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Review Paper

Proton Beam Therapy in Clinical Oncology: Indications, Outcomes, and Future Directions

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ABSTRACT

Proton beam therapy (PBT) is an advanced form of radiation therapy that offers distinct physical and dosimetric advantages over conventional photon-based radiotherapy. The characteristic Bragg peak enables protons to deposit most of their energy at a defined depth within the tumor while minimizing the radiation dose delivered to surrounding healthy tissues. This review discusses the principles, clinical applications, advantages, limitations, and future directions of PBT in clinical oncology. Evidence from various cancer types indicates potential benefits in reducing normal-tissue exposure and treatment-related toxicities, particularly in pediatric malignancies, head and neck tumors, thoracic cancers, breast cancer, and selected skull-base tumors. PBT techniques, including passive scattering, pencil beam scanning, and intensity-modulated proton therapy, have improved dose conformity and treatment precision. However, uncertainties related to proton range, relative biological effectiveness, tumor motion, imaging, and anatomical changes remain important challenges. The high cost of proton therapy facilities and limited availability also restrict its widespread use, while evidence of superior clinical outcomes compared with modern photon therapy remains inconsistent for several cancers, including prostate cancer. Recent developments involving artificial intelligence, adaptive proton therapy, FLASH proton therapy, compact accelerator systems, and advanced imaging may further improve treatment accuracy, safety, and accessibility. Overall, PBT represents a promising modality for selected oncology patients, but continued clinical research and long-term comparative studies are required to establish its role and cost-effectiveness across different cancer indications.

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INTRODUCTION

One type of radiation therapy (RT) is conventional proton beam therapy (PBT). As PBT is administered properly, it has fewer side effects and more therapeutic efficacy than typical RT using X-ray particles. Thus, despite the demand for costly equipment, PBT facilities are being developed all over the world. Wilson (1) first proposed PBT in 1946. A year later, scientists at the Lawrence-Berkeley National Laboratory published the first conventional BT patient series (2). by scientists at the Lawrence Berkeley National Laboratory.In the years that followed, a number of other proton centers developed worldwide, and PBT has been used in clinical environments for approximately sixty years, curing tens of with many malignancies of different types.The volume of fresh programs under development has been rising over the years due to the growth of PBT applications worldwide. This is due a potential proton dose distribution is typically higher than the dose-dependent distribution of classic photon RT. By enhancing the local tumor treatment rate and avoiding destruction of healthy tissues, PBT can raise the rate of survival for patients while minimizing radiation-induced adverse effects.The bigger subatomic particles can more precisely convey their energy to the tumor with less scattering to surrounding tissues than typical photon RT.. Especially compared to photon therapy, PBT can be observed to have lesser repercussions. However, owing to the elevated treatment costs related to the building and upkeep of proton based facilities, the value of PBT still remains questionable. However, the effectiveness of photon therapy, improved quality of life, and reduced treatment costs for progressive illness may outweigh this higher expense. To figure it out what individuals will benefit from PBT, a broader clinical evaluation needs to be conducted.Substantial research and discussions are required to address the application of PBT for various cancer types and for safeguarding patients' quality of life.while getting high In the last two decades, there has been a growth in research on the effectiveness of care.Standard primarily photon therapy performe d with linear accelerators, is required for 6070% of cancer sufferers.People who are suffering. Heavy ion therapy, which includes proton therapy is something that a lot of people know about. Heavy ion therapy is used to help people who are suffering. It is a type of treatment that includes proton therapy. Heavy ion therapy for many benefits over photon therapy as the mos t recent research and use of radiotherapeutics is b ecause of Its physical features, known as the Bragg peak. Boron neutron capture therapy (BNCT) a binary medical approach based on the capture and fission reactions that occur when the stationary isotope boron10 emits particles called neutro produce high energy α particles 6Linuclei going through phase II clinical trial.Pro tons deposit most of the vitality in Bragg peak, a depth closest to the terminus of the penetration di rection, during which they have a limited entranc e dose and little departure dose. For the past thirty years, proton This treatment has been used to help a lot of people with cancer. It is used to treat cancer patients. The treatment is used for people who have cancer. worldwide due to the favorable part [3].Starting out, there was a lot of enthusiasm about the possibility that proton therapy could dramatically improve the therapeutic ratio because of the physical features of proton dose distributions. However, it emerges that the initial high aspirations may have been overstated based on an assessment The clinical effects of proton therapy are important to consider. Over time we can see how they work. We should also compare the effects of proton therapy with photon radiation surgery. This will help us understand the effects of proton therapy . The field of proton therapy has

realized that in order to fully maximize protons' therapeutic potential, a range of obstacles must be resolved.The increased degree of the sensitivity of proton dose distributions to changes in the body from one treatment to another. Even during a treatment and the simple ideas about how well protons work compared to photons, which is called the relative biological effectiveness of protons.We are talking about the sensitivity of proton dose distributions to changes in the body that happen between treatments and, during a single treatment. The relative biological effectiveness of protons is also important which is how well protons work compared to photons. compared to photons, addresses with respect to the clinical superiority of proton therapy and the lack of sufficient evidence to date, and skepticism regarding the value of protons are some Here are some examples of these challenges. These are explained in the sections that come next. Thankfully what we know now shows that protons are really different from photons. This is true when we look at how protons and photons affect living things, the system and other things. Protons and photons have differences in how they work with the immune system and living things. We see that protons are different from photons in ways especially when it comes to how they affect the body and the immune system of humans. The differences between protons and photons are important to understand. Protons are different, from photons, and pharmacologic alters that go beyond fundamental dose distribution mistakes. To significantly boost the curative capabilities of proton therapy, it is vital that one understand these variations and employ the knowledge gained in a clinical setting.Particle therapy facilities based in physics labs have numerous disadvantages as beam orientations (which is typically just horizontal beams), animosity for beam-on time,sufficient medical logistics,etc.Elements of Physics Braggs Peak Protons are charged, massive particles having about 800 times the mass of protons. Each proton is given a specific momentum by the large mass and acceleration applied, Which is mostly gone after moving a distance and then stopped by meeting the target.This ends up in a sharp rise in energy deposition at the end of the proton's path, followed by no further dose delivery, which is known as the Bragg peak (4). Relative photons or electrons this special thing, about how they work gives us ways to measure the dose of energy.As a result unlike photons that keep going through the target electrons stop moving when they reach a depth in the target that depends on their energy.Electrons have no exit dose, which's a good thing when we are talking about relative photons or electrons.,and totally spare the normal tissue downstream. Cyclotron or photobooth produces proton beams, which are later accelerated to the target location.The percentage distance-dose allocation curves of the nuclear and photon beams are shown in Fig. 1, proving that the photon beam produces a dose at the stipulated depth whereas the proton beam does.Compare electrons and photon ,the proton the dosage in RT, is computed through To figure out the effect of a treatment we need to multiply the physical dose by the relative physiological effectiveness or RBE for short. This RBE is very important because it helps us understand how the treatment is really affecting the body. Multiplying the dose by the RBE gives us a better idea of what is actually happening. The relative physiological effectiveness or RBE is a part of this process. As a result, when the radiation quality fluctuates although the amount of medicine given is the same the results in patients can be different. The effect on the body is similar to a type of radiation called 60 Co using the RBE. For external beam RT, which uses photons and electrons, the RBE is generally to be considered 1 (5,6).Compared to photons, protons have totally different dose distribution characteristics and can potentially avoid the majority of the extra-target

radiation emitted by the system of acceleration that transports protons into a body by providing them certain momentum. The velocity drops by interactions related to their mass and charge after a certain amount of time, and it abruptly halts at a particular depth. At this moment, the proton in question will contact nearby electrons to transfer its energy, ionizing molecules and destroying the target cell's DNA with radiation. Low linear energy transfer radiation is characteristic of protons, and single-strand DNA breaks produce tissue damage with sublethal damage from radiation and potential recuperation of radiation damage.The dose per therapy controls the biological effect, which is significantly more than that of high-energy X-rays and 60 Co. The percentage deep-dose allocation lines of the proton versus photon beams that are typical are shown in Fig. 1, proving that the photon beam transmits a dose at the stipulated depth where as the proton beam does not.Lack of exit frequency Although improvements in photon RT delivery, such intensity-modulated RT (IMRT), have lowered the risk of these toxicities, increasing data indicates PBT may also reduce risk (8–12). At least certain individuals with esophageal cancer may benefit clinically from PBT's zero exit dose, which further lowers the radiation exposure to normal cellular tissue. Additionally, treating patients with throat cancer with proton beams may lower mortality and heart-related problems (13). It became apparent that treating old people with esophageal cancer with high-dose PBT without chemotherapy was effective and safe (14). In general, an increasing body of research suggests that the dosimetric benefits of PBT may lead to a medically significant reduction in treatment-related hazards compared with conventional photon RT (15). Re-irradiation, RT, and chemotherapy intensification are prospective future uses of PBT for esophageal cancer. PBT has been proven to be cost-effective for breast cancer, whereas regular photon radiation treatments induced major side effects in women who were considered at high risk of heart disease (16).Partial breast irradiation with PBT was found to be safer, more effective, and technologically feasible compared with traditional X-rays and electron beams. It. It added to normal tissue sparing and supplied proper target coverage. Additionally, PBT was found to be cost-effective either intra cavitary and interstitial brachytherapy(17–24).

BEAM

As was previously pointed out, Cyclotrons or synchrotrons are used to accelerate protons to help with things. Cyclotrons and synchrotrons are really important for making protons go fast so they can be used for therapeutic purposes. The main goal of using cyclotrons and synchrotrons is to get protons to move quickly for uses.vitality, generally at 70 and 250 MeV. To reach the deepest tumors seen in clinical practice, the upper end of this spectrum is necessary. The Bragg curve in Table 1 illustrates the depth dose characteristics of a very thin accelerated proton beam as it approaches the therapy delivery head. Thus, it can't be used to treat tumor targets that are three-dimensional and have arbitrary configurations. When compared to photons, this particular physical attribute has larger dosimetric advantages. Protons are stopped at a layer, in the target that depends on how energy they have. This means protons have no exit dose so they do not affect the tissue that is downstream of the target. The protons really avoid damaging the normal tissue, in lieu of passing through the target. A type of cyclotron or accelerator produces proton beams, which are next accelerated into the target. The physiological aspect, the proton dose in RT, is determined by multiplying the physical amount by the related biological effectiveness (RBE). As an outcome,when the radiation quality differs while the physical dose is constant,clinical and biological consequences could be different.

The biological effect is connected to a guide dose (60 Co) via the RBE. The RBE is usually considered as 1 for external beam RT, which employs electrons and photons (4,5).At this point, the proton will come into contact with surrounding electrons and exchange its energy, ionization molecules and breaking the target cell's DNA with radiation. Low linear energy transfer radiation is a property of protons, and single-strand DNA breaks because tissue damage alongside sub lethal radiation injury and potential radiation damage recovery. Most individuals believe that the proton beam's RBE is 1.1 (7). However, the stopping power rises close to the threshold of the protons range, thus increases RBE. The oscillating RBE at the extreme of the range is not fully When you are planning with protons you have to think about something called proton planning. Proton planning uses a thing called RBE which is 1.1.When doctors are using proton beams to treat a tumour they try not to point the proton beams at important parts of the body that are, near the tumour. This is because they are not really sure what will happen.Instead doctors use proton beams and point them from different angles. This helps to make sure that the proton beams do not damage the organs. The doctors do this because they want to spread out the uncertainty of where the proton beams will stop. They want to make sure the proton beams stop at the tumour and not in the organs.

Uncertanities The variation in relative biological effectiveness (RBE), particularly near the distal edge of the Bragg peak where RBE increases, is one of the primary uncertainties in proton beam therapy.Protons' biological interactions with human tissues are also little known, thus highlights need for bigger study in order to completely comprehend these consequences.

TECHNICAL DETAILS

Proton therapy methods have progressed from The treatment uses scattering and also pencil beam scanning, which is often called PBS.providing better dose conformity and less exposure of adjacent healthy tissues. Technological progress in proton beam therapy features different beam delivery methods, including passive scattering and pencil beam scanning (PBS). Although passive scattering ensures uniform dose distribution, PBS enhances accuracy by delivering thin proton beams that systematically scan the tumour volume one layer at a time. Moreover, intensity modulated proton therapy (IMPT) improves this method by adjusting beam intensity, enabling a highly conformal dose. Nonetheless, various technical issues persist. Imaging support in proton therapy remains constrained, with numerous systems depending on two-dimensional methods. Moreover, managing motion presents a major obstacle, as the movement of tumours from breathing or patient positioning can result in dose delivery inaccuracies, especially in dynamic delivery methods such as PBS.

CLINICAL APPLICATIONS

Research on the head and neck (25-28) indicated that Individuals with head and neck cancer might gain advantages from PBT.PBT might reduce the risk of recurrence by raising the dosage.to the tumour and, because of the minor dose to the mandible, glands and maxilla, it might lower the chance of xerostomia, Tooth removals, tooth decay and bone tissue death due to radiation. In cases of Sino nasal mucosal malignant melanoma, there exists Proof that hypo fractionated high-dose PBT might enhance the regional management rate. In comparison to surgical procedures in individuals With Sino nasal mucosal malignant melanoma, the persistent

Management of the main lesions might lead to increased survival rate (29) Right now, it looks like surgery is the best option, but some checks suggest that both PBT and plaque brachytherapy could work well too (30). PBT has a few benefits

over radioactive plaques – you do not need surgery, healthcare People who work there are not, around radiation. There is no need for workers to stay. Workers do not have to worry about radiation so workers can go home.in the hospital, with treatment wrapping up in just 5 working days. Because of these benefits, more and more patients are choosing PBT over radioactive plaques.

When it comes to chondral in the skull base, past studies have shown that PBT is better than X-ray therapy because it offers a higher chance of keeping the tumour under control long-term, without increasing the risk of temporal lobe damage. PBT has proven helpful for many skull base tumours, according to retrospective studies.Further research focusing on higher doses and more precise treatment plans with PBT could lead to even better results in these areas, without causing more harm to healthy tissues. (31) PBT is also seen as a go-to treatment for growths in the nose, sinuses, and at the base of the skull, as it can lower the radiation dose to vital parts like the eyes, optic nerves, and the central nervous system. (32)..For chest tumors lung cancer is the frequent cancer globally and radiation therapy (RT) is a key treatment. PBT is a form of RT that can potentially lessen the side effects of RT thanks to its unique Bragg peak. Compared to photons, PBT plans can deliver less radiation to nearby organs, like the oesophagus, lungs, and bone marrow, which can lead to better treatment outcomes. (33) So, when doctors looked at how proton beam therapy (PBT) worked for lung cancer patients(34-41) early on, they found that using it along with chemotherapy seemed to lower the chances of bad side effects and might even help patients live longer compared to regular radiation like photon beam therapy and 3DCRT(42). Initial findings (43-47) also hinted that PBT allows doctors to give a higher dose of radiation(15), which could mean patients survive longer, have fewer relapses,experience less severe side effects, and can handle stronger chemotherapy(15).For people with stage III non-small cell lung cancer, PBT looks like a good and safe treatment choice. Still, we do not know much about the long-term side effects yet, so patients will need to be monitored to figure out those risks (48). Now, for oesophageal and gastroesophageal junction cancers, (49-53) the oesophagus is right in the middle of the chest. This means it is important to be super careful when giving the right high dose of radiation to the tumour while also keeping the dose as low as possible to nearby vital organs. This is because there is a real risk of serious problems like inflammation of the heart sac, lungs, or even heart attacks.Even though newer radiation methods like IMRT have made these side effects less likely, more and more studies are showing that PBT can reduce these risks even further (54-58). Proton beam therapy (PBT) offers the advantage of not having a dose at the exit point, which could mean less radiation damage to healthy tissues and real advantages for some oesophageal cancer patients. Using proton beams for oesophageal cancer (59) treatment might also lower the risk of heart problems and deaths related to them. Studies have shown that giving older oesophageal cancer (60) patients high doses of PBT without chemotherapy has been both effective and safe.

Overall, more and more research indicates that the precise dose delivery of PBT could significantly decrease treatment side effects compared to traditional photon radiation therapy(61). Future uses for PBT in oesophageal cancer treatment could include intensifying radiation and chemotherapy, as well as re-treating patients.For breast cancer, PBT has proven to be a good value, whereas standard photon radiation caused considerable side effects in women prone to heart issues (64). When compared to traditional X-rays and electron beams, using PBT for partial breast irradiation was found to be safer, more effective, and technically achievable. It also appears to offer

good coverage of the tumour while better protecting healthy tissues. Additionally, PBT has been shown to be more economical (64-72) than brachytherapy techniques that involve inserting radioactive sources inside the body or near the tumour.

Proton beam therapy (PBT) has been used for a while to treat prostate cancer, but people still debate its effectiveness. Even though proton beams have characteristics and do a great job of delivering the right dose current research does not show that Proton Beam Therapy is better than standard Intensity-Modulated Radiation Therapy for prostate cancer.Proton Beam Therapy has some qualities but other treatments like brachytherapy, surgery and Intensity-Modulated Radiation Therapy are less expensive than Proton Beam Therapy.We need studies with good long-term results to see if Proton Beam Therapy really offers an advantage, in controlling prostate cancer tumors and reducing side effects both short-term and long-term when treating prostate cancer with Proton Beam Therapy.

Even though PBT has a theoretical edge over traditional photon radiation therapy, there's no clear agreement on whether it actually leads to less toxicity or better results, or if these potential benefits are worth the high cost of this new technology(73). Therefore, we need to track patients for a long time to see if it's truly worth using PBT more often for prostate cancer.

Studies have shown that PBT is a safe and effective option for men with early-stage prostate cancer(74-77). However, we still need to compare it more thoroughly with other treatments for localized prostate cancer to figure out the best approach for different individual(78). More research looking at side effects, safety, how it affects patients' lives, and financial aspects is needed to determine when PBT is the right choice for prostate cancer. Even though radiation therapy (RT) technology (79) has gotten much better, people are still worried about the immediate and long-term side effects of treatment. This is especially true for kids because their organs and tissues are still developing, and they have a longer life ahead, meaning radiation can affect their growth, learning, hormone production, and even lead to new cancers later on.So, it's really important to lower the radiation dose to healthy tissues in children as much as possible (80-84).Particle beam therapy (PBT) has the benefit of delivering less radiation to healthy tissue, which could mean fewer negative effects. Because of this, PBT could be a good choice for treating childhood cancer(31).Studies looking at radiation doses and patient outcomes have shown that for paediatric cancers like medulloblastoma, retinoblastoma, bone sarcoma, pelvic soft tissue sarcoma, and orbital rhabdomyosarcoma, PBT offers a big advantage over X-ray therapy by lowering the dose and damage to healthy organs (85,86). Research also indicated that children with cholangiocarcinoma treated with RT had the highest risk of developing a secondary cancer after X-ray therapy, and the lowest risk after intensive proton therapy (87). Furthermore, heart radiation during X-ray treatment for Hodgkin's lymphoma has been linked to a higher chance of coronary artery disease and problems with heart valves. Therefore, PBT could be a viable option to decrease the illness, death, pain, and medical expenses for people who survive Hodgkin's lymphoma.(88,89) Since it's especially crucial to minimize radiation to healthy tissues in children, PBT has recently gained global attention as a radiation therapy method for paediatric cancer.(90)

ADVANTAGE OF PBT

In proton beam therapy (PBT), the amount of radiation entering the body is minimized, and the radiation exiting the body is nearly absent. The majority of the proton beam’s energy is deposited

at a specific depth within the body. This attribute offers potential benefits for treating rectal and anal cancers by reducing the radiation dose to adjacent organs such as the bladder, bowel, and hip joints. It may also be advantageous for treating pancreatic, gastric, and hepatobiliary cancers by lowering radiation exposure to the liver, small intestine, lungs, heart, spinal cord, and kidneys. Additionally, PBT can be employed to treat bone and soft tissue sarcomas. PBT may permit higher chemotherapy doses with fewer side effects, particularly for cancers of the gastrointestinal tract, chest, and other regions (73). For patients with Hodgkin's and non-Hodgkin lymphoma, PBT can be used following chemotherapy to consolidate treatment. Advances in proton therapy technology may enhance the balance between effectiveness and safety by preserving the benefits of radiation therapy while reducing potential risks (74). Proton therapy has an ability to change how the immune system works, something that is being studied right now. This effect on the system could be a big benefit especially when used with immunotherapy. Many studies show that how well the disease is controlled and how long people live with proton therapy is similar to what's seen with photon-based therapy (93–95). In addition, proton therapy might lower side effects from treatment, make it better, at controlling the disease in one place and make patients feel better and live longer.

LIMITATIONS AND CHALLENGES

The Swedish study looked at how much proton therapy costs compared to photon therapy for people with medulloblastoma. They used a kind of modeling called Markov modeling to figure this out. What they found was that proton therapy costs a lot more at first it is 2.4 times more expensive, which is $12,364 compared to $5,129 for photon therapy.There are a lot of things that're not certain when it comes to planning and giving proton therapy and there is not a lot of proof that proton therapy is better than photon therapy. Also proton therapy is more expensive. Not as many people know how to do it so it is not as popular as photon therapy.It is hard to make sure the proton beam goes where it is supposed to because the tumor can move and people breathe, which makes it tricky. If the beam does not go where it is supposed to then the good things about proton therapy can actually become bad things.

CURRENT RESEARCH AND DEVELOPMENTS

Recent advances in proton therapy include the integration of artificial intelligence (AI) and adaptive treatment strategies, which assist in treatment planning, dose prediction, and workflow optimization. Adaptive proton therapy is especially important because even minor anatomical changes can significantly affect dose distribution.(98) In addition, FLASH proton therapy, which uses ultra-high dose rates, has gained considerable attention due to its potential to improve tissue sparing and is currently under active investigation(98,101).Technological developments are also focused on designing compact proton therapy systems to increase accessibility and reduce infrastructure requirements. Furthermore, advanced imaging techniques such as CT-guided and MRI-guided proton therapy are being explored to improve treatment precision and enable real-time tumor visualization during therapy(100,98).

DISCUSSION

Proton beam therapy has important benefits, including better targeting of tumors and less radiation to healthy areas around the tumor. These benefits can make treatment easier, on the body. Help patients feel better.. The cost to set up and run proton therapy centers is very high. This makes it hard for many places to offer this

treatment. Even though proton therapy helps reduce side effects, doctors are still not sure if it always leads to life compared to regular radiation. Also there are not big studies that compare proton therapy with regular radiation over a long time. This lack of evidence makes it hard for doctors to know if this treatment should be used for all types of cancer.

CONCLUSION

Proton beam therapy is a step forward in the way we treat cancer with radiation. It helps us control the tumor better and does damage to the healthy tissues around it.. Even with these good things not many people can get this treatment because it is very expensive and not available in many places. We are also not completely sure if it is better than treatments for some types of cancer. We need to do research and find new ways to make the equipment better and cheaper. This will help more people get proton therapy. Will give us more proof that it works well for treating cancer. Proton therapy is a way to treat cancer and we should try to make it available to more people.

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