CHARGED PARTICLE THERAPY FOR CANCER TREATMENT

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Abstract:
Radiotherapy (RT) has been a well-established curative and palliative treatment modality in cancer care, either alone or in conjunction with other treatment options. While traditional photon RT is considered a mature science, it has inherent limitations due to the exponential depth-dose curve, leading to issues like entrance and exit doses in neighbouring tissues. Charged particle therapy (CPT), which employs particles like protons and carbon ions, presents unique physical and biological benefits. The physical advantage comes from conformal dose delivery through Bragg peak, which minimizes entrance/exit dose and spares healthy tissues. In addition, higher relative biological effectiveness (RBE) of CPT allows better biological responses and improved therapeutic ratio. Past two decades have seen a significant expansion and promising outcomes in the management of a wide range of cancer types using CPT, particularly those in delicate anatomical locations. Broader adoption of these therapies however, remains a subject of ongoing discussion within the medical community. Many experts advocate for widespread adoption due to their physical dose superiority, while others argue for more stringent clinical trials before expanding its availability, given the higher associated costs.

Introduction:

Cancer has emerged as a significant public health concern worldwide. With an estimative incidence of 19.3 million, it currently ranks as the second most common cause of death world-wide, second only to cardiovascular diseases (source: GLOBOCAN 2020; https://gco.iarc.fr). In India, projections from the Indian Council of Medical Research (ICMR) indicate a putative 12.8% increase in cancer incidence by 2025 relative to 2020. [1]

Cancer is a group of diseases characterized by unregulated proliferation of cells and a multifactorial etiology with several pathophysiological consequences. Surgery, radiation therapy (external beam or radionuclide) and chemotherapy (systemic or targeted) either as single treatments or through multi-modal approach is among the long-established approaches of cancer treatment. Some of the more pioneering alternatives include immunotherapy, stem cell and dendritic-cell based therapy, chemodynamic therapy, sonodynamic therapy, ablation therapy, nanoparticles, and many more.[2] Being a highly cost-effective regime, radiation therapy (or radiotherapy) continues to be the corner stone for curative and palliative management in almost 50% of cancer patients. [3] In principle, all tumor cells can be eliminated by delivering a sufficiently high dose of radiation, potentially resulting in nearly 100% tumor control probability (TCP). However, in practice, the radiation dose that can be administered to a patient is restricted by the tolerance of surrounding healthy tissue. High TCP with minimal likelihood of complications in normal tissue (NTCP) is typically accomplished by fractionating the total radiation dose. This often involves a total dose of 60-80 Gy, delivered as ~2 Gy per fraction, directed towards the clinical tumor volume (CTV).

Electromagnetic radiation used for therapy includes X-rays and gamma rays, which consists of photons. In modern medicine, high-energy photon beams are commonly generated by accelerating electrons and directing them to strike a target material, typically made of tungsten. This process is the foundation of new-age linear accelerators (LINACs), which is widely employed in radiation therapy across the world. State-of-the-art treatments employ innovative advances such as 'Conformal Radiotherapy' (CRT) and 'Intensity Modulated Radiation Therapy' (IMRT). These allow more precise and targeted treatment delivery to the tumor volume leading to high TCP. [2] Despite these remarkable enhancements, the physics of X-ray dose distribution remains suboptimal for radiotherapy, with the highest dose delivered at the entrance.

Particle therapy for cancer treatment uses protons, neutrons, alpha-particles or other heavier ions (e.g., helium or carbon ions). Except for neutrons, all of these are charged particles. These charged particles are characterized by a superior dose-depth profile and a higher relative biological effectiveness (RBE) in terms of causing damage to biomolecules. Nonetheless, widespread adoption of charged particle therapy (CPT) has been sluggish, since it demands cost-prohibitive particle accelerators such as cyclotrons, synchrotrons or synchrocyclotrons and, intricate beam transport lines, in contrast to the cost-effective LINACs and compact gantries employed in photon therapy. Proton beam therapy (PBT) and carbon-ion beam therapy (CIBT) are the most commonly used forms of CPT in the field of oncology.

Emergence of Charged Particle Therapy:

The discovery of X-rays by W. C. Röntgen and, radioactivity by Henri Becquerel, Marie Curie and others in the late 19th century laid the foundation for the use of radiation in medicine. Soon after their discovery in 1895, the potential for X-rays in cancer treatment, as well as their primary diagnostic use, was recognized. During early days, poor understanding of their properties and mechanism of action made radiation treatment (radiotherapy) imprecise and often ineffective. [4] Much of the improvement in the field of radiotherapy in the following decades directly paralleled machine development. This era was characterized by

machines that allowed delivery of higher energies and higher outputs. This resulted in better depth-doses for deep-seated tumors and better localization within the tumors with greater skin sparing. By the middle of 19th century, with the development of teletherapy machines like the cobalt-60 unit and the electron linear accelerators, X-ray and gamma therapy had evolved to become the mainstay of cancer treatment worldwide.

It was in the year 1904 that Sir William Henry Bragg, a distinguished physicist, first noticed that when a charged particle travels through a medium, it tends to deposit a significant portion of its energy towards the end of its path producing a distinctive deposition peak, termed 'Bragg Peak' appearing on the depth-dose plot. [5] Clinical implications of this Bragg peak phenomenon for targeted cancer therapy was originally suggested in 1946 by Robert R. Wilson in his landmark paper wherein he hypothesized minimum damage to healthy tissue and maximum damage to target which would be aligned to the end of the range of the charged particle just before they come to a complete stop within tissue. To treat a tumor that may have varying depths and shapes within the body, a single narrow Bragg peak may not be sufficient. Wilson thus, introduced the concept of spread-out Bragg peak (SOBP), wherein multiple pristine Bragg peaks with different energies are superimposed or combined to achieve broader distribution and cover the entire tumor with an adequate radiation dose. [6] Wilson's ideas were validated with animal studies using the cyclotron at Lawrence Berkeley Laboratory (LBL), University of California (CA, US) [7], paving the way for the first-ever treatment of a cancer patient with proton beams in 1954. Most proton machines used initially for therapeutic trials were built for physics research, but promising potential of these ions in therapy led to construction of hospital located cyclotron-based PBT Centre at the Clatterbridge Oncology Centre (UK) in 1989, and at the synchrotron-based PBT facility at the Loma Linda University Medical Centre (LLUMC, CA, USA) in 1990. To date, there are 97 operational PBT facilities worldwide, and by 2019, almost 222,425 patients had received PBT treatment globally. [8] In India, the first PBT unit was established at the private Apollo Proton Cancer Centre, Chennai; while the first public-sector PBT centre was made operational in May 2023 at the National Hadron Centre, Tata Memorial Centre (TMC), Mumbai.

Ions which are heavier than protons, such as carbon, neon, argon, helium and silicon etc were also tried during various radiotherapy trials at LBL between 1975 and 1982. Through extensive research on several ion species, carbon was identified as the ideal choice for heavy-ion radiation therapy due to its high relative biological effectiveness (RBE) and lower oxygen enhancement ratio (OER).[9,10,11] Heavy Ion Medical Accelerator in Chiba (HIMAC) established in 1994 at the National Institute of Radiological Sciences (NIRS), Japan was the first dedicated medical facility for heavy-ion radiotherapy. [9,10] Since then, CIBT has received significant technological and government support in Japan and Europe. Presently, there are 13 CIBT centres in five countries across the world. [11] In India, as yet, there are no CIBT centres due to expensive infrastructure requirement and paucity of data justifying the advantage of carbon ions *vis-à-vis* costs involved.

Physical Characteristics of Charged Particles:

When radiation is absorbed in biological material, it causes ionisations and excitations. These events which are stochastic in nature are not randomly distributed, but are localised along its track depending on the type of radiation involved. Linear Energy Transfer (LET) is the energy transferred by the radiation to the medium (e.g. tissues) per unit track length (keV/μm). For example, X-rays photons give rise to fast electrons, which carry unit electrical charge but no mass. On the other hand, charged particles such as proton have mass nearly 2000 times more than electron, while carbon ions have huge charge-to-mass ratio. This results in differences in density of ionisations along their tracks. X-rays are thus, sparsely ionising and have low LET, while charged particles are densely ionising and have high-LET. In general, radiations with LET values below 10 keVμm^{-1} are considered low LET, while radiation with LET values above 10 keVμm^{-1} are categorized as high-LET radiation. [12]

From the perspective of physics, the decreased lateral scattering provides a leading edge to high-LET radiations. Furthermore, when these charged particles are accelerated in accelerators, they gain high energy which allows increased penetration. Hence, relative to photon radiation (X-rays and gamma rays), the dose distribution, penetrating power and precision targeting of CPT (protons and C-ions) within the tissues are markedly distinct.

Introduction of charged particle radiation into radiotherapy was based mainly on favourable dose-depth distribution termed 'Bragg peak' (Fig 1a). Upon entering the tissue, CPT imparts lower dose along the path of the beam in front of the target (tumor), deposit maximal dose near the end of the energy range in the 'Bragg Peak' at the target site and little-to-no exit dose beyond the target site. This permits more accurate targeting of tumors while sparing surrounding healthy tissues. This is specifically beneficial for tumors found near critical organs or in pediatric patients. Photons, in contrast, have the versatile characteristic of being highly penetrating that makes them suitable for a wide range of medical applications. However, this also implies that they have a continuous dose distribution all along their path delivering energies even to non-target healthy tissues, both in front and beyond the tumor site (Fig 1b)

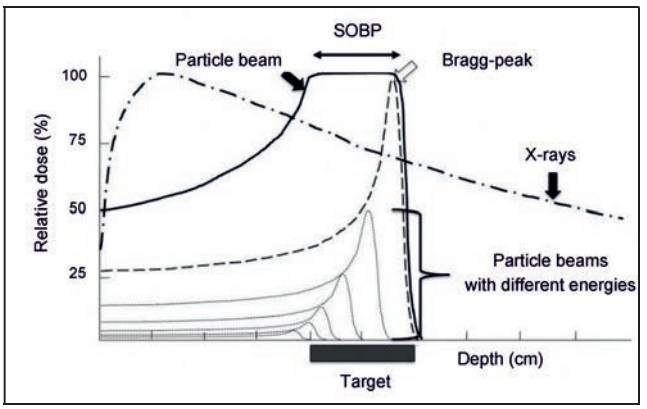

Fig. 1a. Depth-dose curve for clinical X-rays and charged particle radiation (proton and carbon-ion beams). [13]

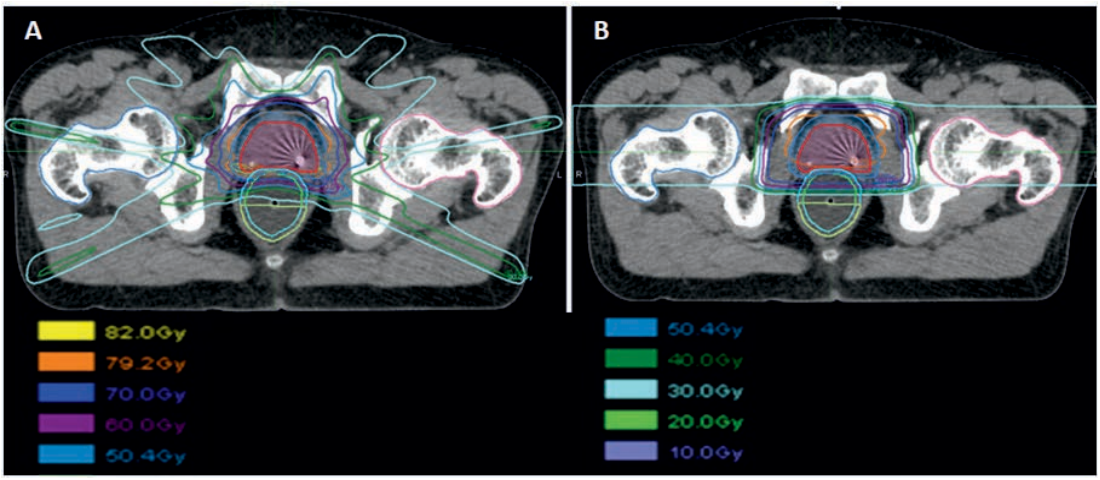

Fig 1b. Dose deposition comparison map for treatment of prostate cancer (A) Intensity-modulated radiotherapy, (B) Three-dimensional proton therapy. [14]

Biological Characteristics of Charged Particles:

The major potential advantage of charged particles lies in the realm of biology as illustrated in Fig 2.

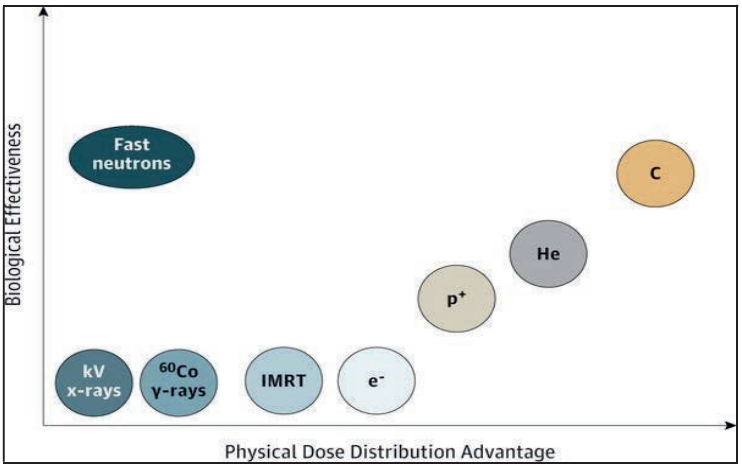

Fig 2. Biological effectiveness *vs* Physical dose distribution advantage for various radiations. ^{60}Co indicates cobalt-60; IMRT, intensity-modulated radiotherapy; e-, electrons; p+, protons; He, helium; C, carbon ions. [15]

Direct and Complex DNA Damage

The biological effects of radiation are influenced by the quality of radiation in terms of LET. As the charged particles with high-LET traverse through biological tissues, they create a

dense trail of ionization events. This increased ionization density results in a higher probability of direct interactions with DNA strands, resulting in the breakage of chemical bonds and the formation of complex DNA lesions. Instead of being uniformly distributed, these damages tend to "cluster" along the path of the particle wherein ≥2 lesions (same or different type) occur within 1-2 helical turns of DNA or a few nm (Fig 3). These lesions which may include combination of strand breaks (double strand breaks; DSBs and single strand breaks; SSBs) or base damages, are referred to as multiply-damaged sites or clustered DNA damages. From a biological perspective, these damages are more persistent and more challenging for the cells to repair. [16]

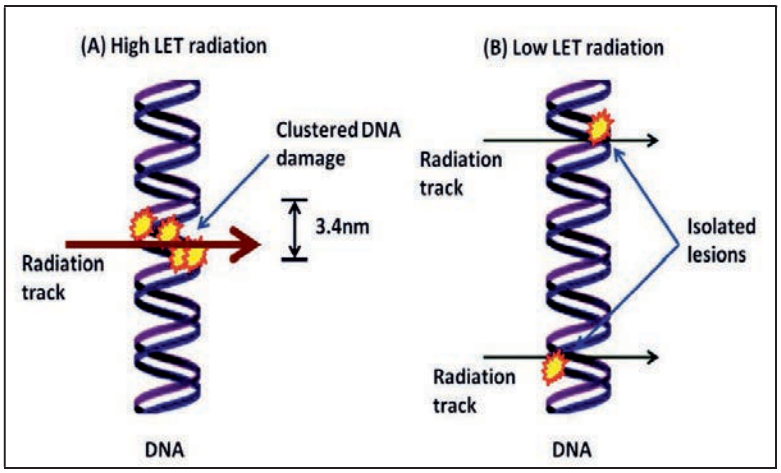

Fig 3. DNA damage by ionizing radiations (A). High-LET radiation (densely ionizing) generates clustered DNA damages, (B). Low LET radiation (sparsely ionizing) generates randomly isolated DNA damages. [17]

Higher Relative Biological Effectiveness (RBE):

An important factor in the context of radiation therapy, particularly when comparing the biological effects of different types of radiation, is RBE. The RBE is defined as the ratio of a dose of photons (reference radiation) needed to produce a specific biological effect to the dose of the particle radiation (e.g., protons or carbon ions) required to produce the same effect under identical conditions. Thus, the RBE tends to increase with higher LET (Fig 2). RBE of a radiation is a complex function influenced by several factors such as varying sensitivity of tissues, radiobiological models used, cell cycle phase, activation of repair mechanisms and intrinsic radiosensitivity. The complex interplay of these multiple factors has led to considerable uncertainties in defining clinically relevant RBE for proton therapy. Since proton is low LET radiation like gamma-rays, a practical RBE of 1:1 has been widely adopted for international standards. Yet, few reports indicate an increase in LET close to the distal edge of proton SOBP that may modulate biological effects and overall RBE may be as high as 1.7. [18] Implications of these radiobiological results need to be validated further in clinical settings. On the contrary, heavier ions, like carbon ions have high-LET across the SOBP with a favourable peak-to-plateau ratio and hence, have distinctively higher RBE. The biological RBE for carbon ions is considered to be ~1.5, while clinical RBE is taken as ~3.0.

[13] In the case of exceptionally large particles like argon, the rise in LET does not solely happen at the Bragg peak but also in the plateau region along the path of the beam, leading to an excess of damage to healthy tissues. This makes extremely small and exceptionally large particles suboptimal for heavy-ion radiotherapy. [19]

Limited Oxygen Enhancement Ratio (OER):

Another critical aspect of biological effectiveness of radiations is their dependence on oxygen. X-rays are more effective in well-oxygenated environments, a phenomenon known as the Oxygen Enhancement Ratio (OER). Conversely, charged particle radiations have a reduced OER, which means they can maintain their potency in hypoxic (low-oxygen) regions within tumors. [20] This property is advantageous in cancer treatment, as many solid tumors contain poorly oxygenated radioresistant hypoxic regions. Photons and protons show a comparable OER ranging between 2.5 to 3 while high-LET radiation like carbon ions show a reduced OER of 1.6 to 2. [21,22]

Higher Immune Response :

Particle radiation therapy has also shown promising results in their ability to elicit higher antitumor immune response, more diverse T cell repertoire (neo-antigens) and reduced metastasis compared to photons. [23] Further understanding of key immune responses of photon vis-à-vis charged particle radiation is thus, important for effective radiation therapy.

DNA Damage Response and Cell Cycle Related Cellular Pathways:

Intrinsic radiosenstivity of biological systems is also attributed to interplay of various molecular pathways that are activated after radiation such as DNA damage response, cells cycle check points, DNA repair and cell death pathways etc. [24] Several studies highlight the quantitative as well as qualitative differences in signaling after high-LET irradiation in distinction to low-LET irradiation. [25] Studies by Ghosh et al (2011) indicated that though both high and low LET radiations may induce activation of identical repair proteins, the ability of high-LET radiation to form distinct macromolecular complexes in response to complex damage sites might lead to distinct end points. [26,27] Mladenova et al (2022) showed that greater toxicity of high-LET DSB-clusters may be due to the inhibition of classical non-homologous end-joining (c-NHEJ) and promotion of alternative end-joining (alt-EJ), thereby counter-balancing the induction of error-free homologous recombination (HR) repair. [28] Several reports also suggest that as opposed to low LET gamma or X-rays, high-LET radiation promote larger induction of endogenous free radicals, leading to high genomic instability. [29] Molecular studies by Narang et al (2015) on A549 lung carcinoma epithelial cells showed that at equivalent dose, the number of genes responding to proton irradiation was almost ten-fold higher than those responding to gamma. [30] Du et al (2022) showed increased induction of γ-H2AX, G_0-/G_1- or G_2-/M-phase arrest and apoptosis in carbon ion and proton irradiated prostate cancer cells. [22] The presence of cancer stem cells (CSCs) is closely associated with several critical aspects of cancer, including tumor recurrence, metastasis and treatment resistance. Proton treatment was observed to be more efficient at lowering specific population of lung cancer cells with characteristics resembling CSCs. Additionally, they exhibited reduced invasiveness and migration capabilities when compared to photons.[30] Furthermore, high-LET radiation showed limited variations in cell cycle sensitivity which may be beneficial for slow-growing tumors. [31] Complex DNA damages

seen with high-LET radiation may result in delayed repair or mis-repair, which can eventually leading to mutations, complex chromosomal aberrations and cell death. [32,33]

It is well-documented that cells that are not themselves in the field of irradiation too show cellular effects through gap junctions or soluble factors released in the medium from irradiated cells; this phenomenon is termed as bystander effect. Bystander effects of irradiated tumor cells can modulate either rescue or adverse effects in the neighbouring healthy tissue. [34] Several research groups have shown that high-LET radiation induces distinct bystander effects, which are typically mediated through differential activation of DNA damage response signaling molecules like ATM, ERK and p38, compared to low LET radiation. [35,36]

Clinical Applications of Charged Particle Therapy:

Among the charged particles, protons have almost zero exit doses beyond the target, while for heavy ions such as carbon, a fragmentation tail is observed. This offers several advantages such as reduced effect on normal growth, preserving organ function and lowering risk of second malignancy later in life, thereby making PBT a preferred treatment modality for treating childhood cancers. In a similar manner, carbon ions due to its substantially smaller (sharper dose deposition) penumbra, provide a significant advantage for treating tumors near sensitive organs like brain, eyes or spinal cord.

Pediatric Tumors:

Children differ from adults with respect to the long-term effects of radiotherapy in two ways. Firstly, they have a higher risk of developing secondary malignancies. Secondly, they are more liable to the adverse impacts of radiation as dividing tissues are more sensitive to radiation. It is therefore, crucial to ensure adequate protection of the surrounding healthy tissue in pediatric patients. CPT is recognized as a successful therapy for brain tumors and sarcomas, which are relatively frequent among children and teens. Clinical trials in pediatric patients treated with proton irradiation have demonstrated favorable tolerance and local control comparable to or even surpassing that achieved with conventional radiotherapy.[37] A study that compared outcomes in patients treated with PBT between 1973 and 2001 versus patients who received photon therapy showed that the incidence of second malignancies was lower in patients treated with protons (5.2%) compared to those treated with photons (7.5%) for a follow up period of 6.7 years. [38] Another study which examined patients with retinoblastoma treated with P between 1986 and 2011 also observed a reduction in the incidence of in-field malignancies within a 10-year period. [39]

Adult Tumors:

Tumors at critical sites, Head and Neck tumors and tumors near neural axis – Head and Neck tumors such as adenoid cystic carcinomas, parotid gland tumors and nasopharyngeal tumors and, primary bone tumors such as chordomas and chondrosarcomas are slow-growing, but aggressive, and exhibit a high relapse rate. Complete surgical resection of the tumor is a necessary requirement for a good prognosis. However, due to juxtaposition of the tumor to critical structures in the skull base and brain stem etc, total resection is practically unachievable. Conventional X-ray therapy offers limited TCP through dose escalation as the

critical organs are often at risk of irradiation. Thus, in these cases, PBT or CIBT is preferred. [40] Patients treated with PBT and CIBT both have shown good overall survival rates, with CIBT showing better rates without a higher grade late toxicity. [41] Meta-analysis of studies showed that though CPT provided comparable local control as X-rays, toxicity effects were markedly reduced [42]. A study at NIRS, Japan on patients with radioresistant head and neck tumours showed higher survival when treated with carbon ions. [43,44]

Eye tumors – Ocular tumours are routinely treated using protons accelerated at energies around 70 MeV in many PBT facilities worldwide. Carbon ion therapy showed increased tumor control probability (TCP) as well as higher (80-90%) ocular conservation rate in patients with locally advanced or choroidal melanoma, especially when located in critical positions. [45] There is sufficient clinical evidence to suggest clear benefit of protons over X-rays in patients with uveal melanomas. [37]

Genitourinary cancers - CPT has been used for the treatment of various genitourinary cancers. This includes cancers which show highest incidence, such as prostate cancer in men, as well as also those associated with the highest mortality, such as renal cell carcinoma (RCC). Initial treatment of RCC involves complete or partial nephrectomy. Prognosis is very poor for recurring tumors as it is highly resistant to both chemotherapy and radiotherapy. [46] A clinical study of 10 patients who underwent carbon ion therapy for primary RCC showed 100% local control rate in all, with only one case of acute toxicity. [47] These studies suggested that CPT can be a better option than surgery for RCC patients.

In case of prostate cancers, IMRT using X-rays remains long-established treatment modality, with proven effectiveness in achieving local disease control and possibility of dose escalation. The advantage of CPT therefore, often revolves around the potential to reduce Normal Tissue Complication Probability (NTCP) and the risk of secondary cancers. Studies analysing use of CPT for prostate cancer have shown better local control (reduced chance of biochemical failure) and lower adverse effects like erectile dysfunction and urinary incontinence in such patients. [48] A study by Talcott et al (2010) evaluated effect of similar doses of proton and photon irradiation in patients with prostate cancer and found comparable late side effects in both groups. [49] In contrast, a study by Takagi et al (2017) reported lower toxicities with protons. [50] In case of carbon ion irradiation modality, a study from the NIRS, Japan analysing chance of secondary malignancies in 1,455 patients who underwent such treatment showed lower chance of subsequent malignancies compared to treatment with photons or surgery. [51]

Lung Tumors – Proton therapy in patients with non-small cell lung cancer (NLCLC) suggested greater sparing of chest organs at risk over photons while delivering optimal dose to the target. A meta-analysis by Tian et al (2013) indicated substantially lower doses to lung and heart with PBT when compared with conventional X-ray therapy. However, meta-analysis of clinical data in cases with inoperable stage I NSCLC did not find major differences in survival between CPT and Stereotactic body radiotherapy (SBRT). [52] In cases where excessive toxicity prevents dose escalation in photon-based SBRT needed to achieve tumor control in centrally located lung tumors, proton-based SBRT or hypofractionated regimens might help in decreased dose to non-target tissues and vital organs. [53] In patients with lung cancer, due to non-static target i.e breathing movement of the lungs, exploiting the benefits of PBT is a technical challenge because sharp deposition in Bragg peak may happen

in the nearby normal tissue due to mobility. Lower NTCP with CPT as seen *in silico* studies needs validation with clinical data.

Gastrointestinal Tumors - Clinical trials of CPT in patients with liver, rectal, pancreatic, and esophageal cancers have yielded inconclusive results regarding its advantage over photon therapy. However for some cancers with poor prognosis, CPT might be advantageous. For example, clinical evidence of CPT for the treatment of hepatocellular carcinoma revealed better tumor control and lower toxicity making it preferred mode of treatment in patients with cirrhosis. [54]

Challenges of Charged Particle Radiation Therapy:

Advantages of charged particle therapy, both in terms of physical properties and clinical outcomes, are widely acknowledged. Nevertheless, the widespread access and full utilization of CPT are hampered by significant expenses associated with facility construction and operational costs, as well as due to limited radiobiological understanding.

Radiobiological considerations - Dedicated research initiatives to understand biological and cellular mechanisms of CPT, their influence on clinical outcomes and RBE, as well as modelling studies are the need of the hour. Animal experiments comparing hypo- and hyper-fractionation for photon and CPT are also necessary to fully harness the benefits of CPT. Detailed radiobiological research with CPT on different tissues such as heart, nerves, eye, blood vessels and comparison with clinical data available for conventional radiotherapy will help comprehend tissue sensitive responses. These insights will also be useful for protection of astronauts from charged particle radiation exposures during space explorations. [55] Equally important is a comprehensive understanding of immune responses elicited by charged particles, their interplay on tumor microenvironment and the combinatorial effects of particle therapy with immunotherapy. Additionally, though bystander effects have been observed for high-LET radiation, not much is known about their mechanisms. Similarly, the potential of proton and carbon-ion radiation to overcome therapeutic radioresistance and the problem of tumor recurrence, and the role of hypoxia and cancer stem cells in these processes, is largely unexplored. Genome-wide association studies for elucidating genetic sensitivity to charged particle radiation is also necessary for wider applicability of CPT. Risk of late morbidity and secondary cancers with CPT should also be addressed.

Physical and infrastructural considerations - Wider expansion of CPT continues to be seriously hampered by the requirement of expensive infrastructure and higher operational costs. Currently, most CPT centres use large circular accelerators which accelerate the particles in an electric field to the therapeutic range, while a magnetic field is used to bend the trajectories which have a lot of spatial requirements. There is thus, a need for compact accelerators while maintaining or improving on the existing machine performance, for example by employing superconducting magnets.

Beam delivery systems contribute major share of the expenses related to CPT. Most existing CPT facilities employ fixed beam ports and passive beam modulation since rotating gantries involve higher expenditure. But using fixed beam ports result in the tilting of patient to secure more beam paths. [56] This is a crucial constraint for CPT as the target has to precisely align in the end of the range of the particle, otherwise the benefits of high TCP and low NTCP are

lost. The widely used pencil beam scanning technique to deliver the proton beam is known for its exceptional precision in delivering radiation. However, inter- and intra-fractional organ motion present large uncertainties in dose application. Robust motion management and cutting-edge image-guided strategies are essential to achieve non-invasive accurate 3D/4D tumor tracking in real-time.

Technological advances in Charged Particle Therapy:

Ultra-high-dose-rate (FLASH) Radiotherapy - In FLASH radiotherapy, therapeutic doses at exceptionally high dose rates that exceed 40 Gy/sec are administered. This technique holds the potential to enhance the therapeutic index by minimizing likelihood of damage to healthy tissue while effectively targeting tumor cells, as compared to conventional dose-rates used for therapy. This concept has been successfully demonstrated with electrons, while studies with protons are ongoing and theoretically looks possible with heavier ions. [57]

Multi-ion irradiation - The idea of using mixed-beam irradiation involving a range of ions, from light to heavy, looks encouraging for selectively elevating the LET in radioresistant areas within target volumes, while maintaining lower LET in normal tissue to reduce toxicity. This approach has the promise to markedly improve tumor control while minimizing the risk of local relapse. However, multi-ion therapy is still in its formative stages and poses several technical challenges that must be addressed before its application in medical settings. Currently, an active effort is underway at NIRS in Japan to develop a multi-ion source synchrotron that combines protons, helium, carbon, and oxygen beams for this purpose. [9]

Extremely compact particle-therapy system - An important advancement in CPT has been underway through installation of a Superconducting Magnet-Integrated Ion Medical Accelerator in Chiba, known as Super MINIMAC. It is designed to be a miniature particle-therapy system, measuring about 10 m × 20 m. [9] This advanced system is anticipated to bring about a notable reduction both in the spatial requirements as well as the overall costs of establishing a heavy-ion radiotherapy facility.

Combination therapy with immunotherapy - Successful synergy of CPT and immunotherapy is enthusiastically awaited. This approach is being actively explored in various clinical trials, particularly among stage IV patients, yielding promising outcomes. Initial findings propose that charged particles may have a superior capacity to trigger immune responses compared to X-rays. [58] If verified, this characteristic could significantly enhance the role of particle therapy in clinical practice.

Conclusions:

There is convincing physical, biological and clinical rationale for CPT. Physically, it leverages the Bragg peak for precise targeting of the tumor, while from a biological and clinical perspective it expands the therapeutic ratio. This opens up a promising avenue for cancer treatment. However, it is important to note that despite these encouraging attributes, the superlative clinical benefits of CPT over other radiotherapy strategies have not been definitively established due to lack of comprehensive clinical trials and related basis research. Although further comparative studies are the need of the hour, performing randomized

controlled trials that directly compare CPT and conventional X-ray radiotherapy can be challenging. These challenges often stem from differences in the cost of treatment and inclusion of patient preferences, making it complex to design and implement such trials. Also, while the clinical outcomes of CPT have shown great promise, they have not yet definitively resolved the ongoing debate regarding the cost-effectiveness of this treatment approach. It is beyond doubt that if CPT was as cost-effective as conventional X-rays, it would provide a credible replacement for conventional photon therapy in many cases. As research and technology continue to advance, particle therapy has the potential to become even more effective, precise, and accessible. This ongoing progress can significantly expand its role in cancer treatment, benefiting both patients and healthcare providers alike.

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