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# Advancements in Proton Therapy for Cancer Treatment: Benefits and Challenges

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**Annotation:** Raised in 2016, the proton treatment center at the Washington University Medical Center in St Louis, Missouri, houses a 230-ton superconducting cyclotron, capable of accelerating proton particles at energies up to 250 MeV (megaelectronvolts). The protons then deliver a radiation dose to a patient as determined by a team of physicians, physicists, and dosimetrists. The machine is able to deliver spot scanning irradiation of protons, in addition to a passive scatter delivery. Clinical examinations and imaging are done in-house with CT, MRI, and PET/CT, and it scans the patient in the treatment position. During radiation therapy, a patient is aligned on the treatment table with respect to the room coordinate system and the treatment plan. A subsequent target ionization chamber (ICs) readout instrument can monitor, in-vivo, the total delivered dose to compare with the treatment plan. Furthermore, it can function as an interlock device in a treatment plan to halt a treatment if it is deemed unsafe. After treatment, a post-

ICs, Gafchromic EBT3 film was placed in the same scan bed to measure the out-of-beam dose from the earlier treatment [1]. During this single-film approach readout, the film was scanned in the film's scan orientation before and after treatment. Crop study has been conducted to ensure that the area of interest was not outside of the beam region or in the steep dose gradient region.

## 1. INTRODUCTION

The use of proton therapy for cancer patients is an advanced approach directed to deliver the radiation dose to precisely defined targets. The sharp drop-off after the Bragg peak and the physical characteristics of the proton dose are used to reduce the exposure to normal tissues located proximally and distally to the target, while allowing higher target doses. However, this high-dose, small-volume, fluence-modulated proton treatment has not been commonly used in clinical practice mainly due to the complexities of treatment planning and treatment delivery, as well as the quality of the equipment. A detailed analysis of the benefits and challenges faced during the clinical implementation of intensity-modulated and pencil-beam-scanned proton therapy after a decade-long development and clinical research effort on the development of the proton/proton treatment system is presented.

Proton therapy as an example of particle therapy has been a subject of ongoing presentation from the early days of groundbreaking work. Later, a systematic comparative analysis of photon vs proton treatment plans in treatment sites of clinical relevance was performed. Proton therapy has been emphasized as an advanced approach to cancer treatment that is theoretically superior to conventional photon-based treatment in terms of dose localization properties. This idea is well-illustrated by the highly recognizable schematic representation of the dose distribution of photon and proton beams, which is still seen in current presentations of proton therapy technology. Additionally, clinical interest in proton therapy is further motivated by a perceived need for modalities that enable a dose escalation to the radiation-resistant tumor cells. It is argued that current approaches to dose escalation using advanced modalities still leave much to be desired in terms of a steepness of the dose–volume histograms of the targets and organs at risk, while this steepness is essentially identical for the target and reference normal tissue in the case of intensity-modulated x-ray therapy. [2][3]

## 2. Historical Development of Proton Therapy

Radiation therapy is one of the primary treatments for cancer. The fundamental principle of radiation therapy is that ionizing radiation damages cellular DNA within a tumor, leading to cell death. Although this is an effective way of controlling the growth of cancer cells, healthy tissue surrounding the tumor is also exposed unnecessarily to high doses of radiation. To address this, planning systems that compute base contours around the tumor have been developed. Beams are then optimized to deliver maximal dose to the tumor while sparing these healthy tissues [1].

From the mid-20th century, protons have been used in radiation therapy to treat deep-seated tumors. Proton beams enter the body with nonlinear energy deposition. They deliver most of their energy directly to the cellular DNA before they come to rest, and then they discontinue, dishing minimal entrance and exit doses. This treatment can potentially spare excess radiation dose to the surrounding healthy tissue. Proton therapy technologies have gradually been improved since the 60s. The cyclotron and synchrotron technology have helped develop current proton therapy systems, which are installed in hospitals in many countries. In recent years, developers have been trying to implement advances in proton therapy, such as Intensity-Modulated Proton Therapy

(IMPT). Beam intensity and modulations are further optimized. This technology uses pencil beams to deliver treatment and has been demonstrated to efficiently decrease radiation doses to a normal organ (from 50% down to about 10% of the prescribed dose). This efficiency is achieved due to the spot scanning of a pencil beam and relatively small volumes irradiated per beam, as compared to the passive scattering approach. However, these advantages can be achieved only when the motion of the target is corrected with motion-monitoring devices which adapt the proton beam delivery. [4][5]

## 3. Principles of Proton Therapy

Despite the potential benefits of proton therapy for cancer treatment, it is still criticized for uncertainties in proton range and relative biological effectiveness modeling, patient setup and organ motion, and dose optimization. The uncertainties in proton range prediction in patient treatment limit the full potential of proton therapy to be realized. The result is a relatively large distal dose fall-off following the tumor volume [1]. Dosimetric and imaging systems using prompt gamma detection, prompt gamma timing, positron emission tomography, and proton CT have been proposed and developed to address this issue. This will allow more accurate and robust methods to determine range in treatment, potentially minimizing range uncertainties and allowing tighter distal margins to be used in dose planning. With the increasing use of particle therapy in treatment of cancer, more advanced tumor tracking and adaptive treatment strategies are necessary to improve the treatment outcome. New technologies including intensity modulated proton therapy, pencil-beam scanning, respiratory-gated proton therapy, proton arc therapy and inter-fraction real-time intra-modality tumor tracking have been developed and are being investigated for their ability to improve treatment precision and patient outcomes. However, daily variations in patient internal anatomy and organ motion and patient setup are still more critical in proton treatment than for photon therapy and are largely responsible for an increased proton therapy delivery time per fraction and potential underdosing of target volumes. Advanced patient setup verification and possible individual immobilization methods are necessary for further improvement in robustness of the proton treatment. Like regular radiotherapy, improved outcome from proton treatments is likely to come from more accurate target definition and better biological optimization regarding the fractionation schedules used. With the possibility of spare performance, methods for robust biologically optimized treatments need to be developed.

## 4. Advantages of Proton Therapy

Proton therapy has recently received a substantial amount of public attention because of the establishment of new proton centers in multiple locations. Protons are accelerated to a specific speed and targeted at bodily tissues to deliver an exact dose of radiation in addition to those tissues. As is true for all antiquated therapies, the key goal is to eradicate the cancer while eliminating the exposure of healthy tissues. This is particularly important for pediatric patients since treating tumors in young children presents many challenges. Many researchers hope to prove that proton therapy will result in improved medical outcomes for pediatric patients, who account for a significant percentage of all patients treated with proton therapy. A major criticism of proton therapy is the lack of strong clinical evidence from randomized clinical trials even as various theoretical benefits are proposed. The relative biological effectiveness of protons, or their effectiveness in causing biological damage increases as a function of depth in the Bragg Peak phenomenon, which produces a maximum point at the end of the particle range. Karnofsky Performance Status (KPS) score, which measures a patient’s functional well-being on a scale from 0 to 100 where higher values indicate better functioning and overall well-being. Treatments were planned using evidence-based guidelines, but individual institutions or proton centers may have slightly different policies. To limit the dose to critical structures or to improve target coverage, pencil-beam scanning techniques may be used in difficult cases. PBS is the most recent advancement of proton therapy in which the protons are delivered using a pencil beam, with the treatment session dynamically optimizing the path of the beam. [6][7]

### 4.1. Precise Targeting of Tumors

Proton therapy is an advanced form of radiation therapy that uses a single beam of high-energy protons to treat tumors. It is a type of particle therapy and is able to deliver more controlled and precise doses of radiation to target tumors located in difficult spots. Proton therapy is an important advanced form of external beam radiotherapy. Compared to traditional radiotherapy with photons, protons deliver a more localized deposition of energy ensuring a more precise irradiation of the tumour. The physical characteristics of the proton beams allow to shape the dose at different tissues depths in the patient, providing optimal treatment: lower entrance dose, no exit dose at the end of the range and sharp dose fall-off at the Bragg Peak, beyond which there is no additional dose deposited. This advanced radiotherapy technique reduces doses to normal tissues, enables 'dose painting' strategies and spare organs at risk.

The precise targeting of tumors in proton therapy requires accurate treatment planning to optimize the dose distribution around the tumor, and proper techniques to set up the patient before treatment delivery. The biologically effective dose, 3D distribution in organs at risk, fractionation, relative biological effectiveness and repair of sub-lethal damage are unknowns. There is insubstantial clinical data and inadequate follow up times for late outcomes, one of the determinants of second baseline value. Despite the theoretical physical advantages of proton therapy, clinical advantages are lacking. The few randomised trials did not use contemporary photon RT techniques and had poor statistical power. Meta-analyses of proton vs photon best dosimetry series showed no consistent advantage of proton therapy in terms of local control or side effects. Analyses of national databases did not detect an actuarial benefit in loco-regional control or overall survival; proton therapy uses 50-60% reduced dose compared to MFO IMRT because of lack of confidence in its efficacy. Relapse usually occurs in the normal tissue surrounding the tumor. PET imaging of hypoxia during therapy is concerning. Prompt gamma detection is similarly improved. PTers have vastly improved dose calculations due to the availability of pCT and the elimination of density effects need to be corrected. [2][8][6]

### 4.2. Reduced Damage to Surrounding Healthy Tissue

The biological and clinical impact of proton therapy beams is widely investigated. A review of analytical articles related to the research question highlights the beneficial aspects of proton therapy. Since the introduction of proton beams for cancer treatment, much research has been devoted to the proposition that this type of radiation is one of the most effective and safe for patients. Many articles suggest that therapy with protons is more effective in the formation of secondary malignancies conventional for X-ray therapy. In a comparison of proton therapy with intensity-modulated radiation therapy, by breast cancer risk group, there was a reduction in the chance of heart exposure by protons compared to three-dimensional conformal radiation therapy alone. The Official Opinion of the Particle Therapy Co-operative Group – External Beam Design (PTCOG-ETD) states that proton therapy is more effective than photon therapy for some groups of adult patients. More complete simulations have been developed, evaluating more complex end effects and errors in the determination of the stopping force at the physical and analytical levels faced by the detectors themselves. The results of the work reveal significant similarities with real measurements. It has been shown that by creating optimal models for the development of clinical capacity, it is possible to effectively determine the use of two types of detectors used in complex at the physical and analytical levels. The use of such research gives impetus to the improvement of real measurements of detectors [9]. On the other hand, a higher level of protection is achieved. The text highlights the specific initial requirements for the design of a computer model.

### 4.3. Enhanced Treatment for Pediatric and Adult Cancers

Proton beam therapy (PBT) has been minimizing late effects in the growing area of pediatric cancers. PDT for pediatric and adult cancers is a focus of prosthetic radiation development in current medical physics. A strong energy-dependent Bragg peak plays a key role in the low dose region near the end of the range of the proton beam. Medical physicists are transporting this energy that is from a beam, generated by a changing range shifter in the passing area through the patient. Currently, scanning beam methods, pencil beam scanning, are mainly used as irradiation timing methods.

PBT is an advanced medical technology for treating cancer in children who are especially vulnerable to the adverse effects of radiation therapy. PBT is heavily used to treat eye, head, and neck of benign as well as malignant tumors [10]. It is a beneficial treatment for saving organs that have high radiation tolerance and a high amount of radiation therapy. PBT plays to increase normal tissues that are exposed to low irradiation as much as possible for selecting treatment plan that meets the patient's clinical condition. A comparative analysis of treatment plans for x-ray therapy (IMPT) is ongoing. Previous studies have shown the superiority of PDT for pediatric tumors. Subsequently, PDT for pediatric and adult cancers have been observed in a growing number of treatments. These treatments have a similar advantageous effect on PEDT and are placed related to the use of therapy in medical physics. The PEDT uses a method that is similar to the passive scattering method and delivers an acquired dose plan on the dose from the fluence through an 'energy-dependent change' range shifter. The passive scattering therapy includes a beam modulation width about 10 cm on a virtual source point, which is assembled by changing collimators.

## 5. Challenges and Limitations

Technological advancements and innovations in proton therapy plan optimization and treatment delivery have shown promise, but additional investigations, development, and clinical outcome studies must be forthcoming for routine adoption in clinical practice at more comprehensive rates. Enhanced electric and magnetic solutions to form protons for therapy must, in fact, be in compliance with these developments. An examination of the generally high LET values of protons and helium ions in the Bragg peak is provided, as well as how Monte Carlo simulations of these ions can be used in the development of treatment planning algorithms for the biological aspects of LET. Optimization of the number of fields, and of monitor units in order to deliver a range of RBE weighted dose values is also touched upon.

It is postulated that unless geographical miss of target areas can be minimised, and blockers can develop maximum homogeneity of complex shapes, disappointing outcomes are likely to arise. Furthermore, questions may arise about the proprietary basis of future developments, and uncertainties could arise through the use of commercial procedures obscuring details about planning or delivery techniques. This technical and clinical review is based on a grand total of references, some of which, although cited in support of more general statements broader than the specific clinical context, are undoubtedly influential. Discrepancies in Fractionation and $\alpha/\beta$ Assumption for which references could not be traced are claimed in support of some highly controversial points. Uncertainties in RBE modeling and poor statistical basis of Results for which the in-house theoretical model has been utilized are evidenced by extensive detailed analysis. Major extensions in the clinically important Findings section are also included. [11][12]

### 5.1. Cost and Accessibility

A major current criticism towards proton therapy is related to its still lacking strong clinical evidence out of the randomized clinical trials. Nonetheless, its theoretical benefits and the anecdotal success evidence in treating certain cancers have stimulated the fast expansion of the technology globally. Majority of prospective clinical studies in proton therapy have been more focused on measuring the risk of toxicities, presumably due to many of the structures closely located to the tumor, rather than on the end-point of treatment outcome. There is, however, an absence of evidence showcasing a significant improvement of local control rate and progression-free survival rate comparing to the photon therapy. In the conventional radiotherapy where the kill mechanism is caused by ionization – radiation dose to healthy tissue is significantly reduced with proton. To increase the local control for cancer through radiation, one has to rely on a higher radiation dose to the local tumor. However, this fundamental concept is not currently practiced in the proton therapy field, meaning that the proton dose to localized tumor is kept the same as in the photon therapy and just the radiation dose to the healthy tissue is reduced. This would result into a decrease of side effects, quality of life improvement and consequently a better disease control is anticipated [1]. Although proton therapy has been in clinical use since the end of the last century, peer-reviewed publications confirming its advantages over the photon therapy are still relatively rare. However, a critical perspective on the topic is needed. To put all this into perspective, one has to comprehend the technological development of the external beam radiation oncology. Since the 1950s, a number of transition have occurred in this field – introduction of megavoltage beams, computer controlled treatment planning, multi-leaf collimators, portal imaging, on-line control, optimization algorithms, including IMRT and VMAT therapy, etc. Nevertheless, there is an absence of published evidence from the randomized clinical trials that those previous revolutionary advancements have led to a significant improvement of the clinical treatment outcomes. Moreover, cancer is a type of disease typically affecting the elderly and many co-morbidities. At any given time, a great proportion of patients undergoing a procedure also have a history of previous treatments. [13][14]

### 5.2. Technical Complexity

Proton therapy operates by accelerating protons to a high velocity and changing their direction to hit the target tumor. The tumor receives a dose of protons while the surrounding normal tissue receives none, or significantly less. Since protons deposit dose at a sharply defined depth, their dose distribution can avoid critical structures that are directly anterior or posterior to the target tumor [1]. Conventional photon therapy treats target tumors by delivering external beam photons or electrons from different angles to ensure the target tumor receives prescribed dose at adequate coverage, while normal tissue is also unavoidably irradiated because of its entrance and exit doses. Therefore, the arrival of intact protons could be considered a technical milestone in cancer treatment that should provide limited benefits to both current patients and patients in the future. Intact proton doses are rare or are never given at most treatment sites due to technical complexity. This has inspired much research into its feasibility, both experimental and theoretical. Emerging results show the clinical potential of the technology, further fostering efforts to tackle the technical challenges. Proton doses are delivered using larger number of fractions compared to conventional photon therapy. It addresses one of the technical complexities of proton therapy: the range and SOBP width accuracy dependence on physical density, requiring daily image guidance to prevent incorrect dose delivery. It is widely used in proton therapy clinic at considerable cost in both time and dose perturbation. There are four new proposed methods: prompt gamma detection, positron emission tomography, proton FLASH effect detection, and proton CT. Though with different theoretical background, all four methods aim to provide online measurement of the delivered protons, in order to verify their position and dose accuracy. Prompt gamma detection is based on the principle that nuclear reactions occur as the proton beam interacts with the patient tissue. Among these reactions, the prompt gamma can be detected and analyzed for in vivo patient measurement.

### 5.3. Clinical Evidence and Research Gaps

Over the past 15 years, proton therapy (PT) with intensity-modulated proton therapy has been implemented at several research centers worldwide. PT has gained increasing attention as an alternative method of photon therapy because of its superior dose distribution in the treatment of tumors. Over the last years, horizontal PT was also established in several research centers. Eye OO located the world's first horizontal treatment room for the treatment of patients with uveal melanomas. Besides conformal techniques, prior experimental and first clinical experiences were utilized exploring the ability of a raster scan technique to produce spread-out Bragg peaks of more complex living than can be achieved by passive scattering. Recently, eye O brain is engaged in the development of an advanced phase space tailorable treatment head as well as the implementation of a so-called spot scanning to pursue treatment of this challenging target area with intensity-modulated pencil beams. Judging by the frequency of publications on proton therapy in major medical physics or radiation oncology journals, PT itself is still an emerging research field as the number of scientific publications is lower than those regarding new developments of the advanced technology used for PT.

Organ motion is widely acknowledged to reduce the precision of radiation beam therapy of lung or liver tumors. The unpredictable shifts and deformations in the position of internal anatomical structures require larger target volumes to ensure that the target is adequately irradiated, which in turn leads to a higher amount of healthy tissues within the treatment volume. For the same process, the improvement in treatment precision by using high-dose conformal treatment techniques like intensity-modulated radiation therapy (IMRT) appears to be rather mixed. From a physical point of view, a particle beam is advantageous from the conception of accurate stopping of the particle fluence at a well-defined position referred to as the Bragg Peak. Thus, particle therapies like protons or carbon ions combine the general advantages of particles with an inherent improved dose distribution within the target. Because of these good intrinsic properties and current worldwide developments of new treatment facilities, particles became an emerging treatment modality for various types of tumors. Another evolving approach for radiotherapy is the notion of organ motion compensation, devising methods to follow the instantaneous positions of internal or external motion. [15][16]

## 6. Current Applications of Proton Therapy

In the past decade, significant advancements have been made in proton therapy (PT) technology, including spot scanning, intensity-modulated PT, and image-guided PT. Owing to the unique physical properties of proton beams, the development of clinical PT has always been extensive. In recent years, the PT technology has advanced significantly, including spot scanning, intensity-modulated PT, and image-guided PT. Many state-of-the-art PT facilities are under construction, or are being planned, making 2018 a milestone year. With increasing availability and clinical application, PT is now reaching the stage where efficacy needs to be demonstrated [1].

Proton therapy is distinguished from traditional photon therapy by delivering beams with proton particles. Compared with photons, protons have specific physical properties such as Bragg peaks and low entry doses that render more conformal dose distributions. Treatment isocenter, the aiming point of proton therapy treatment, is selected to be in the middle of the tumor. For a patient with lung cancer, daily setup uncertainty can be 1.0 cm. In this case, traditional treatment would require a large set-up margin of about 1.5 cm to ensure that the primary tumor and a small extent of organ motion treatment. This large setup margin would cause patient normal lung tissue receiving much higher doses and worse a bunch of complications. On the contrary, in the context of PT, the unique biological properties of protons permit the proton beam to irradiate larger tumors (4 cm clinical target volume) with relative small safety margin (internal target volume - ITU, and set up deviation) (0.5 cm). Due to sharp distal fall of the SOBP region, protons can cause less damage to normal tissues downstream to the tumors. [17][18]

### 6.1. Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in North American men and the second most often diagnosed cancer in men worldwide. Men with localized low or intermediate risk disease have a choice between observation, radical prostatectomy, external beam radiation therapy or permanent seed brachytherapy. Photon intensity modulated therapy delivered in 2 Gy daily fractions is effective and a common choice in the USA. Other techniques are available but are less common. As an adjuvant to radical prostatectomy, conventionally fractionated EBRT was shown to be less effective than IMRT in a non-randomized comparison. A phase III randomized study is comparing protons and photons following prostatectomy.

Proton beam therapy has the potential for improving tumor control and survival through dose escalation, which in turn has the potential to reduce harm to normal organs through dose reduction. If the crystal is cooled, the protons strike the water first, generating radiation and therapeutic effects. The dose of the protons decreases with penetration, so catastrophic damage cannot occur at the entrance to the treatment. The x-ray gantry is adjusted if the 3D reassessment reveals body contour changes since dose calculation, therefore reducing the dose to the non-target tissues. Optic assembly is used to adjust the graphite range modulator position. To achieve a robust dose delivery with the best possible dose homogeneity within the target and in minimization of the dose to adjacent critical normal tissues, proton beam therapy was used to treat primary and metastatic prostate cancer [19].

### 6.2. Lung Cancer

Lung cancer is the most commonly diagnosed malignancy and the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) comprises > 80% of patients. Despite advancements in diagnosis and treatment in recent years, fewer than 11% of patients with metastatic NSCLC are projected to survive 5 years past their initial diagnosis. Radiotherapy (RT) is an important part of the treatment for NSCLC. The use of RT for inoperable stage III NSCLC has a long history. Since the 1960s, the treatment of locally advanced NSCLC has focused on the combination of chemotherapy, RT, and more recently, immunotherapy. The advantage of thoracic PBT over 3D-CRT and IMRT has been revealed in numerous studies. Modern RT techniques have significantly improved clinical outcomes. The primary cost drivers of PCI include the cost of the active treatment modality, the operating cost of the facility, as well as clinical resources. Improved dose distribution occurs when the physical properties of the proton beam are utilized after a sharp increase to maximal dose [20]. Post-PBT outcomes will be determined from emerging decisions and criteria made during PBT treatment planning. Long-term treatment-related burden of commonly occurring toxicities including dysphagia and esophageal stricture may be particularly impactful on QoL. Emerging IMPT dose constraints and planning criteria will guide efforts to improve PBT plan quality in the absence of a current benchmark. On-treatment anatomic changes can have a substantial impact on plan quality and should alert follow-up intervention. Emerging PBT plans meet a number of known pertinent dose and volume constraints, indicating acceptable RTOG protocol adherence. Setup verification and quality assurance procedures for particle therapy necessitated extensive methods implementation compared to conventional radiation. Lowest recorded A.R.E. belongs to a study that employed respiratory-triggered kV imaging and set-up, the same margin reduction strategy that lowers the “penalty” of PBT for atelectasis patients. Four recent studies have investigated anatomic changes specifically in relation to MDT; A minimum of 5 mm intercombinational ITV margin was deemed necessary. While some doctors have suggested adjusting the CTV several patients had fallen below the stipulated planning target volume (PTV) coverage resulting in insufficient dosimetric measures [21]. Optimal adjuvant systemic therapy is a point of ongoing clinical inquiry.

Lung cancer is a lethal disease with poor prognosis and high recurrence after surgery. The risk of locoregional recurrence (LRR) is very high in stage III and an actionable target for curative-intent radiation. Potentially curable patients are treated with definitive concurrent chemo-radiotherapy, but 5-year LRR rates remain high at 15%–50%. With advances in treatment technology, image-guided radiation therapy (IGRT) has programs to reduce the set up errors. Treatments accuracy and it guide future improvements to reduce LRR may be further enhanced with the adoption of magnet resonance (MR)-linac due to superior visibility with respect of kilovoltage cone beam computed tomography. FDG-PET should be used for initial staging of patients but also for surveillance, when treating oligometastatic disease, and for re-irradiation planning. MRit should be the basic standard modality for primary tumor staging of NSCLC, especially for early NSCLC. Oncogenic driver mutations should be required in all cases of advanced disease at the time of diagnosis, during recurrence, but have different indications.

Use of the Effective Volume Correction (EVC) changed the incidence rates, but the tumor volume remained the largest variable associated with LRR. Additionally, recent small studies show a significant reduction in LRR risk and improved survival with treated esophageal minimal residual disease. Nodal volume received from the primary lesion was positively associated with the 2-year

LRR. There is growing literature with heterogeneous use of PET during radiation about the great potential of these techniques. While the evidence base continues to grow, using it part of institutional radiobiology guidelines for planning the optimal radiotherapy treatment design.

### 6.3. Brain Tumors

Gammaknife Radiotherapy has been a main option for brain tumor patients. However, some patients with large or odd-shaped tumors could not be treated with Gammaknife technology. In recent years, the advancement in proton therapy has been growing rapidly, and the usefulness of proton therapy has been shown through many papers and clinical reports. In general, proton beams have almost the same dose distribution as carbon beams, and hence, the dose outside the irradiated area decreases rapidly with a narrow penumbra width. The dose of proton therapy outside the irradiation area is less than that of photon beams. Thus, in patients who have small or odd-shaped tumors in sensitive areas, the added dose to these surrounding areas increases and the damage to surrounding normal tissues becomes severe [22]. Based on this concern, the characteristics of the brain, including the clinical potential, are reviewed, and the benefits and issues of proton therapy on brain tumors are discussed. Complete understanding of this information could improve treatment in the brain tumor area.

## 7. Technological Innovations in Proton Therapy

Recent advancement in PET-based range verification is an attractive extension of existing PET operation [1]. Carbon ion facilities can readily conduct in-beam positron emission tomography (PET) for treatment verification. SIMIND simulations of prompt gamma detection for spot scanning show that events are detectable with modest spatial resolution and reasonable delivery efficiency. In the fight against cancer, efforts for improved accuracy and precision of patient dose distribution have recently been joined by advanced developments in on-line imaging of secondary radiation produced by the very same pencil beams used for dose delivery. Such treatment verification systems aim to reduce systematic range and positioning uncertainties that may result in unintentional irradiation of healthy tissues and are currently the main limitations of proton and ion therapy.

It is well known that with passively scattered and uniform scanning, the distal range of the dose deposition in matters depends mostly on the range shifters and can be quite sensitive to patient size and complexity. This situation is not much improved by robust optimization techniques, as these can only provide better tolerance for uncertainties inherent to the delivery system, and not for patients' treatment-related effects such as changes in filling of hollow organs or tumor shrinkage. Therefore, to overcome one of the critical bottlenecks to a wide clinical spread of particle therapy, countless research efforts and a few technological implementations have been, and are being, carried out worldwide to assure that the dose actually delivered to the patient conforms as best as possible to the one planned.

### 7.1. Pencil Beam Scanning

Proton therapy has been used for treating cancer increasingly in recent decades, because it can take advantage of the Bragg peak and deliver more dose to the tumor than x-ray therapy while sparing organs at risk. Due to its issues of set-up uncertainty, patient motion, and beam range uncertainty, its utilization is limited in the non-cranial sites and also in the current commercially available systems. Pencil Beam Scanning is currently the standard beam delivery method in the new proton systems, offering its advantage over scattering methods to disease sites that have complex geometries, organs that are close to the target, small children or infants, or patients who may be prone to developing secondary cancers from treatment [23]. While passive scattering systems are still the foundation for many proton facilities worldwide, regions that intend to invest in new proton facilities are likely to choose pencil beam scanning due to its versatility. The spread-out Bragg peak of a proton beam and the lateral beam penumbrae are delivered to the patient by the energy degrader, range shifter, and range modulator wheels. The scanning beamlets in pencil beam scanning are created in the snout downstream of the spread-out Bragg peak and ridge filter. The MLC shapes the laterally spread out Bragg peak to match the size of the target and the patient's planned aperture. There is also an energy absorber and monitor chamber integrated into the MLC system. In spot scanning, all pencil beams corresponding to the layer needing treatment have to be delivered. Each layer is broken into slices in the Z direction using a range compensator. Movements of the patient table and/or an energy degrader adjust the starting depth of each slice. Subsequently, the nozzle rotates in the Gantry assembly, and the given slice is irradiated with spots in a specific sequence, to build up the spread-out Bragg peak dose distribution.

### 7.2. Intensity-Modulated Proton Therapy

Protons can maximally spare organs from exposure to low-doses, integral dose, and normal tissue volumes over the depth of the beam [24]. Despite this, there remain challenges in the implementation of proton therapy. This section will provide a comprehensive literature review of the advances that have been made, as well as barriers that currently exist, in the state-of-the-art delivery of proton therapy. Substantial reductions in radiation dose to OARs are possible with protons, resulting in lower rates of treatment related morbidity and secondary cancers. Nevertheless, the use of protons remains limited due to the high construction cost of a PT centre, despite their lower delivered treatment cost and potential benefits for various cancer patients. Temporal trends indicate matchline fields decreased daily shifts of up to 2.1cm in pleural patients on average over 20 fractions, affecting dose distribution and highlighting the care needed when planning spot-scanning proton chest wall patients. Smaller spot sizes or layer shifting could help improve robustness. Spot-scanning increases the dosimetric advantages of protons, but patient setup errors can lead to a lack of robustness.

### 7.3. Image-Guided Proton Therapy

The aim of image-guided proton therapy is to provide the accurate and time-efficient guidance of therapy delivery, with the intent to minimize the treated volume and ensure that the dose distributions matches the intended. Various techniques for image-guided proton therapy have been suggested. Modern proton therapy centers typically use some form of planar image-guidance where kilovoltage X-ray sets are used to acquire 2D radiographs of the patient before treatment. These 2D images may then be used to estimate the 3D position of the patient's internal anatomy, and the treatment is altered accordingly [25]. In the second form, 3D images of the patient may be directly used to guide the therapy, for instance, cone-beam CT scans acquired by linacs or tomotherapy machines. A third form, applied in proton therapy involves the direct use of the 2D projector of the planning computed tomography (CT) on a fixed number of angles about the patient. In most proton therapy delivery systems, the beam is positively guided by elements such that the beam-on is ensured only when the spot is within a tolerance specified by a mechanical surface. This approach is potentially problematic in centres delivering intensity modulated proton therapy (IMPT) treatments, since the setup might not be as accurate as the delivery. Therefore, within the framework of image-guidance, methods have been suggested by which an uncertainty associated with the beam-specific isocentric point is considered when optimizing the treatment setup [26]. This uncertainty is included in an optimization procedure in one of three ways: it is subtracted from the allowed geometrical uncertainties, included in the geometry optimization overriding the above-machined tolerances on volumetric displacement, deflected from the nominal treatment setup by a mechanical bar to change the treatment setup, or implicitly taken into account in a beam-specific expansion of the current geometrical uncertainties.

## 8. Comparative Analysis with Conventional Radiation Therapy

Technological advancements and subsequent innovations in the realm of treatment planning and delivery for proton therapy are bridging gaps when compared to conventional radiation therapy. However, given the heterogeneity in proton techniques, the gap between technology advancements and routine clinical adoption remains quite broad. A more granular look at this comparison for head and neck cancer and skull-base tumors with proton and photon therapy will help set a technical and clinical foundation and investigate where evolving technologies can still be further developed for improved patient outcomes. For example, potential has been seen in LET/RBE metrics with plan optimization evaluation metrics beyond the clinical target volume (CTV)/planning target volume (PTV), and also as protons transition to robust optimization and evaluation.

In head and neck and skull-base proton therapy with intensity-modulated photon radiation therapy (IMRT), there have been mixed clinical outcomes seen with no superiority of either modality in most clinical settings. The number and heterogeneity of CTVs and PTVs, along with nearby critical structures, have made robust treatment planning and plan assessment difficult. Technological improvements have been seen in plan optimization evaluation metrics beyond the PTV with a higher utilization of dosimetry endpoint statistical robustness (DRESt), which better combines anatomic and dosimetric variability during plan assessment. Additionally, as photons begin to preferentially use SPArc, it has significantly outperformed existing proton binary rescanning (PBS) surgical avoidance RT (SAR) delivery for certain skull-base surgical cavities and irradiated parotid glands. Far less impact or outperformance is seen outside of these seemingly well-suited cases, both indicating specific situations where one technology outperforms the other. However, comparisons are technical and the direct relationship to clinical outcomes, trade-offs, or patient heterogeneity is less clear. Further clinical outcome studies are needed ( [27] ).

## 9. Global Trends and Adoption of Proton Therapy

Proton therapy is an advanced radiation therapy used to treat cancer. Since 2000, it has been increasingly adopted and is expected to replace conventional radiation therapy in the treatment of certain cancers. Protons deposit less energy as they travel through the body compared to photons, the standard of care in conventional radiation therapy. Proton therapy would deposit the maximal energy once it hits the target, known as the Bragg peak, and by varying the energy level of protons, the Bragg peak can be placed within the tumor, theoretically sparing unnecessary high doses to healthy tissue surrounding the tumor compared to standard radiation therapy [1]. For decades, proton therapy has been advocated for the treatment of pediatric cancers or other tumors located close to critical structures. Since early 2000, research has been on-going to evaluate the opportunity for universal access to proton, including publicly-funded facilities and portable technology.

A few national healthcare systems have started with childhood cancers cases, evaluating the possibility of a distant treatment location for tumors that could justify the cost. It should be noted, however, that within a publicly funded system, a parallel investment must be made in the production of protons generating equipment, besides the immobile heavy weight machinery. Technical developments for compact technology are struggling to adapt this frontier modality to low income scenario. The ‘mismatch’ between the public desire for proton treatment and a financially sustainable access scenario was strongly expressed in the UK. At the national level, the solution was seen in the increasing use of multicourse proton treatment and/or in the involvement of the private sector to build, maintain and manage proton facilities. Conversely, since 2008 the number of IC protons members is growing and within the group, Italy is the only country that organized trials and studies to solve the still open clinical questions on this topic. [28][29]

## 10. Economic Considerations and Cost-Effectiveness

Proton therapy is often touted as an advance over conventional radiation for cancer treatment because protons deposited in tissue deliver abnormal cell-killing energy at the target. The advantages of using protons to treat certain cancers have been demonstrated, and continued technical advancements have fueled interest in proton therapy among stakeholders. Over the past decade, substantial investments have been made in the construction of proton therapy treatment centers. However, the deployment of the treatment modality has been slowed by concerns about the economic sustainability of treatment centers as they become more widely available.

Proton radiation is thus often recommended only when dosimetric advantages are expected to outweigh the higher purchase and operation and maintenance costs for proton therapy as compared to additional x-ray therapy [30]. The suggestion that costly technology choices should be examined with analytic procedures is not controversial and is used across industries. The suggestion that medical technology should be also examined is also not controversial and is common practice in the process of obtaining approval for the placement of medical technology. Given the high capital cost of proton therapy equipment and the high ongoing facility operating costs, this modality is the focal point of the present discussion about advanced analytics and a method proposed to ensure a competitive procurement process to justify the capitalized investment. Rarely is a choice of investment by an individual hospital as costly and consequential as a proton therapy center.

## 11. Future Directions and Emerging Research Areas

Important needs to improve in the field of proton therapy to maximize its potential to be the effective modality are finishing The relative biologic effectiveness (RBE) of the clinical proton plans changes with depth. Protons near the entry have a lower RBE than those at the distal edge of the spread-out Bragg peak (SOBP). However, the biologic knowledge of RBE in tumors and organs-at-risk is incomplete. The work-first examines the current understanding of the RBE and the biologic improvements that have been implemented in the treatment planning system [27]. The research then conducts a technical review of the current state-of-the-art in RBE plan optimizations. The new methodologies are designed to generate a proton treatment plan where the therapeutic physical dose consists of static spread-out Bragg peaks (SpDp) with a corresponding variable RBE (SpDp+RBE). This is in contrast to conventional volumetrically modulated arc therapy (VMAT) plan optimizations with a constant RBE. The delivered plan is made unique compared to prior art from current state-of-the-art pencil-beam scanning optimization algorithms that allow the user to approximately define the LET of each spot (spot LET). The findings are validated in a comparative clinical review of RBE plan optimizations of sparsely- and daily-irradiated head and neck and skull-base tumors between the two major proton vendors. The current plan optimization methodologies have limitations and may not deliver the RBE predictions of the plan. There are a number of innovative strategies being developed and tested for LET/RBE plan modulation. The future work that is required in order to further enable the routine translation of LET/RBE plan optimizations to clinical practice includes further biologic studies and secondary neutron production investigations. Furthermore, clinical outcome studies must be validated [19]. New advancements in plan optimizations and treatment delivery have not yet been fully realized as clinical capabilities and merit dedicated collaborative efforts of a multi-disciplinary team landscape. [31]

## 12. Conclusion

This review article has addressed benefits and challenges of proton therapy. In contrast, technological advances and new innovations are identified in the physical, imaging, radiobiological, and planning aspects of treatment. There is a discussion of ongoing developments in plan optimization, plan robustness, treatment delivery, Monte Carlo calculation of dose, metal artifact reduction in computed tomography scans, image guidance, the influence of patient setup uncertainties on the dosimetry, and the role of relative biological effectiveness modeling. The intent of these new technologies and methods is to continually improve the safe and effective delivery of proton therapy. However, they have not been uniformly adopted due to a lack of consensus found in the literature. In consequence, the review also addresses the results of studies and projects that are thwarted. This article concludes that those studies, and other related efforts, will underpin the successful assurance of the reviewed technologies, promising them to be achievable for implementation in everyday clinical practice, offering an accumulation of essential

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