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Fundamental Physical Principles and Clinical Applications of Proton Therapy: A Comprehensive Review

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ABSTRACT

Proton therapy is an advanced modality in external beam radiotherapy that exploits the unique depth-dose distribution of accelerated protons to achieve improved tumor targeting compared with conventional photon-based techniques in selected anatomical geometries. This review synthesizes the fundamental physical principles underlying proton therapy, including proton-matter interactions, stopping power, linear energy transfer (LET), the Bragg peak, and the generation of the spread-out Bragg peak (SOBP). Accelerator technologies such as cyclotrons and synchrotrons, beam delivery methods including passive scattering and pencil beam scanning, and treatment planning approaches incorporating proton computed tomography and range verification are examined. The radiobiological effectiveness of protons is discussed alongside emerging evidence for FLASH proton therapy, which delivers ultra-high dose rates (>40 Gy/s) currently under early-stage clinical investigation. Clinical applications are supported by Level I evidence from randomized controlled trials (e.g., the 2025 Lancet trial demonstrating 90.9% versus 81.0% five-year overall survival for oropharyngeal cancer), Level II evidence from prospective cohort studies, and Level III evidence from meta-analyses showing reduced toxicity and secondary malignancy risks in pediatric cancers and central nervous system tumors. Despite challenges such as range uncertainty and high facility costs, proton therapy continues to evolve as a component of precision oncology in appropriately selected patients. This review underscores how fundamental physics principles translate into measurable clinical benefits when applied to specific tumor sites and patient populations.

Keywords:
Proton therapy,
Bragg peak,
Stopping Power,
Linear Energy Transfer,
Pencil Beam Scanning,
Radiobiological Effectiveness,
FLASH radiotherapy.

INTRODUCTION

Cancer remains a leading cause of mortality globally, characterized by uncontrolled cellular proliferation and division (Brown *et al.,* 2023). About half of all cancer patients will receive radiotherapy at some point during their disease trajectory (Kutuva *et al.,* 2023). The three primary treatment modalities; surgery, chemotherapy and radiotherapy are employed alone or in combination depending on cancer type and patient condition. Surgery often aims to remove tumors, radiotherapy uses controlled radiation to kill cancer cells, and chemotherapy involves drug treatment to target cancer cells systemically (Mee *et al.,* 2023). Cancer cells are generally more sensitive to radiation than healthy cells due to impaired DNA repair mechanisms and higher proliferation rates; however radiation inevitably damages surrounding healthy tissue as well. Thus, radiotherapy planning requires balancing adequate tumor irradiation against the preservation of healthy tissue (Gudur *et al.,* 2025). The DNA of tumors and healthy cells is injured by ionizing radiation, resulting in complex biochemical reactions, prolonged abnormal cell function, and eventually, cellular death. Beams of ionizing photons such as X-rays or gamma-rays have been used for treating various types of cancer a (Byun *et al.,* 2021). Conventional radiotherapy for deep seated tumors relies on X-rays to destroy malignant cells; however, the ionising radiation also affects healthy tissues, resulting in considerable damage to the normal structures around the targeted tumor (Nácher *et al.,* 2024). Because they are uncharged particles, photons primarily interact with matter through indirect processes such as Compton scattering and the photoelectric effect. These interactions result in a relatively uniform deposition of energy along their path through tissue, which leads to broader scatter to surrounding tissue and skin in the setting of conventional radiotherapy (Gao *et al.,* 2025). This physical limitation necessitates a delicate balance between tumoricidal dose and normal tissue sparing, often compromising treatment efficacy to avoid unacceptable toxicity.

The theoretical foundation for proton therapy was established by Wilson (1946), who proposed exploiting the unique depth-dose characteristics of charged particles for clinical applications. Clinical implementation commenced at Berkeley in 1954, with hospital-based facilities emerging in the 1990s at Loma Linda University and Massachusetts General Hospital (Byun *et al.,* 2021). Recent data from the Particle Therapy Co-operative Group (PTCOG) indicate that by the end of 2024, more than 120 proton therapy centers were in operation worldwide, with over 450,000 patients treated. These facilities are largely concentrated in North America, Europe, and East Asia, while emerging markets especially China are driving new developments. Proton therapy has evolved beyond its traditional use in pediatric and skull base tumors to include more common cancers such as lung, liver, and prostate malignancies, reflecting its growing clinical importance (Choi *et al.,* 2024; Zhang *et al.,* 2026). Proton therapy offers fundamentally superior dose selectivity compared to conventional radiotherapy in specific anatomical geometries. Protons, being charged particles, exhibit a characteristic Bragg peak, a sharp maximum in energy deposition at a defined depth enabling maximal tumor dose with minimal exit dose to surrounding healthy tissues (Alme *et al.,* 2020). This physical advantage proves particularly valuable for treating localized tumors adjacent to critical structures such as the brain, brainstem, heart, and spinal cord (Nácher *et al.,* 2024). Recent technological advances have transformed proton therapy into a key component of precision medicine, incorporating pencil beam scanning, intensity modulation, and image-guided delivery (Lane *et al.,* 2023; Das *et al.,* 2023). These innovations reflect growing precision in cancer treatment and have expanded proton therapy's applicability across diverse malignancies. Contemporary practice widely employs proton therapy for pediatric cancers, ocular tumors, skull base malignancies, and re-irradiation scenarios where tissue sparing is paramount (Saito et al., 2024; Frank et al., 2026).

This review aims to provide an updated synthesis of proton therapy physics, radiobiology, and clinical evidence as of 2025–2026, with emphasis on: (i) the fundamental physical principles governing proton interactions with matter; (ii) accelerator technologies and beam delivery systems; (iii) radiobiological effectiveness and emerging FLASH applications; and (iv) quantitative clinical outcomes across pediatric and adult populations, including Level I–III evidence from randomized trials, prospective studies, and meta-analyses. By integrating these dimensions, we seek to illustrate how foundational physics principles translate into measurable clinical benefits for appropriately selected patients.

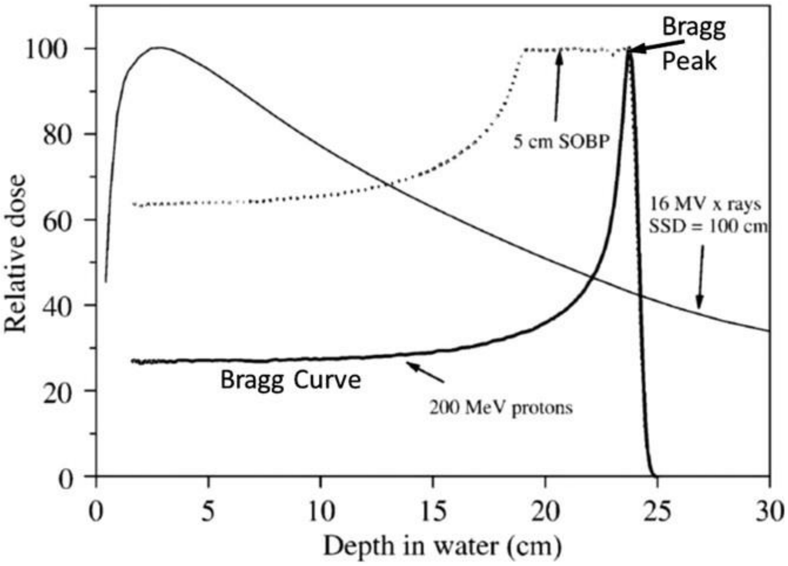

Figure 1: Depth–dose curves for a 200 MeV proton beam, showing both the pristine Bragg peak and a 5 cm spread-out Bragg peak (SOBP), compared with a 16 MV photon (X-ray) beam for a 10 × 10 cm² field. All curves are normalized to 100% at their respective maximum dose. The proton beam demonstrates a pronounced Bragg peak with minimal exit dose, while the photon beam exhibits a gradual dose fall-off with significant exit dose beyond the target (Mohan, 2022)

Theoretical Foundations of Proton Interactions with Matter

Fundamental Properties of Protons

Protons are subatomic particles with positive elemental charge (+1e) and rest mass of $1.67 \times 10^{-27} kg$, approximately 1836 times the electron mass (Young & Freedman, 2020). In therapeutic applications, protons are accelerated to energies of 70–250 MeV, providing water-equivalent penetration depths from approximately 4 cm to 36 cm. This energy range accommodates superficial tumors (skin, eye) through deep seated malignancies (spinal, pelvic) in adult patients, with pediatric applications typically requiring 180–200 MeV due to smaller body dimensions. The proton's charge-to-mass ratio enables precise magnetic control, facilitating beam steering and modulation accuracy on the order of millimeters. Modern beam delivery systems exploit these properties for three-dimensional dose sculpting, allowing radiation to conform to complex tumor geometries with exceptional accuracy (Tay *et al.,* 2021).

Mechanisms of Energy Loss

As proton beams traverse tissue, they undergo both inelastic and elastic Coulombic interactions. Kinetic energy is continuously transferred through frequent inelastic interactions with atomic electrons, while the proton's substantial mass relative to electrons ensures predominantly straight-line trajectories (Hazem, 2023). Occasional elastic interactions with atomic nuclei cause slight trajectory deflections, necessitating consideration in treatment planning (Jason *et al.,* 2024). The maximum energy transfer in a single proton-electron collision is given by:

$$T_{max} = \frac{2m_ec^2\beta^2\gamma^2}{1+2\gamma(m_e/M)+(m_e/M)^2} \qquad (1)$$

Where m_e is electron rest mass, M represent proton rest mass, $\beta = v/c$ is the ratio of proton velocity to speed of light and $\gamma = (1-\beta^2)^{-1/2}$ is the Lorentz factor. For therapeutic protons (70–250 MeV), where$2\gamma m_e \ll M$, this simplifies to:

$$T_{max} \approx 2m_ec^2\beta^2\gamma^2 \qquad (2)$$

When the transferred energy exceeds electron binding energy, delta rays (secondary electrons) are produced, contributing to microscopic energy deposition and biological damage (Attix, 2006; Podgorsak, 2008).

Stopping Power

Stopping power quantifies the average energy loss per unit path length, described mathematically as $S(E) = -dE/dx$. The mass stopping power $S/p = -(dE/pdx)$ normalizes for material density, enabling comparison across different media, where p is the mass density of the material, E is the energy of the proton beam, and x is the distance (Alruhaimi *et al.,* 2025). The Bethe-Bloch equation provides the theoretical framework for calculating stopping power:

$$\frac{S}{P} = -\frac{dE}{pdx} = 4\pi N_A r_e^2 m_e c^2 \ \frac{Z}{A}\frac{z^2}{\beta^2} \ \left[ln\left(\frac{2m_ec^2\gamma^2\beta^2}{I}\right) - \beta^2 - \frac{\delta}{2} - \frac{C}{Z}\right] \qquad (3)$$

Where N_A is Avogadro's number, r_e is the classical electron radius, z is projectile charge, Z is the atomic number of the absorbing medium, A is the atomic weight of the absorbing material, c is light speed,$\beta = v/c,$ where v is the projectile velocity, $\gamma = (1-\beta^2)^{-1/2}$, I is the mean excitation potential of irradiated material, δ is the density corrections arising from the shielding of remote electrons by close electrons and will result in a reduction of energy loss at higher energies; neglecting δ may lead to dose overestimation in proximal tissues, and C is the shell correction item, which is important only for low energies where the particle velocity is close to that of atomic electrons; It influences distal dose accuracy, critical for sparing organs at risk (Newhauser & Zhang, 2015; Mohammed, 2024; Crossley *et al.,* 2025). The two correction items in the Bethe-Bloch equation involve relativistic theory and quantum mechanics and need to be considered when very high or very low proton energies are used in calculations (Newhauser & Zhang, 2015). The inverse square velocity dependence $(1/v^2)$ implies rapid energy increase as protons decelerate, culminating in the Bragg peak phenomenon where maximum energy deposition occurs immediately before particle stop (Mohammed, 2024).

Linear Energy Transfer (LET)

Linear energy transfer represents energy deposited per unit path length, typically expressed in keV/µm. Protons exhibit low-LET characteristics in the entrance region, transitioning to moderate-LET near the Bragg peak (Helm & Fournier, 2023). Mathematically:

$$LET = \frac{dE}{dx}\left[\frac{KeV}{\mu m}\right] \qquad (4)$$

LET serves as a critical indicator of radiation quality and biological effectiveness. High-LET radiation produces more severe cellular damage through complex DNA lesions that resist repair mechanisms. In clinical proton therapy, LET varies with depth, remaining low in entrance regions, increasing toward the Bragg peak, and reaching maximum values in the distal falloff (McIntyre *et al.,* 2023). Typical proton LET values range from approximately 1–3 keV/µm in the entrance plateau, increasing to 5–10 keV/µm near the spread-out Bragg peak, and potentially reaching 20–40 keV/µm at the distal edge. These intermediate values between photons (~0.2 keV/µm) and alpha particles (~100 keV/µm) explain the modestly enhanced biological effectiveness of protons (RBE ≈ 1.1–1.2) relative to photons (Horendeck *et al.,* 2021; Paganetti, 2018).

Proton Range and Range Uncertainty

The range represents the depth at which half of primary particles come to rest, defined mathematically as:

$$R(E) = \int_0^E \left(\frac{\mathrm{d}E}{\mathrm{d}x}\right)^{-1} dE \quad (5)$$

Range depends on initial particle energy and absorber properties, with the inverse relationship between stopping power and velocity ensuring finite penetration and peak energy deposition near the path end. Range uncertainty poses significant clinical challenges, arising from CT calibration inaccuracies, anatomical changes, organ motion, and Hounsfield unit-to-stopping power conversion errors. Current clinical practice assumes approximately 3.5% range uncertainty, corresponding to roughly 3.5 mm misplacement at 10 cm water-equivalent depth (Yang *et al.,* 2012; Paganetti, 2012; Lomax, 2020). Reducing these uncertainties remains a major focus of ongoing research, driving development of proton imaging and real-time verification techniques.

The Bragg Peak Phenomenon

The Bragg peak constitutes the cornerstone of proton therapy's physical advantage. As protons traverse matter, they initially deposit minimal dose due to high velocity and correspondingly low stopping power. As deceleration proceeds, stopping power increases inversely with velocity squared, producing maximum energy deposition immediately prior to particle stop. This creates a characteristic depth-dose distribution featuring a low-dose entrance plateau, rapid distal build-up, sharp peak maximum, and steep fall-off. Statistical fluctuations in individual particle energy loss produce range straggling; uncertainty in penetration depth that broadens the Bragg peak for polyenergetic beams. Understanding range straggling is essential for predicting clinical dose distributions and designing spread-out Bragg peaks (Paganetti, 2012; Werner *et al.,* 2025).

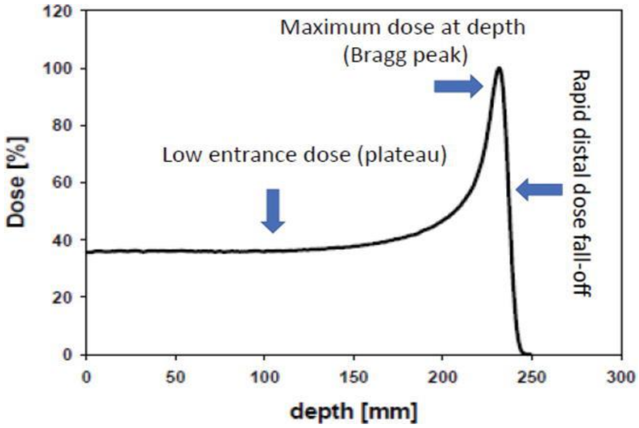

Figure 2: Typical dose deposition as a function of depth for a proton beam (Hazem, 2023)

Spread-Out Bragg Peak (SOBP)

Clinical tumors extend over finite volumes, necessitating dose coverage across depths rather than at a single point. The spread-out Bragg peak achieves this by superimposing multiple Bragg peaks of different energies with carefully calculated weighting. In passive scattering systems, rotating range modulator wheels with varying thickness sectors implement these weights mechanically. Pencil beam scanning achieves equivalent modulation through intensity-modulated delivery of discrete energy layers (Kristensen *et al.,* 2024). The SOBP creates uniform dose distribution across the target volume while maintaining the advantageous distal fall-off characteristic of the pristine Bragg peak. This enables conformal dose delivery to extended targets while preserving proximal tissue sparing and distal critical structure protection.

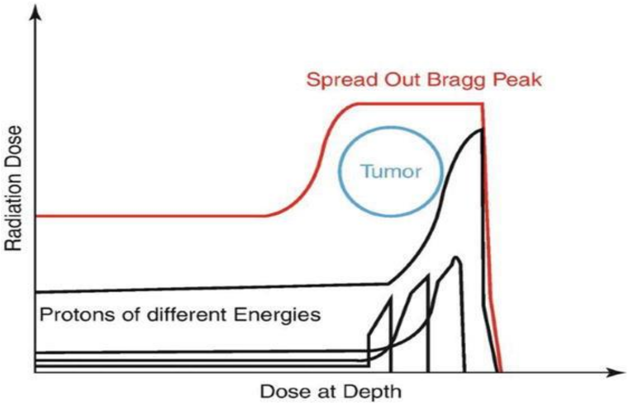

Figure 3: Superimposition of Bragg peaks of different energies to have spread-out Bragg peak (SOBP) (Hazem, 2023)

Nuclear Interactions

Beyond electromagnetic interactions, protons may undergo nuclear reactions when approaching within ~10^{-15} m of nuclei. These inelastic processes produce secondary particles including protons, neutrons, deuterons, tritons, and gamma rays. While less frequent than electronic interactions, nuclear reactions profoundly affect individual proton fate and dose distribution (Mohammed, 2024; Battistoni *et al.,* 2021). Prompt gamma emission during nuclear de-excitation provides potential for real-time range verification, as these gamma rays emerge immediately from the interaction site. Secondary neutrons, being uncharged, may travel significant distances from the beam axis, contributing dose outside the planning volume and raising radioprotection considerations (Hälg &Schneider, 2020; Cox *et al.,* 2024).

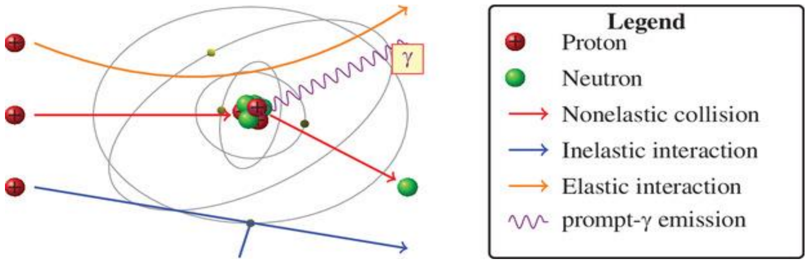

Figure 4: The three main interactions of a proton with matter. A non-elastic proton–nucleus collision, an inelastic Coulomb interaction with atomic electrons and elastic Coulomb scattering with the nucleus (Cox *et al.,* 2024)

Accelerator Technologies and Beam Delivery Systems

Proton Accelerators

Particle accelerators generate high-energy proton beams through electromagnetic field application. Clinical proton therapy requires energies of 70–250 MeV, necessitating efficient acceleration mechanisms for massive charged particles. Unlike electrons suitable for linear acceleration, proton mass requires multi-pass circular accelerators or specialized linear designs to achieve therapeutic energies (Byun *et al.,* 2021; Mohan, 2022).

The accelerator landscape has evolved significantly, with superconducting magnet technology now enabling dramatic size reduction and economic accessibility. Traditional normal-conducting cyclotrons and synchrotrons required massive infrastructure, limiting proton therapy to major academic centers. Contemporary superconducting isochronous cyclotrons and compact synchrotrons have transformed this paradigm, facilitating single-room installations and reduced capital costs. Representative examples include the IBA Proteus ONE and Varian ProBeam 360°systems. While they retain the traditional accelerator-beamline-gantry architecture, the adoption of more compact superconducting cyclotrons, shorter beamlines, and highly integrated control systems successfully consolidate the core functionalities of multi-room systems into a single-room configuration. The Mevion S250i system employs the world's first superconducting synchrocyclotron, innovatively integrating the accelerator directly onto the rotating gantry, achieving an integrated "accelerator-gantry" design that allows the entire device to fit within a standard radiotherapy room (Zhang *et al.,* 2026; Choi *et al.,* 2024).

Circular Accelerators

Cyclotrons

Cyclotrons employ constant magnetic fields and alternating electric fields to accelerate protons in spiral trajectories. The Lorentz force constrains particles to curved paths while radiofrequency cavities provide repeated acceleration. Isochronous cyclotrons maintain constant particle revolution frequency regardless of energy, enabling continuous beam extraction at fixed maximum energy determined by magnetic field strength and machine radius (Xiao *et al.,* 2024; Collings *et al.,* 2022). Cyclotrons produce a continuous proton beam at a fixed energy (e.g., 230–250 MeV), which is then degraded via an Energy Selection System (ESS) to meet the treatment requirements of tumors at different depths. Although cyclotrons offer high beam intensity and stable operation, the energy degradation process generates secondary neutron radiation, affecting the surrounding environment and equipment maintenance (Zhang *et al.,* 2026). Cyclotron advantages include continuous beam output, compact size, and high intensity, though energy flexibility requires mechanical modulation systems.

Synchrotrons

Synchrotrons utilize variable magnetic and radiofrequency fields to accelerate protons in fixed-radius circular paths. Protons are injected at low energy and accelerated through synchronized magnetic field ramping and RF frequency adjustment. This design enables precise energy selection through control of maximum magnetic field and RF parameters, producing pulsed beams with narrow energy spread (Zhang *et al.,* 2023; IAEA, 2023). In the synchrotrons, mainly used for carbon ions, the energy of proton beam can be controlled, and no energy degradation system is required. Therefore, proton beams with narrower Bragg peaks are produced by the synchrotron. Compared to the cyclotron, the generated spot sizes are potentially smaller (Hazem, 2023). Synchrotron advantages include flexible energy selection without mechanical degraders, superior energy resolution, and efficient beam utilization. Disadvantages include pulsed output (1–2 second repetition rates), larger footprint, and higher complexity compared to cyclotrons (Xiao *et al.,* 2024). Modern facilities increasingly employ superconducting magnet technology to reduce size and infrastructure requirements (Mohan, 2022).

Linear Accelerators

Linear accelerators (linacs) accelerate protons along straight trajectories using high-frequency RF fields. While traditional proton linacs faced limitations in size and complexity compared to circular machines, recent advances in high-gradient accelerating structures and novel designs demonstrate potential for compact, efficient proton linacs suitable for clinical deployment (Seeman *et al.,* 2020).

Gantries and Beam Delivery

Gantries enable beam delivery from multiple angles by rotating the beam transport system around the patient. Proton therapy gantries incorporate multiple dipole magnets for beam bending and quadrupole magnets for focusing, achieving 360° treatment angles. Typical proton gantry dimensions include 4–5 meter radius and 8–10 meter length, with magnet systems weighing up to 70 tons (Collings *et al.,* 2022; Zhang *et al.,* 2023). The source-to-axis distance (SAD) from scanning magnets to isocenter influences gantry design, with modern systems optimizing this geometry for pencil beam scanning applications. Emerging compact gantry designs employing superconducting magnets promise reduced footprint and cost.

Beam Delivery Techniques

Passive Scattering

Passive scattering broadens and flattens narrow accelerator beams to cover tumor cross-sections uniformly. Single scattering employs high atomic number (high-Z) foil scatterers, while double scattering utilizes contoured secondary scatterers for improved flatness. Range modulation wheels create SOBP through time-varying energy degradation, while patient-specific collimators and compensators shape lateral and distal beam boundaries (Asadi, 2022; Mohan, 2022). Passive scattering advantages include robustness, simplicity, and established clinical implementation. Disadvantages include neutron production from scattering materials, limited conformity for complex geometries, and requirement for patient-specific hardware.

Pencil Beam Scanning

Pencil beam scanning (PBS) represents the current state-of-the-art, employing magnetic scanning systems to deflect narrow proton beams across target volumes in raster patterns. Energy modulation for each spot positions the Bragg peak precisely at desired depths, enabling intensity-modulated proton therapy (IMPT) with exceptional conformity in both distal and proximal directions (Mohan, 2022; Paganetti, 2020). PBS eliminates scattering materials, reducing secondary neutron production and enabling treatment of complex, irregular target volumes. Disadvantages include sensitivity to organ motion and range uncertainties, necessitating robust planning strategies and quality assurance protocols.

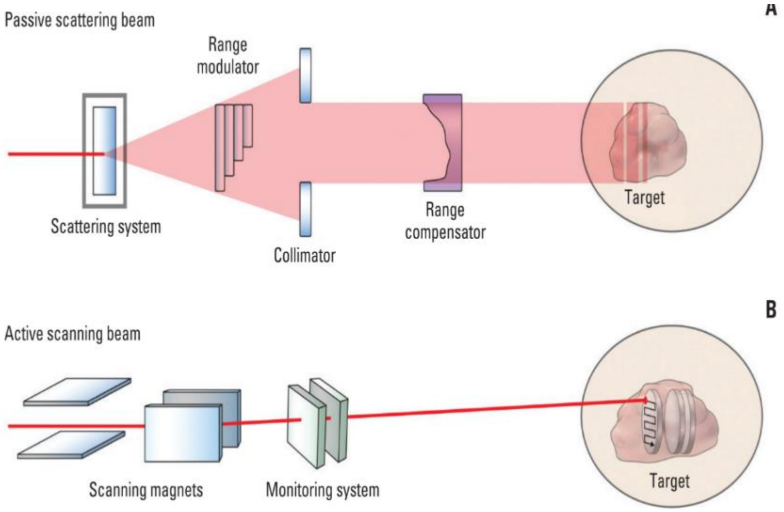

Figure 5: Schematic designs of passive scattering beam (A) and active scanning beam (B) delivery systems used in particle therapy (Byun *et al.,* 2021)

Treatment Planning, Range Verification, and Advanced Imaging

Imaging for Proton Therapy

Accurate proton therapy planning relies on high-quality imaging to characterize tissue properties and define target volumes. Conventional computed tomography (CT) remains the clinical standard, though this conversion introduces 2.7–3.5% range uncertainty (Alme *et al.,* 2020; Nácher *et al.,* 2024). Advanced modalities such as dual-energy CT and magnetic resonance imaging (MRI) improve stopping power estimation and soft-tissue delineation, thereby enhancing planning accuracy (Nácher *et al.,* 2024; Nien *et al.,* 2022).

Range verification is essential due to the finite penetration depth of protons. Prompt gamma imaging enables real-time monitoring of beam range during treatment, while positron emission tomography (PET) provides post-treatment verification of dose distribution. Both techniques achieve spatial accuracies on the order of a few millimeters and contribute to improved treatment reliability (Moglioni *et al.,* 2022; Chin *et al.,* 2025).

Range uncertainty remains a major limitation in proton therapy, arising from imaging inaccuracies, patient setup errors, and anatomical changes. Clinically, this is addressed by applying safety margins of approximately 2.5–3.5% of the proton range plus 1–2 mm, ensuring adequate tumor coverage while minimizing dose to surrounding tissues (Lomax, 2020; Paganetti, 2012).

Modern treatment planning incorporates robust optimization techniques that explicitly account for uncertainties in patient positioning and proton range. By optimizing dose across multiple error scenarios, this approach improves plan stability and has become standard in intensity-modulated proton therapy (IMPT) (Yang *et al.,* 2019; Lomax, 2020).

In addition to optimization strategies, accurate dose calculation is essential for reliable treatment planning. Monte Carlo simulation methods are widely regarded as the gold standard for proton dose calculation due to their ability to model complex physical interactions, including nuclear reactions, multiple scattering, and secondary particle production. Compared to analytical algorithms, Monte Carlo methods provide superior accuracy, particularly in heterogeneous tissues such as lung and bone, with typical uncertainties reduced to within 1–2% (Mohan, 2022)

Another critical development in proton therapy is adaptive treatment planning, which accounts for anatomical changes that occur in the course of treatment. Adaptive strategies include periodic offline replanning based on updated imaging, as well as emerging online adaptive approaches that enable near real-time plan modification. These techniques are particularly important for head and neck and thoracic cancers, where anatomical variability is pronounced (Dueholm *et al.,* 2025).

Furthermore, growing evidence indicates that the biological effectiveness of proton therapy is not constant but varies with linear energy transfer (LET), dose, and tissue characteristics. Although a constant relative biological effectiveness (RBE ≈ 1.1) is commonly assumed, evidence shows that RBE increases with linear energy transfer (LET), particularly near the distal edge of the Bragg peak. Emerging planning strategies incorporate LET and variable RBE models to enhance tumor control while minimizing toxicity (McIntyre *et al.,* 2023; Overgaard *et al.,* 2024).

Proton Computed Tomography

Proton CT (pCT) directly measures proton stopping power by tracking individual protons through the patient, potentially eliminating HU-to-RSP conversion errors.

Prototype systems demonstrate feasibility for head-sized volumes, though body imaging requires >330 MeV protons presenting technical challenges (Perotti *et al.,* 2025; Nácher *et al.,* 2024). Dual-energy CT offers practical alternatives with sub-millimeter resolution and established regulatory pathways (Wohlfahrt *et al.,* 2018).

Magnetic Resonance Imaging

MRI provides superior soft tissue contrast without ionizing radiation, increasingly integrated into proton therapy workflows. MR-guided proton therapy exploits real-time imaging capabilities for adaptive treatment, though magnetic field interactions with proton beams require careful consideration (Nien *et al.,* 2022).

Positron Emission Tomography

PET enables functional imaging and treatment verification through detection of positron-emitting isotopes produced during proton irradiation. In-beam PET monitors beam range through detection of activated tissue, identifying anatomical changes affecting dose delivery with precision of 2.3–2.5 mm (Moglioni *et al.,* 2022; Chin *et al.,* 2025).

Radiobiological Effectiveness

Relative Biological Effectiveness

Relative biological effectiveness (RBE) compares biological damage from different radiation qualities, defined as:

$$RBE = \frac{D_{reference}}{D_{proton}} \tag{6}$$

Where $D_{reference}$ represents photon dose and D_{proton} represents proton dose producing equivalent biological effect. RBE-weighted dose accounts for enhanced biological effectiveness:

$$D_{RBE} = D_{physical} \times RBE \tag{7}$$

Clinical practice conventionally assumes constant RBE of 1.1, indicating protons are approximately 10% more biologically effective than photons. However, accumulating evidence demonstrates RBE variation with LET, tissue type, dose per fraction, and biological endpoint (Paganetti, 2014, 2018, 2021).

A major unresolved issue in proton radiobiology is the selection of an appropriate RBE model for clinical use. Several models have been proposed, including the linear-quadratic-based models, the Carabe, Wedenberg and the McNamara model, each incorporating LET and dose dependencies to varying degrees. Despite their theoretical advantages, no consensus has been reached regarding routine clinical implementation due to uncertainties in parameterization and lack of large-scale clinical validation (Lee *et al.,* 2025). Consequently, most treatment centers continue to use a fixed RBE of 1.1, while research efforts focus on integrating variable RBE models into treatment planning systems (Paganetti, 2014; McNamara *et al.,* 2020; Overgaard *et al.,* 2024).

Variable RBE Considerations

Experimental data reveal RBE increases from ~1.0 in entrance regions to 1.3–1.5 or higher near the distal Bragg peak edge, with values up to 1.7 under specific conditions. This variation challenges the constant RBE assumption, particularly for critical structures positioned at beam distal edges where high-LET components may enhance biological effect (Dalalas *et al.,* 2024; Pardo-Montero *et al.,* 2023; Overgaard *et al.,* 2024). Emerging treatment planning systems incorporate LET-based or variable RBE models to better reflect true biological dose distributions, potentially improving toxicity prediction and dose constraint optimization for sensitive organs.

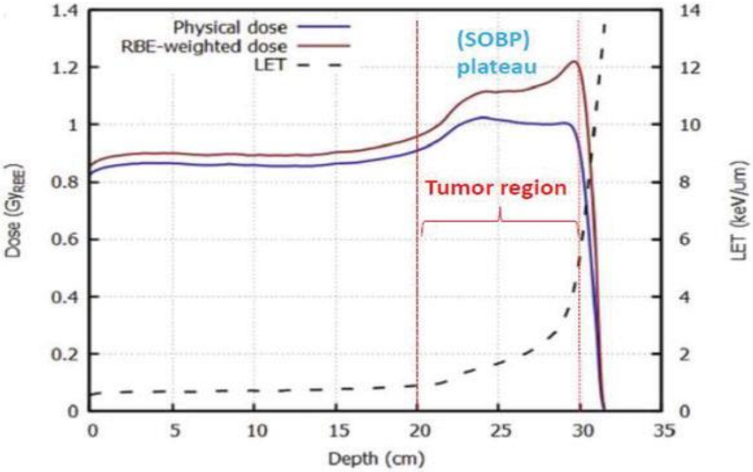

Figure 6: Physical dose, biological dose (RBE-weighted dose), and LET evolution versus penetration depth. The RBE (ratio of biological/physical dose) increases from ~1.0 at entrance to ~1.15-1.2 near the Bragg peak due to LET dependence, though clinical practice currently applies a fixed RBE of 1.1 across all depths (Harabi *et al.,* 2021)

Clinical Applications and Case Studies

Pediatric Cancers: Neurocognitive and Long-term Benefits

Proton therapy demonstrates particular value in pediatric oncology, where reduced integral dose translates to decreased risks of secondary malignancies, neurocognitive impairment, and endocrine dysfunction. Craniospinal irradiation for medulloblastoma exemplifies these advantages, with protons sparing heart, lungs, cochlea, and endocrine structures compared to photon techniques (Young *et al.,* 2023; Zając-Grabiec *et al.,* 2025). Pediatric proton therapy demonstrates profound benefits in neurocognitive preservation and reduction of late effects. A comprehensive 2024 systematic review of 75 studies (2019–2024) concluded that children treated with proton radiotherapy experience better neurocognitive and academic outcomes than those receiving photon therapy, with particular advantages in full-scale IQ, verbal comprehension, and perceptual reasoning (Patel *et al.,* 2025). Specifically, Kahalley et al. (2019) reported that children receiving focal proton therapy maintained stable neurocognitive functioning comparable to surgery-only patients, while craniospinal proton irradiation remained a risk factor for cognitive decline. Longitudinal data show consistent neurocognitive advantages across multiple domains for proton-treated patients (Patel *et al.,* 2025).

A 2024 meta-analysis of 5,848 pediatric brain cancer patients across 33 studies found no significant difference in five-year overall survival between proton and photon therapy (OR 0.80, 95% CI 0.51–1.23; $p = 0.22$), confirming equivalent oncologic efficacy. However, proton therapy significantly reduced chronic endocrine toxicity; hypothyroidism was reduced by 78% (OR 0.22, 95% CI 0.10–0.42; $p = 0.002$) and improved neurocognitive outcomes, with a 13.06-point advantage in global IQ (95% CI 4.97–21.15; $p = 0.009$). Nausea was reduced by 70% (OR 0.30, 95% CI 0.11–0.78; $p = 0.028$), and thrombocytopenia grade 3+ was reduced by 45% (OR 0.55, 95% CI 0.50–0.61) (Kiss-Miki *et al.,* 2025).

Despite clear advantages in selected cases, the benefit of proton therapy remains controversial in several common malignancies, including prostate, breast, and lung cancers. Recent evidence suggests that while proton therapy reduces radiation exposure to surrounding normal tissues, this does not consistently translate into improved survival outcomes or clinically significant toxicity reduction across all disease sites (Corrao *et al.,* 2024).

In prostate cancer, recent systematic reviews and meta-analyses indicate that high-level comparative evidence remains limited, with no clear demonstration of superior clinical outcomes for proton therapy over photon techniques. A 2024 meta-analysis reported no significant differences in biochemical control or survival outcomes, while toxicity profiles particularly gastrointestinal and genitourinary toxicities, were largely comparable between modalities (Corrao *et al.,* 2024).

In breast cancer, proton therapy offers clear dosimetric benefits, particularly in reducing cardiac and lung dose. However, recent reviews emphasize that clinical outcome data remain insufficient to confirm a survival benefit, and randomized trial evidence is still emerging. Current literature suggests that while proton therapy may reduce long-term cardiac toxicity risk, particularly in left-sided breast cancer, its routine use remains limited to selected high-risk patients pending stronger clinical validation (Chen *et al.,*2023).

For lung cancer, the role of proton therapy remains highly debated. A recent 2026 systematic review and meta-analysis found that although proton therapy can reduce dose to normal lung and cardiac tissues, evidence of improved survival or consistent toxicity reduction remains inconclusive (He *et al.,* 2024). Similarly, earlier meta-analyses report that current data are insufficient to establish clear superiority of proton therapy over photon-based approaches, largely due to heterogeneity in study design and limited randomized evidence (He *et al.,* 2024).

Recent meta-analyses indicate that proton therapy primarily provides reduced severe (grade ≥3) toxicities (~15–30%) and a lower risk of secondary malignancies due to decreased normal tissue exposure. However, these benefits do not translate into significant survival advantages, as most studies report no statistically significant differences in overall survival (OS) or progression-free survival (PFS) between proton and photon therapies across major adult cancers. For instance, pooled analyses in non-small cell lung cancer show comparable OS and PFS outcomes, despite improved normal tissue sparing with proton therapy (Fang *et al.,* 2026). Therefore, the principal clinical advantage of proton therapy remains toxicity reduction rather than improvement in survival outcomes (Chen *et al.,* 2023; Corrao *et al.,* 2024; Fang *et al.,* 2026). Overall, contemporary literature indicates that while proton therapy provides superior physical dose distribution, its clinical benefit in common adult cancers remains uncertain, with outcomes often comparable to advanced photon techniques such as intensity-modulated radiotherapy (IMRT). The lack of large-scale randomized controlled trials and consistent survival advantages continues to limit definitive conclusions regarding its routine use in these indications (Chen *et al.,* 2023).

Central Nervous System Tumors: Population-Level Survival Advantage

A groundbreaking 2025 study of 162,506 patients from the National Cancer Database, spanning nearly 20 years of data (2004–2022) showed that proton therapy was linked to meaningfully better long-term survival outcomes than traditional photon radiation treatment (HR 0.67, 95% CI 0.64–0.71; $p < 0.001$). This advantage persisted across all histologies and treatment modalities:

Glioblastoma: HR 0.79 (95% CI 0.71–0.88; $p < 0.001$) with surgery; HR 0.81 (95% CI 0.73–0.90; $p < 0.001$) without surgery.

Astrocytoma: HR 0.65 (95% CI 0.53–0.81; $p < 0.001$) with surgery; HR 0.44 (95% CI 0.39–0.50; $p < 0.001$) without surgery.

Other CNS tumors: HR 0.60 (95% CI 0.37–0.98; $p = 0.04$) with surgery; HR 0.41 (95% CI 0.28–0.60; $p < 0.001$) without surgery (Amin *et al.,* 2025).

Adult patients treated with protons achieved a median overall survival of 111.7 months compared to 24.8 months with photons, with five-year survival rates of 59% versus 37%, respectively. Pediatric patients demonstrated even greater relative benefit (HR 0.57, 95% CI 0.50–0.66; $p < 0.001$) (Amin *et al.,* 2025).

Head and Neck Cancers: Survival Breakthrough

Recent groundbreaking research has established proton therapy as a new standard of care for oropharyngeal cancer. The largest randomized Phase III trial conducted to date, published in The Lancet in 2025, enrolled 440 patients across 21 leading U.S. medical centers, including MD Anderson Cancer Center, Memorial Sloan Kettering, and Mayo Clinic. At five years, overall survival was significantly higher with intensity-modulated proton therapy (IMPT) compared to intensity-modulated photon therapy (IMRT): 90.9% versus 81.0% (HR 0.58, 95% CI 0.34–0.99; $p = 0.045$), representing a 10% absolute survival benefit (Frank *et al.,* 2026). This survival advantage emerged even though both therapies controlled the cancer equally well, local recurrence rates were nearly identical at 2.9% for IMPT versus 5.6% for IMRT, regional recurrences were 3.4% versus 3.2%, and distant metastases occurred at 9.1% versus 8.9%. The improved survival appears to stem from fewer deaths related to treatment itself and better outcomes after the cancer progresses rather than superior tumor control. Notably, the survival advantage only emerged after three years, emphasizing why extended follow-up is so crucial in evaluating these therapies (Frank *et al.,* 2026).

Toxicity reduction was substantial: grade 3+ lymphopenia occurred in 76% (IMPT) versus 89% (IMRT), severe dysphagia in 31% versus 49%, severe xerostomia in 33% versus 45%, and feeding tube dependence at 60 days in 26.8% versus 40.2% ($p = 0.018$). Treatment-related deaths were lower with IMPT (3 deaths) compared to IMRT (6 deaths), and the gap widened further for deaths occurring after cancer progression, 9 with IMPT versus 18 with IMRT.

For adenoid cystic carcinoma, a rare head and neck cancer, proton therapy delivered impressive outcomes: 93% of patients had their tumors controlled locally, and 77% were still alive at five years. Additionally, 56% remained free of disease, and 62% had not developed distant metastases at the five-year mark. Two years out from treatment, contemporary studies report excellent outcomes: over 9 in 10 patients kept their cancer in check locally, almost 89% were still alive, and serious late complications remained uncommon, occurring in just 6% of cases. (Sami *et al.,* 2024).

For reirradiation of recurring cancers of the head and neck, a 2019 study explored this challenge in 16 patients with recurrent nasopharyngeal cancer, using proton therapy to deliver a second round of radiation. The median dose was 60 Gy, and the median follow-up was 10 months (Sami *et al.,* 2024). The researchers reported no acute grade 3 or higher toxicity, whereas 23.5% of patients presented with late ≥ 3-grade toxicities. The 18-month OS was reported to be 54.4%, and the local control was 66.6%. Unlike photon reirradiation, which comes with increased chances of severe toxicity, proton reirradiation in cases of recurrent head and neck cancers is recommended due to its significantly reduced chances of toxicity and improved OS (Sami *et al.,* 2024; Mohamed *et al.,* 2022).

Esophageal Cancer: Improved Survival and Reduced Toxicity

A 2023 meta-analysis of 45 studies combining both randomized trials and real-world data, demonstrated that esophageal cancer patients treated with proton therapy lived significantly longer than those receiving traditional photon radiation (HR 1.31 for photon vs. proton, 95% CI 1.07–1.61; $I^2 = 11\%$) and reduced high-grade toxicity. In the curative treatment subgroup, hose getting traditional photon radiation faced a 42% higher risk of death (HR 1.42, 95% CI 1.14–1.78) and a 48% greater chance of their cancer progressing compared to proton therapy recipients (HR 1.48, 95% CI 1.06–2.08) (Zhou *et al.,* 2023). Isolating just the proton therapy results revealed the following:

1-year overall survival: 89% (95% CI 84–93%)
2-year overall survival: 71% (95% CI 63–78%)
3-year overall survival: 63% (95% CI 53–73%)
5-year overall survival: 56% (95% CI 46–67%)

The side effect profile strongly favored proton therapy. Severe radiation pneumonitis (grade 2+) affected just 2% of proton patients versus substantially higher rates with photons, Serious fluid buildup around the heart occurred in only 3%, and dangerous drops in white blood cells were seen in 17% (Zhou *et al.,* 2023).

Secondary Malignancy Risk Reduction

The lower total radiation dose to the body with proton therapy directly translates into a substantially reduced long-term risk of secondary malignancies. Dosimetric modeling studies estimate that proton therapy reduces the expected incidence of radiation-induced secondary cancers by factors of 2 to 15 compared to IMRT or conventional photon therapy, depending on tumor site and patient age (Zhou *et al.,* 2015). Clinical data support these predictions. A large case-matched comparison of 588 proton patients (Harvard Cyclotron, 1973–2001) and 588 photon patients (SEER database) with median follow-up of 6.7 years demonstrated a 48% reduction in second malignancy risk with proton therapy (adjusted HR 0.52, 95% CI 0.32–0.85; $p = 0.009$) (Zhou *et al.,* 2015).

In pediatric populations, prospective studies report zero secondary malignancies after proton therapy for medulloblastoma (59 patients, median follow-up 7 years), low-grade glioma (32 patients, median 7.6 years), ependymoma (70 patients, median 3.8 years), and rhabdomyosarcoma (57 patients, median 3.9 years). By comparison, matched photon cohorts showed cumulative second malignancy rates of 9.3–19% at 30 years in historical series. For retinoblastoma, the 10-year cumulative incidence of radiation-induced second malignancies was 0% with protons versus 14% with photons ($p = 0.015$) (Zhou *et al.,* 2015).

Flash Proton Therapy Clinical Translation

FLASH proton therapy delivers ultra-high dose rates (>40 Gy/s) in millisecond durations, potentially sparing normal tissues while maintaining tumor control. Proton systems, particularly isochronous cyclotrons, achieve FLASH dose rates readily. Preclinical studies demonstrate significant normal tissue protection, with initial clinical trials showing safety in bone metastasis treatment (Cengel *et al.,* 2024; Natelauri *et al.,* 2024). FLASH radiotherapy (ultra-high dose rate >40 Gy/s) represents the most significant paradigm shift in radiation therapy since the introduction of intensity modulation. Following the landmark FAST-01 trial (NCT04592887) the first-in-human proton FLASH study conducted at Cincinnati Children's/UC Health Proton Therapy Center, that milestone has since ignited explosive growth in follow-up research, transforming the landscape of radiation science (Di *et al.,* 2026). The first human use of FLASH radiotherapy in 2019 offered an important proof of concept. A patient with skin lymphoma saw their cancer disappear completely with few immediate side effects. Still, with just one person treated, this remains a single anecdote from one center. While encouraging, this N = 1 case remains anecdotal and site-specific, leaving the technical and biological challenges of deep-seated tumors unaddressed.

To address this gap, the FAST-01 non-randomized trial evaluated proton FLASH-RT in 10 patients with symptomatic bone metastases (Di *et al.,* 2026). The FAST-01 trial treated 10 patients with painful extremity bone metastases using single-fraction 8 Gy proton FLASH, demonstrating workflow feasibility, 67% pain relief, and 50% complete response rate, with toxicity profiles comparable to conventional radiotherapy. Treatment couch time averaged only 18.9 minutes per patient (Mascia *et al.,* 2023). Building on this success, FAST-02 (NCT05524064) is evaluating proton FLASH for thoracic bone metastases. Interim data presented in June 2024 demonstrated 75% pain relief with no cardiorespiratory toxicity, supporting further development for deep-seated tumors (Di *et al.,* 2026).

Recent study highlighted that there has been 1 published case report of the use of FLASH therapy in a human—a single patient with cutaneous T-cell lymphoma and extensive prior radiotherapy to the skin who was safely and effectively treated with electron FLASH therapy for a recurrent cutaneous lymphoma lesion. A single dose of FLASH therapy delivered with electron radiotherapy to 15 Gy was delivered. This resulted in a complete response of the lesion with minimal toxic effects of the heavily pretreated surrounding skin. Electron radiotherapy is limited to superficial targets such as skin lesions. In contrast, proton radiotherapy can deliver FLASH at depth, for example, to bone, lymph node metastases, or visceral organ tumors. In addition, proton FLASH may provide superior uniformity of dose distribution compared with electrons (Mascia *et al.,* 2023).

The clinical translation of FLASH radiotherapy remains in its early stages, with most ongoing studies limited to small, early-phase trials focused on feasibility and safety. Notably, the first-in-human proton FLASH study (FAST-01) was a single-arm, phase I–type trial involving a small cohort of patients with symptomatic bone metastases, primarily designed to evaluate workflow feasibility, toxicity, and preliminary efficacy, reflecting the current predominance of palliative clinical applications (Mascia *et al.,* 2023; Daugherty *et al.,* 2024).

Additional ongoing FLASH trials include:

LANCE (NCT05724875): Phase II randomized trial of electron FLASH versus conventional radiotherapy for basal cell and squamous cell carcinoma (60 patients, recruiting)

IMPulse (NCT04986696): Phase I dose-escalation study of electron FLASH for cutaneous melanoma metastases (22–34 Gy single dose)

FLASH-Skin I (NCT06549439): Phase I trial of electron FLASH for melanoma skin metastases (active, not recruiting) (Di *et al.,* 2026).

The transition from electron to proton FLASH is critical for treating deep-seated tumors. Proton FLASH systems, particularly isochronous cyclotrons, are well-suited to achieve ultra-high dose rates required for the FLASH effect. Preclinical studies demonstrate that proton FLASH maintains tumor control while significantly mitigating normal tissue toxicity in animal models, with mechanisms involving reduced reactive oxygen species production in normal tissues (Di *et al.,* 2026).

Emerging Technologies and Research Frontiers

Artificial Intelligence and Machine Learning in Proton Therapy

Artificial intelligence and machine learning are rapidly transforming proton therapy workflows, from patient selection through treatment delivery and verification. A comprehensive 2024 systematic review identified 38 relevant studies published between 2019 and 2024, demonstrating exponential growth in machine learning (ML) applications (Wildman *et al.,* 2025).

Automated Treatment Planning: Deep reinforcement learning has achieved breakthrough automation of proton pencil beam scanning (PBS) treatment planning. In 2024, researchers applied the proximal policy optimization (PPO) algorithm, utilizing reward functions based on dose distribution, specifically for treating head and neck cancer (Wang *et al.,* 2024). This approach continuously refines planning objective parameters within a continuous action space, producing treatment plans that better protect organs at risk while maintaining or exceeding the target coverage quality of manually created plans. Remarkably, the model demonstrated the ability to apply its learning to liver cancer cases without requiring additional training, highlighting its potential for broader clinical use across different anatomical sites (Wang *et al.,* 2024).

The AI-PROTIPP system (Artificial Intelligence Predictive Radiation Oncology Treatment Indication to Photons/Protons) employs 3D U-Net convolutional neural networks to predict dose distributions for both modalities, using normal tissue complication probability (NTCP) models to select the superior treatment approach. In oropharyngeal cancer cases, this achieved 87.4% accuracy in treatment selection with computation time reduced from hours to 11 seconds per modality (Wang *et al.,* 2024). Similar deep learning-based selection for prostate cancer achieved 90–93.5% accuracy (Wildman *et al.,* 2025).

Knowledge-Based Planning (KBP): Machine learning optimization (MLO) algorithms for oropharyngeal carcinoma have demonstrated capability to generate clinically acceptable IMPT plans with adequate robust target coverage in 92% of cases (23/25 patients), though with slightly increased average organ-at-risk dosages requiring further refinement (Wildman *et al.,* 2025). Among various approaches tested, post-processing pipelines that used RayStation dose mimicking without any additional post-processing steps (NPP-RSM) yielded the best results in terms of plan robustness while still providing adequate protection for healthy tissues (Wildman *et al.,* 2025).

Synthetic CT Generation for Adaptive Therapy: Unsupervised 3D deep learning networks now enable proton dose calculation on cone-beam CT (CBCT) critical for adaptive proton therapy where poor CBCT image quality traditionally hindered dose assessment. A 2024 study evaluated three architectures (CycleGAN, CUT, and fused CycleCUT) trained on 102 head-and-neck cancer patients (Dueholm *et al.,* 2025). All networks generated synthetic CT images with gamma passing rates >97% compared to ground-truth CT, with mean absolute errors of 53–55 Hounsfield units. The fast generation speed makes these networks feasible for online adaptive proton therapy, enabling immediate plan adaptation based on daily anatomy (Dueholm *et al.,* 2025)

Real-Time Dose and Range Verification: Advanced neural network architectures including general deep inception convolutional neural networks (GDI-CNNs) and deep cascaded CNNs (DC-CNNs) are being deployed for real-time dose verification and range monitoring during treatment delivery (Wildman *et al.,* 2025). These systems analyze prompt gamma signals, PET emissions, or beam's-eye-view imaging to verify proton range with millimeter accuracy, enabling immediate intervention if deviations occur.

Machine Learning for Patient Selection: Pre-screening models using Gaussian naïve Bayes classifiers can reduce formal selection procedures with manual intensity-modulated proton therapy (IMPT) planning by 67% by automatically identifying patients likely to benefit from proton therapy based on predicted xerostomia, dysphagia, and feeding tube dependency differences between photon and proton plans (Wildman *et al.,* 2025). This tackles the crucial challenge of identifying suitable candidates for treatment when resources are scarce or constrained.

Limitations: Despite rapid progress, significant challenges remain. Deep learning models in radiotherapy suffer from restricted training datasets that lack both size and diversity, which may undermine their ability to generalize across varied equipment vendors, patient anatomies, and institutional protocols (Gao *et al.,* 2025). This data scarcity is particularly acute in proton therapy compared to conventional photon treatments, where large, high-quality public datasets are more readily available (Wildman *et al.,* 2025). Bringing AI into clinical practice demands thorough validation of machine-generated treatment plans against established safety benchmarks (Glatzer *et al.,* 2025). Furthermore, variations between institutions in contouring practices, planning preferences, and treatment protocols introduce additional complexity that hinders the development of robust, broadly applicable models (Gao *et al.,* 2025). Clinicians and physicists need transparency in how AI arrives at its recommendations to ensure patient safety and maintain professional accountability (Wildman *et al.,* 2025). Multi-institutional collaborations and standardized evaluation frameworks are increasingly recognized as essential to overcome these barriers and ensure external validation of model performance (Lastrucci *et al.,* 2024).

Challenges and Future Directions

Despite physical advantages, proton therapy faces significant challenges. Range uncertainty remains the primary limitation, requiring conservative margins that partially compromise the Bragg peak advantage. These uncertainties necessitate safety margins that partially offset the theoretical precision of proton dose delivery (Nácher *et al.,* 2024; Mohan, 2022).

One of the most significant barriers to widespread adoption of proton therapy is its high capital and operational cost. Traditional multi-room proton centers require investments exceeding $100–200 million, although newer compact and single-room systems have reduced this to approximately $30–50 million (Brodin *et al.,* 2021; Huang *et al.,* 2021). Nevertheless, recent economic analyses indicate that proton therapy is most cost-effective in pediatric cancers and selected high-risk cases, where reductions in long-term toxicity and secondary malignancies translate into improved quality-adjusted life years (QALYs). In contrast, for common adult cancers such as prostate and breast, cost-effectiveness remains uncertain due to comparable survival outcomes with photon therapy (Verma *et al.,* 2016; Mohan, 2022; Zhang *et al.,* 2026). Ongoing development of compact, lower-cost systems using superconducting magnets and innovative accelerator designs aims to broaden accessibility.

Access to proton therapy remains highly uneven, with the majority of facilities concentrated in high-income countries. In low- and middle-income countries (LMICs), including many regions in Africa, adoption is limited by infrastructure costs, lack of technical expertise, and competing healthcare priorities. Recent literature highlights the need for scalable solutions, including compact systems, international collaborations, and regional treatment centers, to improve global access. Addressing these disparities will require coordinated efforts in policy development, workforce training, and sustainable financing (Datta *et al.,* 2020; Zhang *et al.,* 2026).

CONCLUSION

Proton therapy has evolved from a physics-driven innovation into a clinically relevant modality in modern radiation oncology. Advances in the understanding of proton interactions with matter, beam delivery technologies, and treatment planning methodologies have enabled highly conformal dose distributions with reduced irradiation of normal tissues. This progression from fundamental physical principles to clinical implementation underscores the transformative potential of proton therapy in improving therapeutic ratios, particularly in anatomically complex and radiosensitive cases.

Clinically, proton therapy has established a clear role in selected indications, including pediatric malignancies, skull base tumors, ocular tumors, and re-irradiation scenarios, where its dosimetric advantages translate into meaningful reductions in toxicity. However, in more common adult cancers such as prostate, breast, and lung, current evidence demonstrates largely comparable survival outcomes to advanced photon techniques, with the primary benefit being reduced treatment-related toxicity rather than improved overall survival. These findings reinforce the position of proton therapy as a niche but highly valuable tool in precision oncology, rather than a universal replacement for photon-based radiotherapy.

Despite its promise, several limitations continue to constrain the widespread adoption of proton therapy. Persistent challenges include range uncertainty, which affects dose accuracy, high capital and operational costs, and limited high-level randomized evidence in certain disease sites. These factors contribute to ongoing debates regarding cost-effectiveness and optimal patient selection, particularly in healthcare systems with constrained resources.

Looking forward, the future of proton therapy will be shaped by both near-term and long-term innovations. In the near term, advancements in pencil beam scanning (PBS), robust optimization techniques, and improved range verification methods are likely to have the most immediate impact on clinical practice by enhancing treatment precision and reliability. Over the longer term, emerging approaches such as FLASH radiotherapy and LET/RBE-guided biological optimization hold the greatest potential to redefine treatment paradigms by improving the balance between tumor control and normal tissue toxicity. Among these, biological optimization and real-time verification strategies are particularly promising for integration into next-generation treatment planning systems.

Finally, addressing global disparities in access remains a critical priority. The high cost and technical complexity of proton therapy have limited its availability in low- and middle-income countries (LMICs), including much of sub-Saharan Africa. Expanding access will require the adoption of compact and single-room systems, investment in workforce training, and the development of sustainable healthcare financing models. Improving global equity in access to advanced radiotherapy technologies will be essential to ensuring that the benefits of proton therapy are realized beyond high-income settings.

In summary, proton therapy has matured into a clinically validated modality with clear benefits in selected patient populations. While significant challenges remain, ongoing technological and biological innovations, coupled with efforts to improve accessibility, are expected to further define and expand its role in the future of precision cancer care.

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