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Review Article

Oncology Section

Current Perspectives on Proton Therapy: Techniques Shaping the Future of Cancer Treatment

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ABSTRACT

Traditional Radiation Therapy (RT) predominantly comprises a targeted therapeutic strategy focused on improving localised tumour control and achieving a cure while minimising the occurrence of adverse side effects. It could be feasible to take advantage of the better dose distribution by enabling larger RT dosages to the malignancy while preventing a rise in the toxicity of RT-induced healthy tissue, or by reducing adverse reactions to manageable levels. Poor local disease control and important dose-limiting normal tissue, which prevent safe dosage increase with conventional photon RT, have been the key justifications for RT. Proton treatment, on the other hand, delivers therapeutic protons or positive particles using proton beams. The potential advantage of protons' physical properties allows for more localised RT delivery. By increasing the dosage to equitoxic levels, it is also possible to take advantage of the potential improvement in normal tissue sparing to support local tumour management and, ideally, longevity. Proton treatment preserves more important structures than photon therapy because of its unique physics. Thus, there is a need for wide usage of Proton Therapy (PT) for successive cancer treatment. The present review focuses on PT based on tumour site, clinical studies, biological barriers, instrumentation of PT, significance, and limitations.

Keywords: Proton beams, Proton treatment, Radiation therapy, Tissue toxicity

INTRODUCTION

The primary goal of Radiotherapy (RT) is to deliver an appropriate dose to a malignancy while causing the least amount of injury to adjacent natural tissues. Clinical evidence indicates a correlation between radiation dosage and positive outcomes in malignancies, with higher doses improving overall survival and local control rates [1]. However, the challenge lies in balancing the benefits of increased doses with potential damage, especially when combined with chemotherapy. Conventional RT aims for targeted intervention, optimising dosage distribution for effective tumour control while minimising harm to healthy tissues.

Proton Therapy (PT), utilising therapeutic protons, offers advantages in localised delivery compared to conventional photon therapy. Since 2015, PT has expanded globally, initially focusing on uveal melanomas and cranial base tumours, and later extending to various other disease areas [2]. Research into PT started in 2020 [3], with initial efforts in 2015 at the Lawrence Berkeley Laboratory. The partnership between Uppsala University, Harvard University, and Massachusetts General Hospital contributed to the clinical introduction of proton treatment [4]. The rise in treatment facilities worldwide reflects a preference for PT due to its precision in delivering ionising radiation [5].

The PT aims to enhance dosage distribution, sparing normal tissues and potentially improving therapeutic outcomes. The preservation of healthy tissue is considered crucial in radiation oncology, even in the absence of extensive clinical evidence, according to proponents of Proton Beam Therapy (PBT). The assessment of PT's potential benefits often relies on previously published clinical data, given the limited availability of prospective randomised outcome trials [6].

Patients are increasingly exploring proton radiation as an alternative for locally advanced malignancies, drawn to its unique physics that preserve critical anatomical structures more effectively than conventional photon therapy. Proton beams, with their distinctive physical properties, allow for conformal radiation dosages, strategically adjusting proton energies to preserve neighbouring healthy tissues [7]. PT is particularly favoured when the primary goal is to safeguard crucial organs, as protons demonstrate heightened sensitivity to organ motion and anatomical changes compared to photons. The features of PT and conventional RT are tabulated in the following table [Table/Fig-1] [8,9].

Aspect	Proton Therapy (PT) [8]	Conventional Radiotherapy (RT) [9]
Type of radiation	Uses therapeutic protons	Utilises conventional photons
Dosage delivery	More precise and accurate proton delivery is feasible to a specific site than RT	Aims for targeted intervention with optimised dosage distribution
Precision in delivery	Precisely targets tumours, sparing healthy tissues	Targets tumours while minimising harm to healthy tissues
Advantages	Enhanced dosage distribution, potential better outcomes	Focuses on effective tumour control but not effective dosage distribution
Treatment zone irradiation	Reduces irradiation dosage outside treatment zone	May irradiate healthy surrounding tissue
Sensitivity to organ motion	Demonstrates heightened sensitivity to organ motion	Less sensitivity to organ motion
Preservation of healthy tissues	Emphasises on preserving healthy tissues	Risk of hazard on healthy tissues is present
Clinical evidence	Limited availability of prospective randomised trials	Relies on extensive previously published clinical data
Application focus	Favoured for safeguarding crucial organs	Emphasises disease management with larger radiation doses
Mortality risk	Potentially lowers mortality risk compared to photon therapy	Can be associated with higher likelihood of mortality

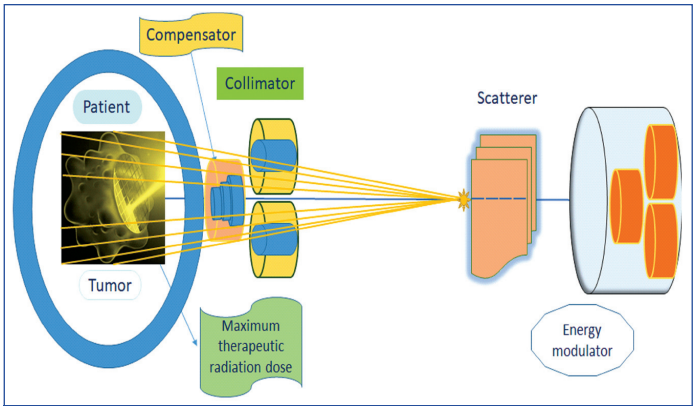
[Table/Fig-1]: The difference between Proton Therapy (PT) and conventional Radiotherapy (RT) [8,9].

The primary distinction between protons and X-rays lies in the physical characteristics of the proton beam [10]. PT directs a stream of proton particles specifically to the tumour, reducing the risk of harming surrounding healthy tissues. In contrast, conventional radiation uses X-rays or photon beams that can extend past the tumour, potentially damaging adjacent healthy tissues and leading to notable side effects. PT utilises the Bragg peak phenomenon to achieve precise dose distribution, safeguarding healthy tissue. It employs proton beams, which have low linear energy transfer, and the effective dose is calculated by multiplying the physical dosage by the Relative Biological Efficiency (RBE), which is influenced by tissue type, dosage, dose rate, energy, and penetration depth. Estimates suggest that the elevated RBE might reach 2.05 at the conclusion of the Bragg peak [11]. The RBE of protons is expected to be 1.1, similar to photons. Understanding the molecular mechanisms behind PT for treating resistant cancer cells, particularly cancer stem cells, is limited. Ionisation, a process involving alteration of atomic properties, is the basis for the advantages of RT [12]. Ionisation damages Deoxyribonucleic Acid (DNA), affecting cell activities like division and growth. Enzymes repair damage, but severe damage prevents repair. Cancer cells cannot repair molecular damage, causing longer-term harm and cell death. This allows harmful cells to develop alongside healthy ones, ultimately destroying healthy cells [13]. Protons regulate energy release in the body, slowing down and interacting more frequently with electrons. The greatest energy release is experienced by the cancer volume. Compared to the cells in the defined volume, the surrounding healthy cells are substantially less damaged [14]. Radiation oncologists can increase radiation dosage to tumour sites while minimising exposure to healthy tissues, enabling higher doses beyond lower conformity therapies, potentially reducing side effects, enhancing tumour impact, and improving management [15].

Instrumentation of PT

A proton beam for therapeutic purposes requires a source of protons accelerated to the required energy levels using hydrogen and an electrical field. Cyclotrons and synchrotrons are commonly used for proton acceleration, progressing in a spiraling motion, accumulating energy and allowing for the generation of protons with varying energy levels [16]. Synchronous technology directs protons towards the gantry for tumour treatment, using various energy levels for precise beamline delivery.

Methods include 360-degree rotation gantry, inclined beam systems, and fixed beams for specific treatment angles [17]. Protons are delivered to the patient using nozzles, which comprise several parts. There are two primary categorisations for proton delivery systems in the field of RT: passive beam scattering (scatterer) and dynamic spot scanning. The essential components integrated into the nozzle of a passive scatter system encompass scatter foils, a ridge filter or energy modulator wheel, an aperture, collimator, and a range compensator [Table/Fig-2]. In this particular context, the objective is to irradiate the targeted tumour using high-energy ionising particles, specifically protons, which have been accelerated via a particle accelerator [18]. Proton beams harm cells' DNA, leading to cell death. Cancerous cells are more susceptible due to rapid division and reduced repair capacity. The Bragg peak, the depth-dose dispersion, represents the peak. Investigative studies have demonstrated that proton fields possess the capacity to decrease the radiation dose to nearby healthy tissues by roughly 50% in contrast to photon beams [19]. Protons' comparatively enormous mass prevents them from scattering much through tissue, keeping the beam narrowly concentrated on the tumour's form without harming the tissue around it. No proton can go more than a set distance with all protons of a certain energy.



[Table/Fig-2]: Radiation Therapy (RT) system.

Patient Selection for PT

The PT treatment is most effective when it considers the risk of hazard and tumour control. PT facilities have limited space and high costs, making patient selection crucial. PT is essential for parietal tumours and brain tumours with radio-resistant malignancy, as protons carry more energy than X-rays. PT is recommended for head and neck malignancies, nasal cavity tumours, nasopharyngeal cancer, metastatic carcinomas, medulloblastoma, endocrinologically reactive adenoma, sarcoma, retroperitoneal sarcomas, endocrinologically reactive adenoma, sarcoma near vital organs, lung cancer [20]. Laryngeal cancer responds well to low radiation doses, while hypopharyngeal cancer, which cannot be surgically removed, has worse survival and RT [21]. Patients with local or early non-small cell lung cancer, lymph nodes overlapping with T7, and centrally located tumours near the brachial plexus should undergo PT [22]. In liver cancer, any tumours larger than five cm if standard irradiation is unable to provide sufficient coverage or beyond the average hepatic threshold, as well as dome and central tumours larger than three cm, PT was a choice for allowing for maximal liver sparing and perhaps lower radiation damage [23]. Thus, precision in identifying eligible cases remains paramount for leveraging the advantages of PT in oncological care.

PT on Different Tumour Sites

Randomised proton bombardment investigations primarily employ two distinct proton dosage levels subsequent to photon irradiation, and they corroborate the findings of photon trials, indicating that a higher dose is associated with enhanced disease control, albeit at the expense of heightened late gastrointestinal complications [24].

Treating patients with Central Nervous System (CNS) cancers presents a challenge in balancing morbidity and cure. PT is effective in reducing radiation exposure to critical structures like the orbit bone, reducing morbidity, and maintaining treatment efficacy in CNS cancer cases. It significantly reduces the mean dose to the temporal lobes, with the most pronounced sparing effect observed when using Intensity-modulated Proton Therapy (IMPT) with fine pencil beams [25]. PT, particularly advanced techniques like IMPT, offers superior precision and targeted treatment, minimising radiation exposure to critical brain structures like the temporal lobes. It also safeguards healthy tissues, reducing exposure to radiation in organs like the thyroid, heart, oesophagus, liver, and gastrointestinal tract [26]. PT's precision in dosage distribution allows for targeted radiation delivery, reducing exposure to critical organs and tissues, reducing acute toxicities, and improving patient quality of life. It is expected to significantly impact oncology, potentially saving cancer survivors from late effects [27]. By precisely targeting tumours while significantly limiting radiation to surrounding healthy tissues, PBT offers a promising prospect for cancer patients [28].

Tumours at the Skull Base and Brain

Chondromas and chordomas are common neoplasms near the skull's base, with a more pronounced presence in the sacrum and cervical regions. Proton treatment primarily targets cranial tumours, leading

to RT. However, evidence supporting RT's superiority over surgery in managing chordomas and chondrosarcomas remains limited [29]. RT is recommended for individuals presenting unresectable and residual tumours postsurgery due to the growing prevalence of such chordomas that are challenging to remove completely. The primary rationale for employing PT is to reduce radiation exposure to the brainstem, facilitating a safe increase in radiation dosage to the primary tumour. This escalation in radiation dose aims to enhance tumour control and overall survival. The most widely accepted measure for assessing the efficacy of surgical intervention and RT is the actuarial assessment of local tumour control, commonly referred to as local Progression Free Survival (local PFS). It compares Proton Beam Cancer Therapy (PBCT) and RT. PBCT employs a high-energy proton beam to precisely administer radiation to target tumours, contrasting with conventional RT, which utilises high-energy X-rays [30]. PBCT is a newer form of RT that irradiates tumours with minimal impact on adjacent tissues, unlike RT, which can damage surrounding tissues. It is particularly effective for tumours near sensitive organs like the brain, spine, and eyes.

Tumours of Eye

Numerous therapeutic modalities, including but not limited to local excision, enucleation, transpupillary thermotherapy, photodynamic therapy, and the utilisation of brachytherapy techniques employing isotopes such as ruthenium-106 and iodine-125, alongside advanced treatments like stereotactic photon RT and PT, are accessible to individuals who have been diagnosed with uveal melanomas. The efficacy of these therapeutic interventions, with regard to achieving local tumour control and enhancing overall survival, exhibits a striking degree of comparability, especially among patients with early-stage tumours [31]. Plaque brachytherapy is not a viable treatment option for tumours that extend near the optic disc or the fovea on their posterior edge, or for tumours with a height exceeding 5.5 mm, as it may lead to the development of optic neuropathy [32]. Hence, proton RT has been recommended as an alternative. Photons in fractionated stereotactic RT have also been used to treat patients with ocular melanoma who were not candidates for plaque treatment. The outcomes are comparable to proton therapy, both in terms of local tumour reduction and morbidity [33].

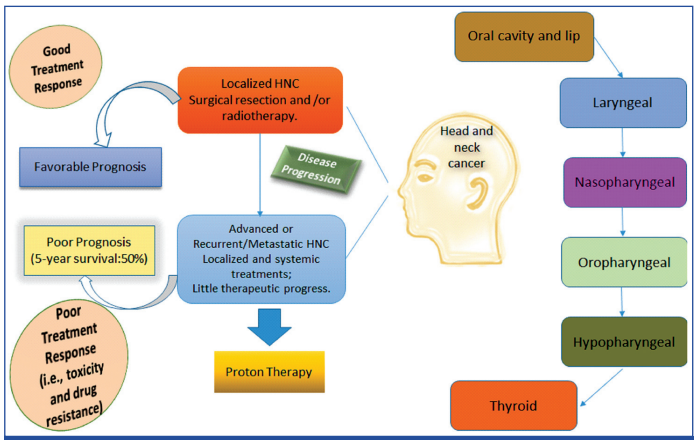
Prostate Cancer

The RT, including modern photon methods like conformal, Intensity-modulated Radiation Therapy (IMRT), and brachytherapy, is effective in treating locally advanced prostate cancer, but no trials show protons' use improves tumour control or survival. High-dose proton improvement in prostate cancer treatment may reduce disease recurrence, but RT may cause negative side-effects due to damage to healthy tissues. The primary manifestations frequently observed in individuals undergoing RT pertain to complications affecting the urinary and rectal systems [34]. It is noteworthy that a majority of these issues are of a temporary nature, although there exist the potential for radiation-induced morbidity to endure over an extended duration. In the context of radiation treatment, it is imperative to restrict the administered radiation dose in order to minimise toxicity-related concerns. Consequently, the utilisation of PT offers a viable strategy to enhance the radiation dose delivered to tumours while preserving the integrity of adjacent tissues within their tolerance limits [35].

Tumours at Head and Neck

The PT effectively addresses head and neck malignancies, particularly skin, early-stage tonsil tumours, salivary gland tumours, and mouth and throat cancers, as it targets only one side of the head or neck [36]. Since very little proximal dose sparing is required for those situations, the geometries of these targets often make such situations amenable to successful treatment using passive scattering approaches. The efficiency of PT due to its single-field optimisation permits reliable treatment planning and minimises risk in these head and neck cancers.

In these kinds of circumstances, proton dosimetry is perfect as it allows for significant organ sparing by eliminating the exit dose using PT [37]. Intensity-modulated PT stands out for its efficacy in significant reduction of doses to these sensitive areas [38]. Proton-based approaches offer significant dose reduction to multiple organs at risk, enhancing treatment outcomes and minimising side-effects for patients with carcinomas. This innovative treatment method reduces neurological and visual side-effects, improving patient outcomes and treatment tolerability. A study showed optimal dose-volume coverage improved results in patients with recurrence of nasopharyngeal carcinoma [39,40]. The present research highlighted that individuals having PT showed significantly better outcomes than those with conventional treatment, emphasising the critical role of dosage precision in PBT for recurrent cases of nasopharyngeal carcinoma. Research on PT dosimetry has demonstrated the superiority of PBT over photon-based treatment for oropharyngeal carcinoma [41]. PT can serve as an effective modality for addressing the heterogeneous nature of head and neck malignancies. It is imperative to differentiate between primary areas of concern and those that do not warrant special attention. For instance, laryngeal cancer does not merit significant consideration since it routinely receives low-dose RT and typically exhibits a favourable prognosis. Conversely, hypopharyngeal cancer, which cannot be surgically excised and is often managed with radiation over larger target volumes, presents a markedly poorer prognosis [42]. The utilisation of PT presents a potentially superior alternative to conventional chemotherapy due to the demand for higher curative doses, which often exceed what can presently be administered, while also taking into account the associated adverse effects [43]. Surgical and RT are the primary treatments for localised head and neck cancer, with the prognosis varying based on the cancer's stage and treatment response. Patients with favourable treatment tend to have a more optimistic prognosis [Table/Fig-3].



[Table/Fig-3]: Different types of treatments for head and neck cancer.

PT based on Tumour Site for Children

Children with cancer can benefit from proton treatment since it has a lower potential for damaging healthy, growing tissue [44]. PT could offer advantages to children afflicted with malignancies affecting the eye and CNS, including conditions like retinoblastoma and orbital rhabdomyosarcoma [45]. PT is a state-of-the-art radiation method that can significantly reduce the adverse effects of conventional RT for paediatric tumours. Customised to individual patient needs, it minimises long-term side-effects and maximises therapy effectiveness, especially in brain tumours [46]. In paediatric cancers affecting the eyes, such as retinoblastoma, PT's precision is vital in preserving vision. PT is a site-specific cancer treatment for children with rare sarcomas or spinal tumours, reducing damage to organs and tissues and improving overall survival rates to 80% over the past few decades [47]. Despite numerous clinical trials aimed

at reducing its impact, radiation continues to play a substantial role in the treatment of over half of paediatric patients. IMRT offers improved dose precision, yet it also presents a challenge by exposing a considerable amount of healthy tissues to low levels of radiation, potentially posing risks for younger patients [48].

Breast Cancer

The PT has emerged as an exciting RT modality for breast cancer due to the ability to minimise exposure to the heart, lungs, muscle, and bone. Breast cancer accounts for 30% of new cancer diagnosis in women. As the number of patients cured from breast cancer increases with improvements in multidisciplinary care, emphasis on reducing late therapeutic toxicity has increased to improve long-term quality of life [49]. PT not only reduces non target normal tissue exposure but also may improve target coverage of difficult-to-treat areas such as the Internal Mammary Nodes (IMNs), which lie adjacent to the heart and lungs. Therefore, PBT represents a promising approach to improve long-term treatment outcomes. PT presents an exciting RT option for breast cancer by minimising heart, lung, muscle, and bone exposure. Constituting 30% of new cancer diagnosis in women, breast cancer's rising cure rates emphasises the need to reduce treatment toxicity, enhancing long-term quality of life [50]. PT's potential to reduce non target tissue exposure and improve coverage in challenging areas like IMNs is promising for long-term treatment effectiveness. However, the risk of major coronary events increases with mean heart dose, emphasising the need to limit low-dose cardiac exposure [51]. The Surveillance, Epidemiology, and End Results (SEER) study on breast cancer survivors found a rise in secondary malignancy risk due to factors like age, follow-up duration, and tissue irradiation. Proton PT could potentially minimise radiation exposure and mitigate long-term risks. A study suggests that PT may be more effective than photon therapy in treating left-sided breast cancer, potentially reducing cardiac-related complications and reducing the risk of recurrence by about 1% and 3%, respectively [52]. Accelerated Partial Breast Irradiation (APBI) stands as a well-established adjunctive therapy subsequent to lumpectomy, particularly for women aged over 50 years, exhibiting favourable early-stage breast cancer characteristics such as absence of lymph node involvement and hormone receptor positivity. APBI combined with PBT highlights its efficacy in maintaining high rates of breast tumour control [53].

Clinical Studies of PT

Numerous clinical investigations have extensively analysed PT's efficacy across various tumour sites, with each study typically involving a cohort of no fewer than 20 patients and a follow-up period of atleast two years [54]. Critical research areas include head and neck tumours [55,56], with two studies covering 62 patients, revealing valuable insights into PT's application for these conditions. Additionally, studies focusing on prostate cancer (involving 1,642 patients) [57,58], ocular tumours (encompassing 1,406 patients) [59], gastrointestinal cancer (involving 76 patients) [60,61], lung cancer (with 125 patients) [62-64], and CNS tumours (encompassing 146 patients) [65,66] have significantly contributed to understanding PT's impact across these specific cancers. Furthermore, investigations into sarcomas (with 47 patients) [67], and studies exploring PT's potential for less common tumour sites (61 patients) [68,69] further enrich the diverse body of evidence supporting its utility. Overall, this collective research, involving studies with 3,565 patients, greatly enhances comprehension of PT's effectiveness, aiming to refine treatment options and improve outcomes for oncology patients across various cancer types. These studies were tabulated in the following [Table/Fig-4] [55-69].

Significance of PT in Clinical Oncology

Current clinical evidence indicates that PT is atleast as proficient as photon techniques in disease control, and there is a growing body

	Tumour site	Author's name and year	Place of study	Number of studies	Number of subjects/ patients	Objective	Conclusion
1	Head and neck	Tokuuye K et al., (2004); Slater JD et al., (2005) [55,56]	Japan	2	62	The study evaluates PT for head-neck cancers and accelerated photon-proton radiation	PT: higher local control, fewer toxicities; late toxicity in high-dose areas
2	Prostate	Slater JD et al., (2004); Zietman AL et al., (2005) [57,58]	USA, Boston in New England	2	1642	The study assessed if higher doses of proton radiation benefit prostate cancer outcomes	High-dose conformal radiation improves prostate cancer control without increased side-effects; conventional therapy may not eradicate cancer in many cases
3	Ocular	Dendale R, et al., (2006) [59]	France	1	1406	The study evaluates long-term effects on uveal melanoma, factors and enucleation, retrospective series	Improves local control in large tumours
4	Gastrointestinal	Koyama S, Tsujii H (2003); Kawashima M et al., (2005) [60,61]	Japan	2	76	Study evaluates proton beam RT for oesophageal and hepatocellular carcinoma	Higher proton doses enhanced control in oesophageal carcinomas; PT yielded superior results with less toxicity
5	Lung	Chen J et al., Nihei K et al., (2006); Shioyama Y et al., (2003); (2019) [62-64]	Japan, China	3	125	Study assesses high-dose PT for Stage I lung cancer outcomes	PT for Stage I NSCLC showed increased effect; Stage IB outcomes needed further study; Recommends trials to evaluate merit
6	Central nervous system	Noel G et al., (2005); Sugahara S et al., (2005) [65,66]	France, Japan	2	146	Evaluates, prognostic factors, irradiation of PT on skull, cervical spine, chordoma, oesophageal cancer	PT found effective for skull, cervical spine tumours and oesophageal cancer
7	Sarcomas	Hug EB, et al., (1995) [67]	United States	1	47	Study assessed combined high-dose proton and photon therapy for axial skeleton tumours	3D treatment, proton-photon therapy, axial tumours, higher doses, tissue constraints, improved control
8	Urinary bladder cancer	Hata M, et al., (2006); Kagei K, et al., (2003) [68,69]	Japan	2	61	Study assessed efficacy of proton beam on bladder-preserving, invasive bladder cancer, uterine cervix carcinoma	Bladder-preserving strategy with proton beam improves invasive bladder cancer outcomes
	Total			14	3565		

[Table/Fig-4]: Current clinical investigations of Proton Therapy (PT) [55-69].
NSCLC: Non smal cell lung cancer

of evidence suggesting reduced toxicities associated with proton treatments. PT exhibits dosimetric superiority compared to photon therapy by better preserving normal tissue, especially at lower to moderate dose levels. This capability enables the delivery of increased tumouricidal doses. Proton treatment minimises harm to surrounding healthy tissues while accurately targeting malignancies. Malignancies close to vulnerable or vital organs benefit greatly from this precision. In comparison with standard RT, its focused nature lowers the likelihood of long-term problems and adverse reactions, therefore being appropriate for juvenile patients and less damaging to normal tissues. PT may result in fewer side effects both during and following treatment, improving the quality of life by protecting healthy tissues. Since proton beams focus most of their energy on the tumour, they may target it with a greater radiation dosage while exposing fewer adjacent healthy tissues to radiation. For certain malignancies, including those in children, tumours near vital organs, malignancies in the brain, and tumours in the eyes, proton treatment is very beneficial. Even with the significant installation expenses at first, proton treatment could eventually prove to be more affordable due to the possibility of fewer problems and shorter long-term healthcare requirements. Utilising PT requires tumours near critical structures and robust evidence supporting increased radiation dosage for improved tumour control and survival. Growing interest exists in tumour treatment via PT to minimise healthy tissue exposure [70].

Limitation(s)

While PT offers superior dose precision compared to photons, several unanswered queries persist. These include identifying the patient demographics that benefit most from PT, assessing whether proton dose escalation enhances curative outcomes for a broader range of patients, understanding how PT reduces treatment-related toxicities to improve patients' quality of life, exploring the potential for shorter treatment durations, and determining the synergies between PT and other modalities like surgery, chemotherapy, and photon therapy [70]. Protons may be cost-effective for certain tumour groups, but evidence is lacking for superior treatment outcomes compared to photon therapy. Higher costs of PT, primarily due to extended facility hours, are a critical limitation for this therapy [71]. PT offers fewer severe side effects, but questions remain about patient demographics, treatment schedule feasibility, and collaboration potential. Challenges include the complexity of proton acceleration equipment.

CONCLUSION(S)

The PT, though technologically advanced, lacks substantial clinical evidence in demonstrating clear survival or toxicity benefits compared to standard radiation treatments. Despite its potential in reducing normal tissue toxicity and allowing dose escalation for improved disease control, the absence of peer-reviewed data showing its superiority remains a critical concern. The proliferation of PT units seems commercially driven, lacking emphasis on evidence-based medicine. However, this absence of proof shouldn't dismiss the technology but should incite well-structured trials focused on clinically relevant endpoints. Identification of suitable tumour targets and prospective studies devoid of commercial influences are crucial for validating the theoretical benefits of PT, particularly in cancers near critical organs like lung, oesophageal, and hepatocellular cancers, ensuring improved outcomes with tangible clinical evidence.

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