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REVIEW

A review of proton therapy – Current status and future directions

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Abstract

The original rationale for proton therapy was its highly conformal depth-dose distributions compared to photons, which allow greater sparing of normal tissues and escalation of tumor doses, thus potentially improving outcomes. Additionally, recent research has revealed previously unrecognized advantages of proton therapy. For instance, the higher relative biological effectiveness (RBE) near the end of the proton range can be exploited to increase the difference in biologically effective dose in tumors versus normal tissues. Moreover, the smaller "dose bath," that is, the compact nature of proton dose distributions, has been found to reduce the exposure of circulating lymphocytes and the immune organs at risk. There is emerging evidence that the resulting sparing of the immune system has the potential to improve outcomes.

Protons accelerated to energies ranging from 70 to 250 MeV enter the treatment head mounted typically on a rotating gantry. Initially, the beams of protons are narrow and, to be suitable for treatments, must be spread laterally and longitudinally and shaped appropriately. Such spreading and shaping may be accomplished electromechanically for the "passively scattered proton therapy" (PSPT) mode; or it may be achieved through magnetic scanning of thin "beamlets" of protons. Intensities of scanning beamlets are optimized to deliver intensity-modulated proton therapy (IMPT), which optimally balances tumor dose and the sparing of normal tissues. IMPT is presumably the most powerful form of proton therapy.

The planning and evaluation of proton dose distributions require substantially different techniques compared to photon therapy. This is mainly due to the fact that proton dose distributions are highly sensitive to inter- and intra-fractional variations in anatomy. In addition, for the same physical dose, the biological effectiveness of protons is different from photons. In the current practice of proton therapy, the RBE is simplistically assumed to have a constant value of 1.1. In reality, the RBE is variable and a highly complex function of numerous variables including energy of protons, dose per fraction, tissue and its environment, cell type, end point, and possibly other factors.

While the theoretical potential of proton therapy is high, the clinical evidence in support of its use has so far been mixed. The uncertainties and assumptions mentioned above and the limitations of the still evolving technology of proton therapy may have diminished its true clinical potential. Although promising results have been reported for many types of cancers, they are often based on small studies. At the same time, there have been reports of unforeseen toxicities. Furthermore, because of the high cost of proton therapy, questions are often raised about its value. The general consensus is that there is a need for continued improvement in the state of the art of proton therapy. There is also a need to generate high level evidence of the potential of protons.

Fortuitously, such efforts are taking place currently. Current research, aimed at enhancing the therapeutic potential of proton therapy, includes the determination and mitigation of the impact of the physical uncertainties on proton dose distributions through advanced image-guidance and adaptive radiotherapy techniques. Since residual uncertainties will remain, robustness evaluation and robust optimization techniques are being developed to render dose distributions more resilient and to improve confidence in them. The ongoing research also includes improving our understanding of the biological and immunomodulatory effects of proton therapy. Such research and continuing technological advancements in planning and delivery methods are likely to help demonstrate the superiority of protons.

KEYWORDS
intensity-modulated proton therapy, proton therapy, relative biological effectiveness (RBE), uncertainties in proton therapy

1 | INTRODUCTION

Historically, the therapeutic potential of protons was first recognized by Wilson in 1946.[1] The first patient was treated with proton therapy in 1954 employing the synchrocyclotron at the University of California, Berkley.[2] Following this initial experience, research accelerators at numerous physics laboratories were adapted for radiotherapy with protons and, to a smaller extent, with heavier particles. These laboratories had significant limitations, including beam orientations, competition for beam-on time, and inadequate medical logistics. Loma Linda University Medical Center, CA was the first to establish a hospital-based proton therapy facility in 1990.[3] Ten years later, the second hospital-based proton therapy was opened at Massachusetts General Hospital. This was followed by proton therapy centers at MD Anderson Cancer Center (MDACC) in Houston and the University of Florida in Jacksonville in 2006. The MDACC facility was the first in the world to have two-dimensional scanning beams.[4–7]

Over the last two decades there has been an explosive growth in proton centers around the world, so much so that at the time of writing this article there are over 100 proton centers in operation around the world and about 60 more under construction or planned (http://www.ptcog.ch). Even so, <1% of the radiotherapy patients worldwide receive treatments with protons or heavier ions. The vast majority of the remainder (~90%) are treated with intensity-modulated photon radiotherapy (IMRT) or its newer cousin volumetric modulated arc therapy (VMAT).

Initially, persuaded by the physical characteristics of proton dose distributions, there was great excitement about the potential of proton therapy to improve the therapeutic ratio significantly. However, the review of the clinical results of proton therapy over time and the comparison of these results with conventional photon therapy suggests that the initial high expectations might have been inflated. The proton therapy community has come to the realization that there are numerous challenges that must be overcome to exploit the full therapeutic potential of protons. Examples of these challenges, elaborated in the sections below, include the greater sensitivity of proton dose distributions to inter- and intra-fractional variations of anatomy, the simplistic assumptions about the relative biological effectiveness (RBE) of protons compared to photons, questions about the appropriateness of extrapolating photon experience to greatly disparate proton dose distribution patterns, the still maturing treatment planning and treatment delivery technologies, and limited experience. In the face of the high cost of proton therapy and insufficiently strong evidence of the clinical superiority of proton therapy to date, there has been skepticism about the value of protons. Fortuitously, ongoing research is leading to the awareness that protons are very different from photons in terms of their complex biological, immunomodulatory, and clinical effects beyond just the differences in dose distributions.

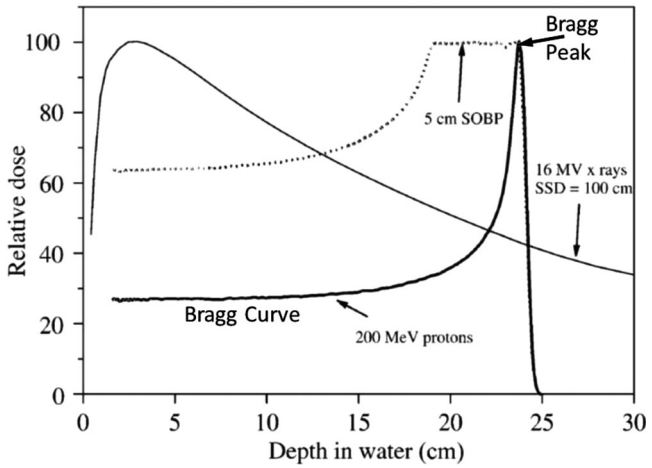

FIGURE 1 Depth–dose curves for a 200 MeV proton beam: both unmodulated and with a 5 cm spread-out Bragg peak (SOBP), compared with a 16 MV X-ray beam (for 10×10 cm^2 fields). The curves are normalized in each case to 100 at maximum dose. (Adapted from Jones, reproduced with permission)[8]

Understanding such differences and translating the knowledge thus gained clinically is critical for significant enhancement of the therapeutic potential of proton therapy.

When a beam of monoenergetic protons enters a medium, protons slow down continuously as a function of depth of penetration. The rate of energy transferred to the medium (i.e., "linear energy transfer" or LET) increases correspondingly until all of the energy is lost and protons come to a nearly abrupt stop. For a broad monoenergetic beam of protons, this process leads to the characteristic "Bragg curve," in which the point of highest dose is the Bragg peak (Figure 1). During the slowing down process, protons also scatter laterally, producing a penumbra at the beam boundary.

The physical rationale of using protons for sparing normal tissues has always been obvious. In addition, protons ionize more densely than photons and the ionization density and the LET increase with depth, and so does the RBE. Such an increase in RBE can be taken advantage of to further enhance the therapeutic potential of proton therapy. Another recently recognized rationale for the use of proton therapy is that its compact dose distributions (smaller "dose bath") can spare the immune system, which is likely to have a significant impact on outcomes. To date, however, treatments exploiting the variability of RBE have not been used widely and the use of protons to spare the immune system has yet to be introduced clinically.

To take advantage of many decades of clinical experience with photon radiotherapy, it is essential to understand the biological effects of protons relative to photons. Paganetti et al.[9,10] have summarized extensive in vitro and in vivo studies conducted to determine the biological effectiveness of protons relative to photons (i.e., the "relative biological effectiveness" or RBE). These studies suggested the use of an average proton RBE of 1.1 clinically. However, as mentioned above, this approximation is simplistic and not appropriate, and its continued use could compromise the benefits of proton therapy. Further research is necessary and is currently occurring to better understand and model the biological effects of protons. In addition, the distinct immunomodulatory potential of proton therapy is being investigated and may turn out to be a major advantage of proton therapy, especially in combination with immunotherapy.

2 | PROTON THERAPY DELIVERY MECHANISMS AND SYSTEMS

For radiation treatments, protons are accelerated with cyclotrons or synchrotrons to energies of therapeutic interest, typically 70–250 MeV. Cyclotrons, which produce a continuous stream of protons, are more compact and have higher beam intensity. Protons, accelerated to the maximum of the energy of the cyclotron, are degraded to the required lower energies by inserting energy degraders in the path of protons. Synchrotrons, in contrast, accelerate batches of protons to the desired energy. Synchrotrons have smaller energy spread and lower power consumption.

Accelerated beams of protons are guided through the beam line into the treatment room and into the nozzle mounted, in most cases, on a rotating gantry. The thin narrow beams of protons entering the nozzle are not appropriate for treating arbitrarily shaped tumors in inhomogeneous patients. Such beams must be broadened longitudinally and laterally and shaped to conform to the target shape and spare normal tissues. There are two methods for achieving this: (1) scattering and energy modulation of incident monoenergetic proton beams for passively scattered proton therapy (PSPT), and (2) magnetic scanning of narrow "beamlets" of protons of a range of incident energies to deliver IMPT. In either case, multiple beams, incident from different directions, are focused on the target volume.

Until recently, almost all proton therapy employed PSPT.[5–7,11] In this mode, the lateral and longitudinal spreading of the thin beam of an appropriate energy is accomplished using a rotating modulation wheel (RMW) and scatterers to create a spread out Bragg peak (SOBP) of sufficient dimension at the desired depth. Apertures, typically made from thick blocks of brass, are used to conform the dose distribution laterally to the target volume. To conform the dose distribution to the distal shape of the target, the spread-out Bragg peak of the scattered and modulated beam is shaped further using a range compensator.

Modern techniques employ scanning "beamlets" of protons to achieve significantly superior dose distributions that conform to the shape of the target volume and optimally spare normal tissues. For each beam, the treatment is delivered in "layers," one layer per energy. Cumulatively, contributions from multiple beams produce the desired pattern of dose. The scanning approach is more efficient and clinically more effective.[12–14] Magnetic scanning of beamlets allows the delivery of IMPT, potentially the most powerful mode of proton therapy. For IMPT, the energies of beamlets are defined based on the positions of spots (terminal ends of the beamlets) within the target volume. The intensities of beamlets are determined using optimization techniques to achieve the closest approximation of the desired dose distribution.

Incident beamlets of protons are essentially monoenergetic and Gaussian in shape laterally. A small full-width-at-half-maximum

(FWHM) of the Gaussian is highly desirable since it allows for sharper penumbrae and the ability to tailor dose distributions more precisely. It is possible to reduce the FWHM of the incident beams through improvements in technology; however, once the beamlet enters a medium, the FWHM increases unavoidably due to scattering, especially near the end of the range of protons.

One might think that there is no need for an aperture for IMPT due to the fact that proximal and lateral field shaping for IMPT is achieved by confining the spots to be within the target volume. However, because of the substantial FWHM of the incident beamlets, dynamic apertures that can change their shapes layer by layer have been developed.[15,16]

IMPT was first used for patient treatments at the Paul Scherrer Institute beginning in 1996.[17] One-dimensional scanning of proton beamlets of a range of energies to treat one transverse plane at a time was employed. The whole target volume was irradiated by moving the patient along his/her longitudinal axis. The two-dimensional scanning for volumetric irradiation was first introduced in May 2008 at MDACC.[14,18–20] Considering the potential of IMPT, new proton therapy facilities employ scanning beams exclusively. Since PSPT is now being replaced in clinical practice with IMPT, we will not discuss PSPT further in this article.

The technology of accelerators and ancillary systems, such as gantries and treatment delivery control systems, continues to be further developed to reduce their cost, to make them more compact and efficient, and to improve their clinical functionality.

3 | PROTON TREATMENT PLANNING AND TREATMENT PLAN EVALUATION

Software systems to compute and optimize proton dose distributions for the planning of proton treatments are integral to the practice of proton therapy. The pioneering work of Goitein et al. in the early 1980s to develop a three-dimensional (3D) conformal radiotherapy planning for protons is most notable.[21,22] In the following two decades, the state-of-the-art of proton therapy planning remained relatively static. However, with the rapid increase in the number of proton therapy facilities and with the introduction IMPT, proton treatment planning systems have been advancing steadily over the last 15 years.

Due to the large differences between proton and photon dose distributions, many of the formalisms, algorithms, and techniques used for the design and evaluation of photon treatment plans are not readily extensible to protons. The finite range, sharp distal fall-off, and scattering characteristics of protons make their dose distributions more sensitive to intra- and inter-fractional anatomy variations. Mainly due to such sensitivity, but also because of the uncertainty in converting CT numbers to stopping power ratios (SPRs), which are the relevant quantities for the calculation of proton dose distributions, there are uncertainties in the computed range of protons. In photon radiotherapy, to ensure that the clinical target volume (CTV) receives the prescribed dose over the treatment course in the face of these uncertainties, adequate safety margins are assigned to CTV to form planning target volume (PTV). In proton therapy, however, the range uncertainty depends on the position of point of interest along the path of protons. Therefore, the distal and proximal margins would be different for each beam. Moreover, anatomic changes in the path of protons affect the dose distribution not just near the target boundaries but also within its volume. Therefore, the practice of assigning CTV-to-PTV margins is inappropriate for the planning and evaluation of proton treatments. Similar issues exist for margins for organs at risk.

Due to the lower dose proximally and distally to the target and for practical reasons, the number of beams used for protons is generally much smaller than for photons. This is considered to be an advantage for protons; however, in some respects, for example, with regard to robustness of dose distributions, it is a disadvantage. Directions of proton beams that minimize passage through complex tissue heterogeneities and have shorter path lengths to the distal edge of the tumor are preferable. Moreover, out of concern regarding the higher RBE at the end of proton range and because of the uncertainty in proton range, beam directions that could lead to a higher biologically effective dose to critical normal tissues at or just beyond the distal edge of the target are avoided. An alternative approach, discussed in Subsection 5.2, is to use IMPT to reduce the biologically effective dose (or LET) in such organs at risk.

In IMPT, scanning beamlets of protons of sequences of energies may be used to "sculpt" the dose distributions around complex critical structures, allowing improved sparing of these structures without compromising target coverage.[12,23–26] The energy of beamlets is varied to paint the target layer-by-layer. Intensities of beamlets of multiple beams incident from different directions are optimized using computer-aided mathematical algorithms to balance the tumor coverage versus normal tissue sparing. Because of the ability of IMPT to control proton energies as well as intensities, its dose distributions are, in general, vastly superior not only to the IMRT but also to PSPT.[27] The power of IMPT also has to potential to incorporate variable RBE or LET in the optimization process. (See more details in Subsection 5.2) Moreover, as will be discussed in Subsection 5.6, the reduced "dose bath" outside the target has the potential to spare the immune system.

It is important to note that high and homogeneous target dose distribution and low and optimally balanced normal tissue doses for IMPT plans are the composite of contributions of multiple beams. Individually, the contribution of each field to the target dose distributions may be highly heterogeneous as illustrated in Figure 2. Such dose distributions, when summed, fit somewhat like a 3D jigsaw puzzle to create an exquisite dose distribution. However, in the face of uncertainties, the fit may be lost, creating regions of hot and/or cold dose, meaning that IMPT dose distributions are less robust in the face of uncertainties than PSPT and IMRT dose distributions. To reduce such sensitivity of IMPT to uncertainties, "robust optimization" techniques are being actively investigated and employed clinically (see Subsection 5.5).

Beyond the dosimetric differences between photons and protons, the planning and optimization of IMPT needs to take into consideration some additional factors. One consideration specific to IMPT is the limit on the minimum number of monitor units (MUs) per spot due to the inability of the beam monitoring system to detect extremely low

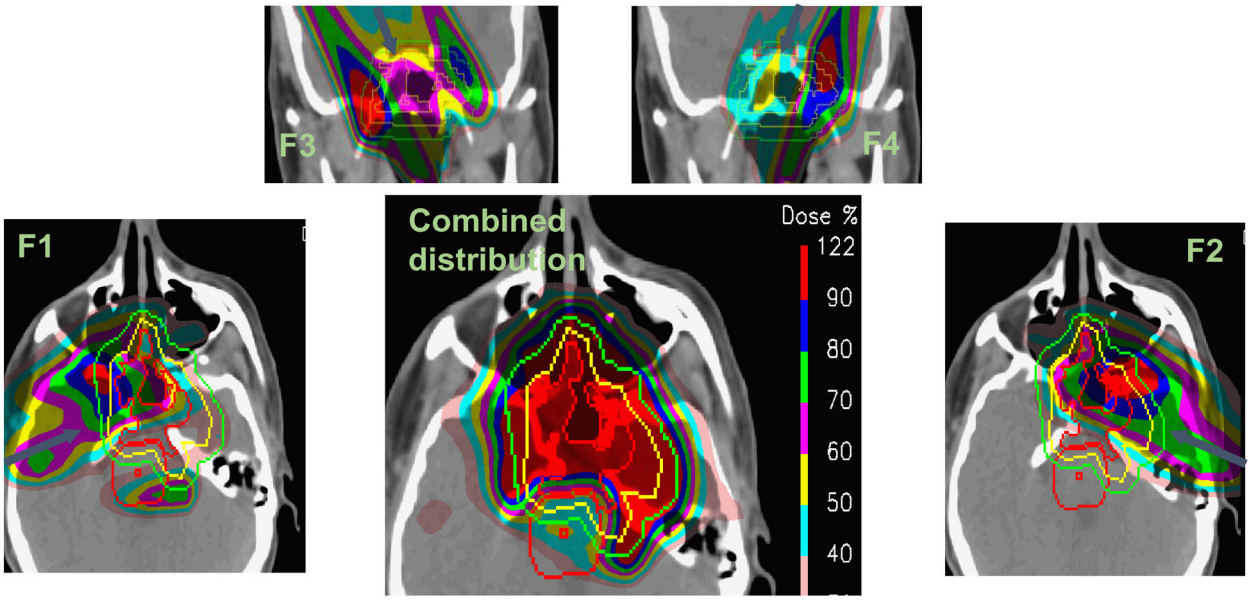

FIGURE 2 Homogenous intensity-modulated proton therapy dose distribution in the target for a head and neck case resulting from the combination of heterogenous individual field (F1, F2, F3, F4) dose distributions. (Adapted from a figure provided by A. Lomax, PSI, private communication)

values. Iterative solutions to account for such constraints and produce deliverable IMPT plans have been developed and implemented.[28]

Moreover, investigations to exploit the variable RBE of protons as well as the ability of proton dose distributions to spare the immune system in IMPT optimization are ongoing. Such optimization would require the development of reliable RBE, normal tissue, and immune system response models and their incorporation in the criteria of IMPT optimization. These issues are discussed in Subsections 5.2, 5.3, and 5.6.

4 | CLINICAL OUTCOMES

While there is clinical evidence to support the use of proton therapy, such evidence is not compelling enough to convince many of the skeptics and, in particular, third-party payors. Moreover, unanticipated toxicities have been observed for some disease sites; the reasons for which continue to be investigated. To date, the majority of the evidence has come from small non-randomized studies. However, with continuing research to better understand the physical, biological and immunological basis of the clinical effects, ongoing randomized trials, and the increasing number of patients being treated with proton therapy, it is expected that clinical data demonstrating clearer evidence of the superiority of proton therapy will emerge.

The list below, which is not comprehensive, summarizes some of the currently available data.

- Due to the reduction in normal tissue doses possible with proton therapy and the potential for the corresponding reduction in adverse effects, proton therapy is widely accepted for childhood cancers. Numerous studies have found that disease control and survival rates seen with proton therapy are comparable to those with photons.[29–33] However, there are concerns that higher LET and RBE near the distal edges could lead to higher severe toxicities.[34–37]
- Proton therapy has been shown to be effective for skull based and sinonasal malignancies. Treatment of these tumors requires high radiation doses in close proximity of critical normal tissues, for example, the brainstem or optic structures. Such high doses are not achievable with photons without causing severe toxicities. Published studies have shown high disease control and acceptable toxicity rates with proton therapy.[38,39] The majority of patients in these studies received PSPT. Notably, investigators from the Paul Scherrer Institute achieved excellent outcomes using IMPT for patients with skull-based lesions.[40] Early results with the use of IMPT from MD Anderson[41] reported improved dose distributions compared to PSPT and favorable disease control and toxicity profiles. For sinonasal tumors, a meta-analysis of a multi-institutional dataset by Patel et al. suggested improved survival outcomes with particle therapy compared to photon therapy.[42]
- Proton therapy has shown promise for brain tumors due to its potential for reduced adverse effects, particularly cognitive dysfunction. Proton therapy has also been evaluated for low-grade gliomas. Initial results suggest high rates of tumor control with acceptable toxicity rates.[43,44] An important study by Shih et al. reported results of a prospective trial of patients with grade II gliomas and assessed cognitive function and quality of life following proton therapy. They found that metrics of cognitive function were stable or improved compared to the baseline.[45] For glioblastoma (GBM), the role of proton therapy has also been assessed in a small phase II trial. Proton therapy was found not to be associated with a delay in time to cognitive failure but did reduce toxicity and patient-reported fatigue. It

was further noted that larger randomized trials are needed to determine the potential of proton therapy for dose escalation for GBM. Similar trials are also needed for cognitive preservation in patients with lower-grade gliomas, who have longer survival time.[46] In fact, a phase II randomized trial of proton versus photon therapy (IMRT) for cognitive preservation in patients with IDH mutant, low to intermediate grade gliomas (NRG-BN005, NCT03180502) is in progress. It is also notable that several studies have shown unanticipated severe toxicities in proton therapy of brain tumors.[34,36,37,47] The higher RBE around the distal edge has been implicated and has been and continues to be investigated in retrospective studies[35,48–50] and in ongoing trials, for example, LET Optimized IMPT in Treating Pediatric Patients With Ependymoma (NCT03750513).

- Lung cancer is one of the most challenging disease sites to treat with proton therapy due mainly to the sensitivity of proton dose distributions to highly heterogenous tissues in the path of protons but also due to respiratory motion. Moreover, if the distal edge of the beam falls in a low-density portion of the lung to allow for margins, protons will continue to travel and may irradiate large portions of the lung until they encounter higher density tissues to stop them. Early retrospective and single-arm early phase trials had suggested excellent toxicity profiles and disease control rates for protons.[27,51–53] However, in a first of its kind randomized phase II trial of IMRT versus PSPT of locally advanced non-small cell lung cancers, which completed accrual in 2014 and for which results were reported in 2018, there was no difference in either of the primary end points of local control or grade 3 pneumonitis.[54] Initial high expectations about the superiority of protons were not born out. Secondary analyses of the data are ongoing to understand the role of various factors, including inter- and intra-fractional variations in anatomy, the simplistic assumption about proton RBE, immature technology (PSPT instead of IMPT), and evolving treatment planning techniques.[55–65] At the same time a multi-institutional randomized phase III study "Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer" (NCT01993810) is underway through NRG and is nearing completion. Another phase II randomized trial "Image-Guided, Intensity-Modulated Photon or Proton Beam Radiation Therapy in Treating Patients with Stage II-IIIB Non-small Cell Lung Cancer" (NCT01629498) is also being conducted.
- For esophageal cancers, retrospective studies suggested reduced toxicity rates and promising disease control rates with proton therapy. Based on these findings, a multi-institutional randomized trial of protons versus photons for esophageal cancer was conducted.[66] This trial (N = 145) showed no difference in survival; however, the total toxicity burden, defined as a composite score of 11 distinct adverse events, was 2.3 times higher for IMRT compared to proton therapy and 7.6 times higher for post-operative patients. An extension of this trial is currently being conducted as "Phase III Randomized Trial of Proton Beam Therapy versus IMRT for the Treatment of Esophageal Cancer" (NCT03801876).
- For primary hepatocellular carcinoma (HCC), cholangiocarcinoma, and isolated hepatic metastases, the normal tissue sparing with proton therapy allows escalation of dose. Such escalation shows great promise, especially for large tumors that are a huge challenge to treat with photons without severe radiation-induced liver disease. An HCC randomized trial "Radiation Therapy with Protons or Photons in Treating Patients with Liver Cancer" (NCT03186898) is being conducted within the auspices of NRG.
- Treatment of head and neck malignancies with protons is challenging due to highly complex anatomy. However, promising results are being reported with IMPT. For example, Manzar et al.[67] conducted retrospective analysis of oropharyngeal cancer patients showing that IMPT, compared to VMAT, significantly reduced toxicities (feeding tube placement, narcotics use, cough, and dysgeusia) and hospitalization (~30% to ~8%) within 60 days post-RT. In another retrospective study, Sio et al.[68] found that symptom burden (five top symptoms of food taste problems, dry mouth, swallowing/chewing difficulty, lack of appetite, and fatigue), as assessed based on patient-reported outcomes within 3 months after treatment, was significantly reduced with IMPT (N = 35) versus IMRT (N = 46) for oropharyngeal cancer patients. While these are examples of small studies, a phase III randomized IMPT versus IMRT trial for stage III-IVB oropharyngeal cancer (NCT01893307) just completed accrual (N = 518), the results of which are awaited and expected to be more convincing.

The non-randomized clinical studies among those listed above are just a small sample from the literature. It is also notable that most studies, non-randomized as well as randomized, published to date have employed PSPT and their results of protons versus photons have been mixed. However, the power of IMPT to control intensities and energies of beamlets allows achievement of significantly more conformal dose distributions. As the use of IMPT increases, it is reasonable to expect that further improvements in its clinical outcomes compared to IMRT and VMAT will be made. Moreover, to reiterate, as our understanding of the biological and immunological effects of proton therapy and the role of physical uncertainties improves and such understanding is incorporated in the design of treatment plans, it is likely that the enhancement in therapeutic ratio with proton therapy may be substantial, especially in combination with immunotherapy.

5 | CURRENT AND FUTURE RESEARCH AND DEVELOPMENT

5.1 | Physical aspects

While protons are considered to have an advantage due to their physical characteristics, they have a larger penumbra. Consequently, normal tissues in the immediate vicinity of the target volume may receive a high biologically effective dose. The penumbra may be reduced using apertures and minimizing the incident beamlet spot sizes. For IMPT the spot dimensions change from one energy layer to the next. Moreover, the intensities of spots vary significantly within the scan. Dynamic collimation systems to sharpen penumbrae of incident beams and to

manipulate dose distributions within anatomic structures more effectively have been developed.[15,16] Continued further enhancement of such systems is expected in the future.

Furthermore, as stated above, IMPT dose distributions are highly sensitive to setup variations, inter-fractional anatomy changes (e.g., due to tumor/nodal regression and weight loss) and intra-fractional motion. Anatomy changes in the path of protons during a single fraction and over the course of proton therapy may significantly degrade the conformality and homogeneity of dose distributions in the target and compromise the sparing of normal tissues.[69,70] For photons (IMRT), such uncertainties are accounted for with the use of CTV to PTV margins. For IMPT, the appropriate solution is to test the resilience, that is, the robustness, of dose distributions in the face of uncertainties, and to use robust optimization to make dose distributions resilient. Robustness evaluation and robust optimization adaptive replanning are discussed in Subsection 5.5.

For interfractional changes, verification CT images are acquired more frequently for protons than for photons. If suggested by the visual inspection of anatomy changes on verification images, the dose distribution is recalculated based on the new image. For larger anatomic variations, the difference between the recalculated and original (or previous) dose distribution may be significant and an adaptive IMPT plan may be required for the remaining fractions.

5.2 | Biological aspects

As mentioned in the introduction, in the current practice of proton therapy, the RBE is simplistically assumed to have a constant generic value of 1.1.[10,9] This value of RBE is based on an average of the results of numerous in vitro and in vivo experiments conducted under varied, often unspecified, conditions and for only a limited number of cell lines, tissues, and endpoints. In reality, the RBE is variable and a complex function of dose per fraction, LET, tissue type, end point, inter-patient variation in sensitivity (e.g., due to DNA repair defects),[71] etc. If the region of low RBE occurs in the tumor or the region of high RBE in a critical normal tissue, the advantage of proton therapy may be compromised and may even lead to unanticipated treatment failures or severe toxicities.

Numerous models for estimating variable RBE have been proposed,[72–78] which can reasonably predict the trend of nearly linearly rising RBE up to the Bragg peak but not in the region of high LET at or beyond the Bragg peak. Being based on limited measured data and because they ignore some of the important dependencies (e.g., inter-patient sensitivity variation), the models have significant shortcomings. They are not commonly used clinically in IMPT optimization.

An alternative approach that has gained acceptance recently is the incorporation of a function of LET in the criteria of IMPT optimization.[79,80] The goal of LET-based optimization is to minimize LET in normal tissues and maximize it in the tumor. In such optimization, the physical dose (or RBE = 1.1-weighted dose) is maintained at the same level as that obtained without LET-based optimization. The evaluation of the resulting dose distribution may be carried out using RBE-weighted dose computed using one of the models.

A problem common to the models that depend on LET, and also to the direct use of LET in the optimization or evaluation of IMPT plans, is that dose (or fluence)-averaged LET is employed. This is an approximation, especially in regions of rapidly and non-linearly rising LET around the Bragg peak, and underestimates the biological effect. Strictly speaking, energy or LET spectra (or the corresponding microdosimetric quantities) should be used. Research to improve our understanding of biological effects and to develop novel more accurate RBE models is ongoing. The tissue, endpoint, and inter-patient variability dependence of such models is also being considered in such research.

5.3 | Treatment response modeling

Predictive models play a critical role in all walks of life, and radiotherapy is no exception. Dosimetric parameters, such as dose-volume constraints, that are used in optimizing and evaluating treatment plans are just models, all be it crude ones. The models are based on observed treatment response data from clinical trials and routine practice. During the last several decades, there have been numerous attempts to develop sophisticated analytical tumor control probability (TCP) and normal tissue complication probability (NTCP) models. These models represent a step forward but have not made significant inroads into the clinic for many reasons, the main being the concerns about their limited accuracy.

Current models, including the simplistic dosimetric models, are one-size-fits-all population averages. Heterogeneities in patients' baseline characteristics, including genomic information, are not considered and diminish the accuracy of the predicted response for an individual patient. Various physical uncertainties mentioned above, and the limitations of the biological effect models, further affect the accuracy of models.

There are several ways to improve the accuracy of treatment response models. For example, reducing the uncertainty in the biologically effective dose distributions actually delivered, more frequent imaging and their use in treatment adaptation, improvement in RBE models, multi-modality imaging, and the inclusion of baseline biomarkers, would improve the accuracy of the response data that these models depend upon. Another important step would be to develop "personalized" models that consider each patient's baseline characteristics, including genetic factors, along with dose distributions. Such models would be able to predict a given patient's risk of a toxicity or treatment failure based on his or her personal baseline clinical and biological factors for a given dose distribution.

5.4 | Evaluation of the robustness of dose distributions for IMPT

There are significant differences in the planning and plan evaluation approaches between photons and protons. This is in part because of the

finite range of protons and in part due to the fact that distal and proximal margins depend on range uncertainty. Moreover, the use of margins does not take into account the impact of anatomy changes on dose distributions within the target volume and normal anatomic structures. Thus, the concept of PTV in the traditional sense is no longer appropriate, although it continues to be used commonly due to lack of alternatives. Ideally, for IMPT planning, robustness evaluation and robust optimization approaches (see Subsection 5.5) should be employed.

A simple approach to evaluate robustness of IMPT dose distributions, regardless of whether they are designed using conventional margins or using robust optimization, is to review individual dose distributions for each of a set of uncertainty scenarios.[81–85] As an example, these scenarios may include shifts along the orthogonal axes, range uncertainty, end-inhale, and end-exhale phases. The magnitudes of shifts may be chosen to be the same as the CTV to PTV margins used for designing photon plans. Such reviews would identify deficiencies in dose distributions in one or more scenarios and steps may be taken to rectify them. These reviews may be supplemented with families (bands) of DVHs for the anatomic structures of interest. The DVH band represents the range of possible dose distributions received by the patient. Quantitative measure of robustness may be represented by the band width at the critical points on the DVH (e.g., at the volume receiving 20 Gy [RBE] or higher for lung).

5.5 | Robustness improvement and robust optimization

Despite the efforts to reduce uncertainties through such approaches as image-guidance, respiratory gating, and adaptive replanning to accommodate inter-fractional anatomy changes, residual uncertainties would remain. They need to be accounted for in treatment planning so that there is high confidence in target coverage and normal tissue sparing in the face of uncertainties.

The robustness of proton dose distributions depends on numerous factors. The use of larger numbers of beams tends to improve robustness. Beams passing through heterogeneous anatomy degrade robustness. Dose distributions are affected by respiratory motion, and the magnitude of the effect often depends on the direction of the beam. To reduce the vulnerability of IMPT to positioning uncertainties and motion, "robust optimization" techniques have been developed and continue to evolve further and be evaluated for their potential.

As an example, a robust optimization process may consider uncertainty scenarios of the type mentioned in the previous section and optimize intensities in the face of all scenarios simultaneously. It may consider (a) six dose distributions obtained by shifting the patient image along three orthogonal directions by, for instance, ±5 mm (i.e., the distance equal to the CTV-to-PTV margin), (b) two additional dose distributions incorporating uncertainty in the range of, for instance, ±3%, and (c) the nominal dose distribution. The optimization algorithm determines the worst-case value of the objective function (i.e., the score) in each iteration by choosing the worst dose in each voxel from among all the scenarios. For the voxels in the target, the worst dose would be the minimum value and for normal tissues, it would be the maximum value. This is the so-called "voxel-by-voxel" worst-case approach.[86–92] Alternate approaches have been proposed and have different strengths.[93–95] Robust optimization has also been extended to four dimensions to make dose distributions resilient in the presence of respiratory motion.[70]

It should be noted that robust optimization does not necessarily mean a reduction in uncertainties. It simply reduces gradients in dose distributions, making them less sensitive to uncertainties, in effect, something like the smearing of dose distributions.

5.6 | Immunomodulatory effects

The effectiveness of cancer therapy, including radiotherapy, relies on an intact immune system.[96] However, RT suppresses the immune system through the killing of lymphocytes traversing the radiation field. Lymphocytes are highly radiosensitive (LD_{50} <2 Gy)[97,98] and are killed by radiation in much greater numbers than other cells, resulting in radiation-induced lymphopenia (RIL), which has been shown to be associated with inferior radiotherapy outcomes.[100–105,99] Preservation of lymphocytes through the mitigation of radiation damage to lymphoid organs and circulating lymphocytes is crucial for advancing radiotherapy. IMPT can have a unique and important role towards this end.

A recent discovery of a potential benefit of proton therapy, attributable to its smaller dose bath, is the sparing of the immune system.[106] However, significant further sparing may be possible through an improved understanding of the dependence of RIL on baseline patient specific clinical factors and dose distribution patterns and the development of RIL risk prediction models. These models may then be incorporated into the criteria of IMPT or IMRT optimization. Compared to IMRT, IMPT, with its additional degree of freedom, that of energy, has the potential to achieve a significantly greater reduction in RIL without compromising standard-of-practice tumor and normal tissue dosimetric constraints. Since the effectiveness of immunotherapy depends on the health of the immune system, it can be hypothesized that the benefit of immunotherapy after IMPT will be greater than after IMRT.

5.7 | Beam configuration optimization

As mentioned above, proton therapy, in general, employs a smaller number of beams for practical reasons. The smaller number of beams may also be important for reducing the dose bath and, thus, increasing the sparing of the immune system. Therefore, the optimization of the number of beams and their directions, that is, beam configuration optimization (BCO), is more important for achieving the most clinically effective dose distributions for protons than for photons. The BCO for protons must take into consideration the variability of RBE, the sensitivity of dose distributions to uncertainties, the sparing of the immune system, and the limit on the minimum MUs per spot. Most of the past

developments of BCO have been for IMRT, which are of limited applicability to IMPT due to the differences in dose distribution patterns between the two modalities. For IMPT specifically, there have been only a small number of developments to date as exemplified by the works of Cao et al.[107,108] and Gu et al.[109–112] BCO remains an open area for further research.

5.8 | Technological limitations and ongoing advancements

Other challenges and obstacles that inhibit achievement of the optimum benefit of proton therapy pertain to the treatment planning and delivery systems technologies. Examples include large spot sizes (as much as 35 mm full width at half maximum for low energies), slow changes in energy that impact efficiency, in-room volumetric image guidance, and respiratory gating. Fortunately, commercial vendors (IBA, Hitachi, Varian, RaySearch, and others) as well as researchers across the world are making serious efforts to overcome these challenges. Newer delivery devices have spot sizes that are less than half the early versions. These devices are also able to change energies much more rapidly through clever approaches such as multi-energy extractions. Examples of other advancements include robotic couches, in-room couch or ceiling mounted cone-beam CT scanners, and the above mentioned dynamic collimation.[15,16]

Another concern about proton therapy has been its high cost. Current three to four treatment room proton therapy facilities cost of the order of $100–200 million, whereas a single room facility costs about $30 million. These costs are an order of magnitude higher than the cost of a high-end photon therapy facility. Efforts to develop novel, lower cost compact accelerators and gantries based on super-conducting magnets and innovative designs are occurring. In addition, numerous studies are being conducted to determine the cost effectiveness of proton therapy.[113–115] While the upfront cost may be significantly higher, considering outcomes, toxicities, and hospitalization rates after radiotherapy, the overall value of proton therapy may be competitive with photon therapy, especially once it achieves its potential. Furthermore, the cost effectiveness may vary significantly from patient to patient, and it is important to identify patients for whom proton therapy will have the greatest benefit. A normal tissue complication model-based approach for the selection of the appropriate modality for each patient is being used increasingly.[116–119] For the success of such an approach, it is important that the models be highly reliable.

6 | SUMMARY

The primary rationale for the use of proton therapy is its exquisite physical dose deposition characteristics. Expectations have been that such dose distributions will allow significant sparing of normal tissues adjacent to the target volume or target dose escalation, or both. However, despite the theoretical promise of proton therapy, and the fact that more than 170,000 patients have been treated with proton therapy to date, the clinical evidence for protons so far has not been unequivocally strong and broad enough to alleviate concerns, particularly among the third party payors, and justify the high cost of proton therapy. The possible reasons are many and include the evolving technology and limited experience with the relatively new technology; the greater uncertainty in delivered biologically effective dose distributions; the assumption of constancy of RBE; etc. Another factor for the lack of unequivocal evidence may be that the vast majority of patients treated with protons to date have been with PSPT, which offers only limited advantages over the much more mature technology of IMRT.

IMPT, with its additional degree of freedom, that of energy, offers the ability to tailor dose distributions more conformally and to optimally balance tumor and normal tissue doses. The commercial widespread availability of scanning beams and IMPT during the last decade or so may change the balance in favor of protons in a big way. In addition, there are numerous ongoing research and development activities that could significantly increase the advantage of protons over photons. Examples of the important ones include:

- Improving our understanding of the biological effects of protons and the development of novel, more accurate and clinically relevant RBE models. Ongoing efforts include experimental acquisition of large amounts of biological response data, derivation of biological effects information from observed clinical responses, and computer simulations of biological effects.
- Developing more accurate personalized treatment response models that can predict the risk of toxicities and the risk of recurrence for a given proton or photon dose distribution based on a patient's personal clinical characteristics and dose distribution.
- Understanding and modeling immunomodulatory differences between protons and photons, modeling the risk of immune suppression, and developing risk mitigation strategies. Clinical implementation of immune suppression mitigation could improve not only the outcomes of radiotherapy but also of adjuvant immunotherapy.

In addition, there are numerous other ongoing technological developments, including advanced on-board imaging devices, image guidance, and treatment planning tools to reduce uncertainties in treatments, and quantify their consequences in proton therapy; the incorporation of residual uncertainties in robust optimization to improve confidence in delivered dose distributions; and much more. In addition, many clinical trials, especially randomized trials comparing IMRT and IMPT, have been initiated. It is anticipated that these trials will provide the data necessary to accurately correlate treatment responses with dose distributions and lead to further improvement in our understanding of various issues related to proton therapy and, therefore, to its further enhancement. One such trial, that for oropharynx, has recently been completed. Ongoing technological advances are also likely to reduce the cost of proton therapy. Thus, despite the current limitations and skepticism about proton therapy, its future is very promising!

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CONFLICT OF INTEREST

The author declares no conflicts of interest to disclose.

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