Radiation Therapy (3D-CRT) provides improved dose targeting over conventional methods but lacks the precision of IMXT or PBT by shaping photon beams to match the tumor's contour. While it provides better dose distribution than conventional radiation, it lacks the precise modulation of IMXT and VMAT, leading to higher radiation exposure in nearby tissues. Helical Tomotherapy, a variation of IMXT, delivers radiation in a spiral pattern for complex tumors but still irradiates more normal tissue than PBT.[10] Lastly, Electron Beam Therapy (EBT) uses electrons

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and is effective for superficial cancers but lacks penetration for deeper tumors.[11]

In contrast, PBT's main distinction lies in its highly precise radiation delivery and superior dose distribution.[3] Unlike photons, protons are charged particles that gradually deposit energy until reaching a sharp peak, known as the Bragg peak, where they release most of their energy and stop.[2] This enables targeted radiation confined to the tumor, sparing surrounding tissues and reducing unnecessary exposure.[3] Such precision is particularly valuable in pediatric oncology, where minimizing toxicity is essential. Tumors near critical organs—like brain tumors close to the brainstem and spinal cord, or sarcomas near the heart and lungs—are especially suited for PBT, as photon-based therapies would expose these areas to potentially harmful doses.[5]

The increasing recognition of PBT's potential in pediatric oncology has led to growing interest in evaluating its clinical benefits. In this review, an analysis of PBT in pediatric oncology will be conducted, evaluating its physical and biological mechanisms, clinical applications, and potential advantages over conventional photon therapy. Also, current challenges in implementing PBT—including financial barriers, accessibility issues, and the need for further comparative studies—will be explored to provide a balanced perspective on its viability.

Discussion

Physics of PBT:

To draw conclusions about PBT, it is essential to understand the underlying physical principles of the therapy.

Proton therapy uses high-energy protons to destroy cancer cells by interacting with atoms in tissue and gradually losing energy. The main mechanism is Coulomb collisions, interactions between positively charged protons and negatively charged electrons, which lead to ionization and molecular damage. This energy loss is quantified as stopping power, which increases as protons slow down, causing them to release most of their energy at a specific depth known as the Bragg Peak.[12]

Another way protons lose energy, although it happens less frequently in PBT, is through bremsstrahlung radiation losses. This occurs when a moving charged particle, such as a proton, is suddenly deflected by the strong electric field of an atomic nucleus. When this happens, the particle loses some of its energy in the form of electromagnetic radiation, which is typically in the X-ray range. However, because protons are much heavier than electrons, they do not lose as much energy through bremsstrahlung radiation as lighter particles do.[7]

The loss of energy by protons does not happen in a perfectly predictable way. Instead, it is a stochastic process, meaning that it involves an element of randomness. Although the overall energy loss follows a general pattern, individual protons may lose slightly different amounts of energy due to variations in their interactions with electrons. This randomness leads to energy straggling, which means that even if all protons start with the same energy, they will not all stop at the same depth. Some protons will stop slightly earlier, while others will travel a bit farther. This makes it necessary to carefully account for variations when planning PBT treatments as those variations broaden and reduce the sharpness of the Bragg Peak.[12]

Another key effect in proton therapy is multiple Coulomb scattering. In addition to electrons, protons interact with positively charged atomic nuclei, causing repulsion and slight deflections. Repeated scattering events lead to beam broadening, reducing dose precision and altering energy delivery at various depths, especially in heterogeneous tissues like bone adjacent to soft tissue. This spread can be modeled using Gaussian approximations to predict deflection angles statistically.[12]

Besides Coulomb interactions, protons can also trigger nuclear reactions when they collide directly with atomic nuclei, rather than just being deflected by them. These nonelastic nuclear reactions are significant because they alter the energy and composition of the proton beam. About 21% of the energy lost by a 250-MeV proton beam in water is due to nuclear reactions, while for a lower-energy 70-MeV beam, this fraction decreases to about 4%. When a high-energy proton, such as a 250-MeV proton, interacts with an oxygen-16 nucleus, about 66% of the proton's energy is transferred to newly created secondary protons, 21% goes to secondary neutrons, and smaller fractions contribute to other nuclear fragments such as alpha particles and recoil nuclei.[12]

Near the end of their range, protons lose energy differently through nuclear reactions. At around 10 MeV, about 17% of this energy goes to secondary protons, with minimal transfer to neutrons. Alpha particles and recoil nuclei still contribute slightly. These heavy fragments have high Linear Energy Transfer (LET), meaning they deposit energy densely and are highly damaging to cells. In contrast, secondary neutrons spread energy over larger areas with less local damage due to infrequent interactions.[7]

As protons travel deeper into tissue, their stopping power increases, peaking at the Bragg Peak where energy deposition reaches up to 80 keV/μm. This concentrated dose enables effective tumor targeting while sparing surrounding tissues. At the distal edge of the Bragg Peak, the dose-averaged LET exceeds 10 keV/μm, enhancing precision. In contrast, Cobalt-60 gamma rays have a much lower LET (<2 keV/μm), dispersing energy over a wider area and increasing damage to healthy tissue.[12]

So, since LET plays a role in how effective radiation is at killing cancer cells, PBT has a higher relative biological effectiveness (RBE) compared to photon radiation. RBE is a measure of how effectively a particular type of radiation causes biological damage compared to standard X-rays or gamma rays. Studies at the Harvard Cyclotron Laboratory and other research centers have found that the RBE of proton beams increases near the Bragg Peak, leading to the adoption of a universal RBE factor of 1.1. What this says is that the dose from a proton beam is 10% more effective than an equivalent dose from standard photon radiation. However, at very high LET values (above 100 keV per micrometer), the RBE decreases because too much energy is being deposited into individual cells, leading to overkill effects, where excess radiation is wasted.[7]

Protons' ability to stop at a specific depth based on their initial energy allows clinicians to use different proton beam energies to control exactly where the Bragg Peak occurs, ensuring that the highest dose is deposited precisely in the tumor.[12] However, a single-energy proton beam would only treat a thin slice of the tumor. Hence, the solution is to create a Spread-Out Bragg Peak (SOBP), to cover a larger tumor volume, multiple proton energies are combined, effectively superimposing multiple Bragg Peaks to provide uniform radiation across the tumor while still preserving the sharp dose falloff beyond it.[10]

In contrast, X-ray therapy delivers radiation in an exponential decay pattern, meaning healthy tissues both before and after the tumor receive a significant dose. This is because photons interact probabilistically, which causes energy to spread unpredictably throughout the body.[9]

Quantitative differences between PBT and other forms of radiotherapy:

PBT significantly lowers the lifetime attributable risk (LAR) of radiation-induced secondary cancers compared to intensity-modulated X-ray therapy (IMXT), especially in pediatric patients. Reported reductions range from 1.02% to 50%, with an average of 22.73%, depending on the treatment area (Table 1).[9] For example, LAR differences are modest in brain and head-and-neck cancers but much greater in whole CNS treatments, where IMXT irradiates broader regions. This advantage stems from PBT's Bragg peak, which delivers radiation precisely to the tumor while sparing nearby tissues, unlike IMXT's wider, less selective dose distribution that raises long-term complication risks.[13]

Table 1: LAR (Lifetime Attributable Risk) differences between PBT and IMXT, and the number needed to treat (NNT) for each organ at risk. Category A: brain, head, and neck; B: chest; C: abdomen; D: whole central nervous system.[9]

Organ at Risk	A. Brain, H&N (LAR Diff. % ± SD)	NNT	p-value	B. Chest (LAR Diff. % ± SD)	NNT	p-value	C. Abdomen (LAR Diff. % ± SD)	NNT	p-value	D. Whole CNS (LAR Diff. % ± SD)	NNT	p-value
Brain	0.77 ± 0.44	131	0.0036**	0.00 ± 0.01	-20000	0.230	-	-	-	-	-	-
Female Breast	-	-	-	7.46 ± 13.34	13.4	0.158	0.59 ± 1.19	171	0.207	15.9 ± 14.2	6.3	0.0960
Lung	-	-	-	3.23 ± 1.41	31.0	0.0003**	3.76 ± 2.59	26.6	0.0642	-	-	-
Colon	-	-	-	9.22 ± 14.96	10.8	0.125	12.5 ± 19.7	8.0	0.115	22.19 ± 6.94	4.5	0.0156*
Stomach	-	-	-	2.02 ± 1.95	49.6	0.0220*	1.89 ± 1.58	53.0	0.0118*	3.45 ± 2.44	29.0	0.0671
Small Intestine	-	-	-	0.63 ± 0.78	160	0.0589	0.72 ± 0.80	139	0.0384*	2.30 ± 2.79	43.4	0.145
Liver	-	-	-	0.60 ± 0.42	166	0.0046**	0.49 ± 0.25	204	0.0009**	1.10 ± 0.14	90.6	0.0026**
Bladder	-	-	-	0.17 ± 0.32	584	0.171	0.14 ± 0.25	698	0.211	-	-	-
Thyroid	0.01 ± 0.01	18900	0.356	-0.03 ± 0.13	-3590	0.565	1.09 ± 0.18	91.8	0.0046**	-	-	-
Bone	0.08 ± 0.05	1210	0.0043**	0.03 ± 0.04	2950	0.0455*	0.08 ± 0.07	1310	0.0183*	0.03 ± 0.02	3230	0.0608
Soft Tissue	0.17 ± 0.16	596	0.0335*	0.10 ± 0.09	1030	0.0231*	0.20 ± 0.17	506	0.0121*	-	-	-
Cumulative LAR	1.02 ± 0.52	98.0	0.0021**	23.3 ± 17.2	4.3	0.0065**	16.6 ± 19.9	6.0	0.0497*	50.0 ± 21.1	2.0	0.0274*

Beyond pediatric oncology, PBT also shows clear benefits over volumetric modulated arc therapy (VMAT) and electron beam therapy (EBT), especially when it comes to reducing the dose to organs at risk (OARs), as shown in Figure 1. Dosimetric studies have found that PBT can lower both the average and peak radiation doses to critical structures, in some cases by as much as 100%, particularly when those organs are centrally located and contralateral OARs. The precision of PBT enables superior dose conformity, making it highly effective for treating superficial skin cancers like angiosarcoma without requiring a bolus.[9] Clinical outcomes also support these findings; for instance, a case study on a patient treated with PBT for recurrent scalp angiosarcoma showed no signs of recurrence six months post-treatment and experienced only mild, manageable side effects such as eyelid dryness.[11] VMAT and EBT, while offering comparable target volume coverage, result in higher unintended radiation exposure to adjacent healthy tissues, increasing the likelihood of toxicities.

PBT also demonstrates clear dosimetric benefits in breast cancer treatment, which is globally one of the most recurrent cancer types, particularly in reducing radiation exposure to the heart and lungs. Compared to 3D-conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and tomotherapy, PBT reduces radiation exposure to non-target breast tissue by 40.9%, 33.3%, and 22.8%, respectively.[10]

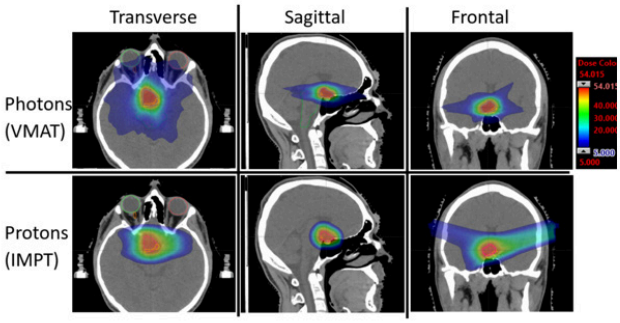

Figure 1: Comparison of dosimetry between VMAT and IMPT on three orthogonal planes. Overlaid structures include targets as well as organs-at-risk (OARs).[14]

Additionally, PBT minimizes the mean heart dose by up to 50% relative to photon-based therapies, which is crucial for mitigating long-term cardiovascular complications associated with breast irradiation. By sparing the non-planning target volume (PTV) breast tissue from receiving 50% of the prescribed dose, PBT enhances treatment safety without compromising tumor control. The dosimetric superiority of PBT over photon-based approaches is a result of its ability to deliver highly conformal radiation while limiting dose spillage to adjacent critical structures.[10]

A significant concern in left-sided breast cancer treatment when using radiotherapy is reducing radiation-induced cardiotoxicity. When conventional radiotherapy often exposes the heart to ionizing radiation, PBT enhances treatment safety, making it the preferred option for breast cancer patients with preexisting cardiovascular conditions or increased susceptibility to radiation-induced heart disease.[15]

In terms of survival outcomes, PBT has demonstrated superior efficacy in specific cancer types. For glioblastoma multiforme, a meta-analysis identified PBT as the modality most likely to improve overall survival (OS) and progression-free survival (PFS), with a 72.6% probability of yielding the best

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effective across multiple tumor types, has a 66.5% probability of improving OS for glioblastoma patients. EBT, primarily used for superficial malignancies like basal and squamous cell carcinomas, achieves high cure rates (90–98%) in these cases but lacks efficacy for deeper or more complex tumors.[13]

Finally, a dosimetric study comparing PBT to IMRT and VMAT found that proton therapy reduced mean and maximum doses to critical organs in pediatric brain tumors by over 50%, particularly in regions like the hippocampus and optic chiasm, which are highly sensitive to radiation.[3] Similarly, in breast cancer irradiation, PBT reduced heart and lung exposure by nearly 90% compared to IMRT, an essential factor in minimizing long-term cardiac toxicity.[10]

Challenges and Limitations:

PBT faces multiple challenges and limitations that can hinder its widespread adoption and clinical effectiveness. One of those challenges is its prohibitively high cost. Establishing a single-room proton therapy center costs approximately $20 million, while multi-room facilities exceed $225 million.[13] Additionally, pre-treatment costs for PBT are estimated to be 1.5 to 3 times higher than those of photon-based therapies such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT).[5] This cost puts it out of reach for many patients, especially in low- and middle-income countries where even standard radiation therapy often lacks enough funding.

Also, the uncertainty surrounding its radiobiological effectiveness (RBE) is an issue. Unlike photon therapy, which has a well-established relative biological effectiveness (RBE) of 1.0, the RBE of protons varies across different tissues and tumor types, typically estimated at 1.1 but potentially higher at the Bragg Peak.[4] This makes it difficult to precisely predict biological effects in different patients, complicating dose calculations.

Additionally, there is still a lack of long-term clinical outcome data for PBT, especially in pediatric patients. Most large-scale randomized trials comparing PBT with IMRT or VMAT are still ongoing or in the early stages.[4]

Finally, the physical properties of protons, while advantageous in dose localization, introduce complexities in treatment planning and beam delivery. One major issue is range uncertainty, where small errors in tissue heterogeneity, CT calibration, or proton beam energy can cause significant deviations in where the Bragg Peak occurs.[5]

Radiosensitivity of developing tissues in children and long-term side effects:

Children are particularly susceptible to the long-term adverse effects of radiation therapy since their developing tissues exhibit heightened radiosensitivity. Proton therapy, with its superior dose distribution and reduced radiation exposure to surrounding normal tissues, has been proposed as a more favorable alternative to conventional photon therapy for pediatric patients. The significance of this approach is particularly evident in pediatric brain tumors, where radiation exposure can lead to cognitive decline, growth disturbances, and endocrine dysfunction. Studies have demonstrated that radiation-induced cognitive impairments are more pronounced in younger children, and PBT has been modeled to reduce this risk by limiting radiation exposure to non-targeted brain regions.[3] The impact of radiation on the developing brain has been observed in various pediatric tumors, including medulloblastoma, where cognitive function, IQ scores, and reading abilities tend to decline post-radiation. Proton therapy, by delivering radiation more precisely, has shown promise in reducing these neurocognitive deficits, particularly in young patients who are at the highest risk for developmental delays.[5]

The risk of secondary malignancies is one of the most critical concerns in pediatric radiation oncology. Given that children have a longer post-treatment life expectancy compared to adults, minimizing radiation exposure to normal tissues is essential in reducing the likelihood of radiation-induced cancers. Dosimetric studies estimate that PBT decreases the likelihood of secondary tumors by a factor of 8 compared to intensity-modulated radiation therapy (IMRT) and by a factor of 15 compared to conventional photon therapy. Consequently, pediatric oncology places strong emphasis on investigating late treatment effects, as demonstrated by long-term studies on survivorship, which indicate that many children treated with traditional radiation modalities develop secondary malignancies decades after treatment. This reinforces the necessity of PBT or some other therapy that is safer.[3]

Additionally, growth abnormalities remain a major concern in pediatric radiation therapy, particularly for patients requiring craniospinal irradiation. The spine and nearby muscles and bones are very sensitive to radiation, and exposure during treatment can sometimes cause lasting problems with spinal growth. How serious these effects are can depend on the patient's age, sex, and which part of the spine is treated. Some studies suggest that avoiding the spine's central canal during irradiation may mitigate these risks, although long-term impacts remain incompletely understood.[4] PBT reduces the risk of exposure to adjacent structures such as growth plates, which are crucial for normal skeletal development, by sparing these structures and is expected to result in fewer skeletal deformities and an overall improvement in quality of life for pediatric cancer survivors.[3]

Neurocognitive and developmental effects are major long-term concerns in pediatric oncology, especially for children with central nervous system (CNS) tumors. Radiation to the developing brain is linked to deficits in memory, attention, and processing speed. Studies in medulloblastoma patients show that lowering radiation to non-targeted brain regions improves outcomes, with PBT outperforming conventional photon therapy.[4] This is particularly important in younger children, where brain plasticity is still forming. Modeling studies also suggest PBT reduces memory loss and IQ decline.[5] By minimizing exposure to healthy brain tissue, PBT helps preserve key cognitive functions, supporting better long-term quality of life.[4]

Also, particularly in pediatric patients with central nervous system (CNS) malignancies, acute toxicities are generally mild to moderate, with fatigue, alopecia, nausea, and dermatitis being the most common. The severity of these toxicities depends on factors such as tumor location and concurrent treatments,

with infratentorial tumors more frequently leading to headaches and nausea. Quantitatively, fatigue was reported in 67% of patients, alopecia in 73%, and nausea in 46%, but these effects were manageable with supportive care.[16] Although PBT reduces long-term toxicities compared to conventional radiotherapy, the evidence shows that continuous monitoring is essential.

In nonsmall cell lung cancer (NSCLC) patients, PBT enables the delivery of higher radiation doses with lower rates of severe esophagitis and pneumonitis, showing a good improvement over 3D-CRT and IMRT, which exhibit much higher toxicity rates.[17]

Thus, overall toxicity across multiple organ systems is lower with PBT than with photon-based therapies, though some unique complications have been reported in case studies, such as radiation necrosis, Moyamoya syndrome, and increased sensitivity to range uncertainties. Despite a lower frequency of pulmonary, cardiac, and gastrointestinal toxicities, long-term effects still require further study.[15]

In pediatric patients, acute toxicities associated with PBT are well-tolerated and manageable. The precise targeting of tumors significantly reduces radiation exposure to normal brain tissue, lowering the risk of cognitive and endocrine dysfunctions compared to conventional radiotherapy.[18] This is particularly relevant for younger patients, as minimizing radiation to the developing tissue is of great importance.

Conclusion

Summarising, PBT represents a major advancement in radiation oncology, offering great precision, superior dose distribution, and significantly reduced toxicity compared to conventional photon-based therapies such as IMXT, VMAT, and EBT.[4] The Bragg peak phenomenon allows PBT to deliver radiation precisely to the tumor while sparing surrounding healthy tissues, making it particularly beneficial in pediatric cancer treatment, where reducing secondary malignancies and long-term toxicities is crucial.[9]

Quantitative data confirm the advantages of PBT, as studies show that it reduces the lifetime attributable risk (LAR) of secondary cancers by up to 50% in whole central nervous system (CNS) treatments, while in breast cancer cases, it minimizes mean heart dose by 50% compared to photon-based therapies.[10] To add, PBT decreases radiation exposure to organs at risk by up to 100%, particularly in tumors near the brainstem, spinal cord, and optic nerves.[11] Its physical properties set it apart from conventional photon-based treatments.[6]

Despite its benefits, PBT faces several challenges. Its high cost remains the biggest barrier, as multi-room proton therapy centers exceed $225 million, and per-treatment costs are up to three times higher than IMXT or VMAT.[13] Accessibility is another issue, with fewer than 100 centers worldwide, leading to long wait times for patients in need.[4] Technical difficulties, such as range uncertainties and motion sensitivity, complicate treatment planning, requiring advanced imaging and real-time tracking to ensure accuracy.[5] Additionally, while dosimetric models predict fewer toxicities, large-scale randomized clinical trials comparing PBT and photon therapy are still ongoing, making some oncologists hesitant to fully replace conventional radiotherapy.[4]

Despite its current limitations, PBT is positioned to become the gold standard in precision radiation therapy. Its consistent superiority in CNS treatments highlights its value in pediatric oncology, where safety margins are narrow. Advances in proton delivery, cost-reduction strategies, and expanding clinical evidence continue to strengthen its role.[5] Innovations like proton-immunotherapy and AI-based planning may further improve its efficacy and accessibility.[13] The long-term benefits of PBT in minimizing complications and enhancing outcomes make it a transformative tool in cancer care. While challenges related to accessibility and cost remain, continued investment and innovation in PBT hold great promise for expanding its reach, ultimately providing more patients with a safer and more precise alternative to conventional radiotherapy. While challenges related to accessibility and cost remain, continued investment and innovation in PBT hold great promise for expanding its reach, ultimately providing more patients with a safer and more precise alternative to conventional radiotherapy.[17]

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