HHS Public Access

Author manuscript

Precis Radiat Oncol. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

Precis Radiat Oncol. 2022 June ; 6(2): 164–176. doi:10.1002/pro6.1149.

A Review of Proton Therapy – Current Status and Future Directions

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Abstract

The original rationale for proton therapy was the highly conformal depth-dose distributions that protons are able to produce, compared to photons, which allow greater sparing of normal tissues and escalation of tumor doses, thus potentially improving outcomes. Additionally, recent research, which is still ongoing, 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 vs. normal tissues. Moreover, the smaller "dose bath", i.e., the compact nature of proton dose distributions has been found to reduce 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 therapeutic energies ranging from 70 to 250 MeV, are transported to the treatment room where they enter the treatment head mounted on a rotating gantry. The initially narrow beams of protons are spread laterally and longitudinally and shaped appropriately to deliver treatments. Spreading and shaping can be achieved by electro-mechanically for "passively-scattered proton therapy' (PSPT); or using magnetic scanning of thin "beamlets" of protons of a sequence of initial energies. The latter technique is used to treat patients with optimized intensity modulated proton therapy (IMPT), the most powerful proton therapy modality, which is rapidly supplanting PSPT.

Treatment planning and plan evaluation for proton therapy require different techniques compared to photon therapy due, in part, to the greater vulnerability of protons to uncertainties, especially those introduced by inter- and intra-fractional variations in anatomy. In addition to anatomic variations, other sources of uncertainty in the treatments delivered include the approximations and assumptions of models used for computing dose distributions and the current practice of proton therapy of assuming the RBE to have a constant value of 1.1. In reality, the RBE is variable and a complex function of proton energy, dose per fraction, tissue and cell type, end point, etc.

Despite the high theoretical potential of proton therapy, the clinical evidence supporting its broad use has so far been mixed. The uncertainties and approximations mentioned above, and the technological limitations of proton therapy may have diminished its true clinical potential. It is generally acknowledged that proton therapy is safe, effective and recommended for many types of pediatric cancers, ocular melanomas, chordomas and chondrosarcomas. Promising results have

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been and continue to be reported for many other types of cancers as well; however, they are based on small studies. At the same time, there have been reports of unforeseen toxicities. Furthermore, because of the high cost of establishing and operating proton therapy centers, questions are often raised about the value of proton therapy. 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 conduct randomized trials and/or collect outcomes data in multi-institutional registries to generate high level evidence of the advantages of protons. Fortuitously, such efforts are taking currently place.

Ongoing research is aimed at better understanding the biological and immunomodulatory effects of proton therapy and the consequences of the physical uncertainties on proton therapy and reducing them through image-guidance and adaptive radiotherapy. Since residual uncertainties will remain despite our best efforts, in order to increase the resilience of dose distributions in the face of uncertainties and improve our confidence in dose distributions seen on treatment plans, robust optimization techniques are being developed and implemented and continue to be perfected. Such research and continuing technological advancements in planning and delivery methods are likely to help demonstrate the superiority of protons.

1 Introduction

Historically, the therapeutic potential of the depth-dose characteristics of protons was first recognized in a report by Wilson in 1946.[1] The first patient was treated with protons in 1954 employing the synchrocyclotron at the University of California, Berkley.[2] Since then, and until about 1990, a number of research accelerators at physics laboratories around the world were adapted for treating cancer patients with protons and, to a smaller extent, with heavier particles. Physics laboratory-based particle therapy facilities had numerous limitations, including beam orientations (typically horizontal beams only), competition for beam-on time, inadequate medical logistics, etc. The first hospital-based proton therapy facility was established in 1990 at the Loma Linda University Medical Center, CA.[3] Approximately 10 years later, Massachusetts General Hospital (MGH)-Harvard University opened the second hospital-based proton therapy center with gantries. It was followed in 2006 by proton therapy centers at MD Anderson Cancer Center (MDACC) in Houston and the University of Florida in Jacksonville. The MDACC Proton Therapy Center is the first one in the US to have scanning beam capability and first in the world to have a two-dimensional scanning beam.[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, less than 1% of the radiotherapy patients world-wide are treated with protons and 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, based on the physical characteristics of proton dose distributions, there was great excitement about the potential of proton therapy to improve the therapeutic ratio considerably. With closer examination of the clinical results of proton therapy over time

and the comparison of these results with conventional photon therapy, it seems that the initial high expectations might have been inflated. This gave way to the realization that there are numerous challenges that must be overcome to exploit the full therapeutic potential of protons. Examples of such obstacles, 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, the questions about the appropriateness of extrapolating photon experience to greatly disparate proton dose distribution patterns, still maturing treatment planning and treatment delivery technologies and limited experience. In the face of high cost of proton therapy and the insufficiently strong evidence of clinical superiority proton therapy to date, there has been skepticism about the value of protons.

Fortuitously, ongoing research is leading to the realization that protons are very different from photons in terms of their complex biological, immunomodulatory and clinical effects beyond just the differences in dose distributions. Understanding such differences and translating the knowledge thus gained clinically is critical for significant enhancement of the therapeutic potential of proton therapy.

In contrast with photons, when protons of a given energy (typically in the range of 70 to 250 MeV) penetrate matter, they slow down continuously as a function of depth. The rate of their energy loss (called the “linear energy transfer” or LET) increases with decreasing velocity. This continues until their entire energy is depleted and then the protons come to an abrupt stop. This process of dose deposition produces the characteristic depth-dose curve (the “Bragg curve”) for a broad monoenergetic beam of protons as illustrated in Figure 1. The point of highest dose is called the Bragg peak. Dose deposited beyond the range is negligible. As protons traverse a medium, they also scatter laterally but the dose outside the boundary of a beam of protons falls rapidly. The practice of proton therapy until the recent past employed the passively scattered proton therapy (PSPT). In this mode, the initially monoenergetic narrow beam of an appropriate energy is spread longitudinally (to create a “spread-out Bragg peak” or SOBP, Figure 1), spread laterally using scatterers and then shaped appropriately to conform the high dose regions to the target volume. Modern techniques employ magnetic scanning of thin “beamlets” of protons of a sequence of energies to achieve significantly superior dose distributions conforming to the shape of the target volume and optimally sparing normal tissues.

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 as 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 can spare the body’s immune system, which is likely to have a significant impact on outcomes. To date, however, treatments utilizing variable RBE are in very limited use and the use of protons to spare the immune system has yet to be introduced clinically.

Currently, most of the proton accelerators in use are cyclotrons and a smaller number are synchrotrons. Each type has advantages and disadvantages. The technology of accelerators

and ancillary systems, such as gantries and treatment delivery control systems, continues to be further developed to reduce their cost and to make them more compact and efficient and to improve their clinical functionality. In addition to the delivery devices, software systems to plan proton treatments and compute and optimize proton dose distributions are also required. Goitein, et al were the first to develop a three-dimensional conformal radiotherapy planning system for protons.[9,10] For nearly two decades, the state-of-the-art of such systems remained relatively static. Only during the last decade and a half has there been further significant evolution of these systems.

In order to relate our clinical experience with photon treatments to the clinical application of protons, it is necessary to understand the biological effects of the latter. Extensive in-vitro and in-vivo studies to determine the biological effectiveness of protons and other particles relative to photon irradiation (i.e., “relative biological effectiveness” or RBE) have been reported. The results of these studies have been summarized in two review articles by Paganetti et al.[11,12] In the current practice of proton therapy, an average RBE of 1.1 is used. It is now being recognized increasingly that this approximation is not appropriate, and its continued use could limit the effectiveness 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

Protons are accelerated to therapeutic energies, typically in the range of 70 to 250 MeV, with cyclotrons or synchrotrons. An accelerated proton beam entering the treatment delivery head (the “nozzle”) is very thin and has depth dose characteristics as depicted by the Bragg curve of Figure 1. As such, it is not suitable for treating three-dimensional, arbitrarily shaped tumor targets in an inhomogeneous patient. It must be broadened longitudinally and laterally and sculpted to conform to the target shape. There are two main approaches for achieving this: (1) passive scattering to deliver passively scattered proton therapy (PSPT), and (2) magnetic-scanning of narrow “beamlets” of protons of a sequence of initial energies to deliver intensity-modulated proton therapy (IMPT).

Cyclotrons produce a continuous stream of protons. They are more compact and have higher beam intensity. Protons are accelerated to the maximum of the energy of the cyclotron, and the required lower energies are achieved by electromechanically inserting energy degraders in the path of protons between the accelerator and the treatment room. Synchrotrons, on the other hand, accelerate batches of protons to the desired energy. Each batch can be of a different energy. Generally, the advantages of synchrotrons are that they have greater energy flexibility, smaller energy spread, and lower power consumption. Regardless of the type of accelerator, the extracted narrow monoenergetic beam is magnetically guided through the beam line to the nozzle mounted, in most cases, on a rotating gantry in the treatment room. A typical proton accelerator can serve multiple rooms. Considering the high cost of establishing and operating multi-room proton therapy centers, single room systems are also available.

For PSPT, [5–7,13] the lateral and longitudinal spreading of the thin beam entering the nozzle is achieved with a combination of a rotating modulation wheel (RMW) and one or two scatterers. To conform the dose distribution laterally to the shape of the target volume (plus appropriate margins), an aperture, typically made from blocks of brass of sufficient thickness to absorb incident protons of the highest energy, is used. To create a dose distribution that conforms to the distal shape of the target, the spread-out Bragg peak of the passively scattered beam is shaped further by using a range compensator.

A more efficient and clinically more effective alternative to the use of RMWs, apertures and compensators to shape the beams is magnetic scanning of thin beamlets of protons.[14–16] Multiple beams incident from different directions, each comprising scanning beamlets of a sequence of energies, are used to produce the desired pattern of dose. For each scanned beam, the treatment is delivered in "layers," one layer per energy.

Protons in a beamlet incident on a patient are very nearly monoenergetic and are distributed essentially as a narrow Gaussian function of position relative to the beamlet's central axis. The lateral dimension of a beamlet is expressed in terms of the full-width-at-half-maximum (FWHM) of the Gaussian or its σ. A smaller FWHM is desirable since it produces a sharper penumbra and allows for greater control of dose distributions. Once the pencil beam enters a medium, such as a phantom or a patient, the FWHM increases substantially due to scattering, especially near the end of the range of protons.

Magnetic scanning of beamlets provides greater flexibility and control for creating the optimum conformal proton dose distribution. It allows the delivery of IMPT, potentially the most effective form of proton therapy. The positions and intensities (in terms of monitor units) for a matrix of spots (terminal ends of the beamlets) within the target volume for each scanned beam are determined using optimization techniques by the treatment planning system to achieve the best possible approximation of the desired dose distribution. Figure 2 shows the schematic of the scanning beam nozzle of an early version Hitachi proton synchrotron and describes its components. Field sizes of up to 30 cm x 30 cm can be achieved with it.

Figure 3 shows the dose distribution of a single beamlet in water for a proton beam of range 30.5 cm (corresponding to an energy of 222 MeV) for the Hitachi proton therapy system at MDACC. The FWHM of the pencil beam at the end of its range in water as a function of energy varies from approximately 18 mm (σ~8 mm) for 222 MeV to 30 mm (σ~13 mm) for 72 MeV. The high dose region at the end of the range of a beamlet is often referred to as a "spot." The spot size is of special interest for scanned proton beam therapy. It affects the width of the penumbra and limits the fineness of the adjustment of the dose possible to achieve optimum IMPT dose distributions. The newer machines have much smaller spot dimensions.

Proton scanning beams have been in use for patient treatments at the Paul Scherrer Institute since 1996,[17] where a one-dimensional scanning of proton pencil beams of different energies in the patient's transverse plane was used. The other dimension was achieved by moving the couch along the patient's longitudinal axis. The first use of two-dimensional

scanning occurred in May, 2008 at MDACC.[16,18–20] Recognizing the potential of scanning beams, new proton therapy installations employ scanning beams only.

For scanning beams, proximal and lateral field shaping is achieved by limiting the positions of the spots to within the target regions only. Presumably, there is no need for an aperture. However, because of the substantial size of the pencil beam spots, dynamic apertures that can change their shapes layer by layer have been developed.[21,22]

Since PSPT is now being replaced in clinical practice with IMPT, we will not discuss PSPT further in this article.

3 Proton Treatment Planning and Treatment Plan Evaluation

The significant differences in the dose deposition of protons and photons mean that many of the formalisms, algorithms and techniques used for the planning, optimization and evaluation of photon treatments are not readily extensible to proton treatments. Their finite range, sharp distal fall-off and scattering characteristics make proton dose distributions more sensitive to inter- and intra-fractional anatomy variations. Mainly due to such sensitivity, but also due to uncertainty in the conversion of the CT Hounsfield Units (HUs) to stopping power ratios (SPRs), which are the relevant quantities for calculation of proton dose distributions, the computed range of protons in patients is uncertain. The conventional practice in photon therapy is to assign an adequate safety margin to the clinical target volume (CTV) to create a planning target volume (PTV) to ensure that the CTV will receive the prescribed dose in the face of variations in treatment setup and anatomy over the course of radiotherapy. For protons, however, uncertainty in the range depends on the depth of point of interest and, therefore, on the direction of each proton beam. Moreover, anatomic variations in the path of protons perturb the dose distribution within the target volume, not just near the boundaries. Consequently, the conventional practice of assigning CTV-to-PTV margins is not appropriate for the planning and evaluation of proton treatments. Similar issues exist for margins for organs at risk.

For proton therapy in general, due to the lower dose proximally and distally to the target, the number of beams needed are typically much smaller than for photons. This is assumed to be an advantage for protons, though, in some respects, e.g., robustness of dose distributions, it may be a disadvantage. Preferred beam directions for protons tend to be those that minimize passage through complex tissue heterogeneities and have shorter paths to the distal tumor edge. Furthermore, because of concern about higher biological effectiveness at the end of proton range and uncertainty in proton range, directions, which could potentially lead to higher biologically effective dose to critical normal tissues, such as spinal cord, at or just beyond the distal edge of the target, are avoided. An alternative approach discussed in Section 5.2 is to use IMPT to reduce the biologically effective dose (or LET) in organs at risk.

The use of magnetic scanning of beamlets of protons of a sequence of incident energies enables the delivery of intensity-modulated proton therapy (IMPT), in which scanning beamlets of protons of sequences of energies are used to “sculpt” the dose distributions

around complex critical structures, allowing improved sparing of these structures without compromising target coverage .[14,23–26] The energy of beamlets is varied to paint the target layer-by-layer. The intensities of beamlets comprising multiple scanning beams, aimed at the tumor from different directions, are optimized using computer-aided mathematical algorithms to balance the tumor dose versus the limits of normal tissue tolerances. Because of its ability to control proton energies and intensities, the process produces dose distributions that 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 Section 5.2) Moreover, as will be discussed in Section 5.6, the reduced "dose bath" outside the target has the potential of sparing the immune system.

The achievement of homogeneous target dose distribution and minimum and optimally balanced normal tissue doses with IMPT would generally lead to inhomogeneous per-field target dose distributions as illustrated in Figure 4. Such highly complex per-beam dose distributions, when combined, fit somewhat like a three-dimensional jigsaw puzzle to create an exquisite pattern of homogeneous dose distribution in the target and optimal sparing of normal tissues as illustrated in Figure 4. However, in the face of uncertainties (e.g., in range), the fit may be lost, creating hot and/or cold dose regions. Thus, in general, IMPT dose distributions are more sensitive to (i.e., less robust in the face of) uncertainties in positioning and motion than PSPT and IMRT dose distributions. To reduce such sensitivity of IMPT to uncertainties, "robust optimization" techniques are being actively investigated (see Section 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 monitor units (MUs) per spot due to the inability of the beam monitoring system to detect extremely low 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 and their incorporation in the criteria of IMPT optimization. These issues are discussed in sections 5.2, 5.3, and 5.6 below.

4 Clinical Outcomes

While there is clinical evidence to support the clinical use and continued study of proton therapy, such evidence is not of sufficiently high level 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. Nevertheless, as larger numbers of patients are being rerated with proton therapy, and with research to better understand physical, biological and immunological basis of clinical effects, it is expected

that clinical data demonstrating clearer evidence of the superiority of proton therapy will emerge.

To date, the majority of clinical evidence supporting the use of proton therapy comes from small non-randomized studies. However, to produce high level evidence, single- and multi-institutional randomized trials and multi-institutional registry studies are required. A small number of such trials have been completed and several others are currently accruing.

The list below, which is not comprehensive, summarizes some of the clinical evidence available to date.

- Children are particularly susceptible to late adverse effects of radiation, including but not limited to secondary cancers, cardiac disease, endocrinopathies, cognitive dysfunction, etc. Given the dramatic reductions in normal tissue exposure using proton therapy and, therefore, the potential for reduction in adverse effects, proton therapy is widely accepted for childhood cancers. Numerous publications suggest that disease control and survival rates seen with proton therapy are comparable to those seen with photons. Disease sites studied include medulloblastoma, ependymoma, craniopharyngioma, and rhabdomyosarcoma, among others.[29–33] However, there are concerns that higher LET and RBE near the distal edges could lead to higher severe toxicities.
- The second disease site where proton therapy has solidified its presence is for skull based or sinonasal malignancies. For the treatment of these tumors, high radiation doses are required to achieve disease control. However, the close proximity of critical normal tissues, e.g., the brainstem or optic structures, frequently precludes the delivery of such high doses with photons even using the most advanced techniques. Physical properties of protons are uniquely suited for the treatment of these challenging cases. The published studies have shown high disease control and acceptable toxicity rates with proton therapy.[34,35] The majority of patients in these studies received PSPT. Investigators from the Paul Scherrer Institute, the first to clinically implement scanning beam proton therapy, have, however, published excellent outcomes using such techniques for patients with skull based lesions.[36] Early results with the use of scanning beams from MD Anderson[37] reported improved dose distributions compared to PSPT and favorable disease control and toxicity profiles. For sinonasal tumors, Patel, et al compiled a multi-institutional dataset suggesting improved survival outcomes with charged particle therapy compared to photon therapy.[38]
- Proton therapy has also shown promise in the treatment of brain tumors, centering on the potential for reduction of adverse effects, particularly cognitive dysfunction, as well as on dose escalation for radiation resistant tumors, such as glioblastoma. Proton therapy for low-grade gliomas has also been evaluated. Initial results suggest high rates of tumor control and acceptable toxicity rates. [39 40] Importantly, a study by Shih, et al. reported results of a prospective trial that enrolled patients with grade II gliomas and assessed cognitive function and quality of life following proton therapy and found that measures of cognitive

function were stable or improved compared to the baseline.[41] For glioblastoma, the role of proton therapy has also been assessed in a small phase II trial. Proton therapy was not found 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.[42] In fact a phase II randomized trial of proton vs. 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.[43–46] The higher RBE around the distal edge has been implicated and has been and continues to be investigated in retrospective studies[47–50] and in ongoing trials, e.g., LET Optimized IMPT in Treating Pediatric Patients With Ependymoma (NCT03750513).

- Perhaps one of the most technically challenging disease sites to treat, particularly for proton therapy, is lung cancer, due mainly to the sensitivity of proton dose distributions to highly heterogenous tissues in the path of protons and 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. Initial retrospective and single arm early phase trials suggest 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 vs. 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 and the secondary analyses of the data are ongoing to understand the impact of various factors. These factors include inter- and intra-fractional variations in anatomy, the simplistic assumption about proton RBE, immature technology (PSPT instead of IMPT), evolving treatment planning techniques, etc.[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 also, excess dose to the heart and/or lungs may be associated with increased morbidity and, potentially, mortality. Retrospective studies suggested reduced toxicity rates combined with promising disease control rates with protons. Based on these findings, a multi-institutional randomized trial of protons vs. 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 vs. 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. A 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 also challenging due to highly complex anatomy. With IMPT, where both high and low dose conformality are easily achieved even for the most complex target volumes, promising results are being reported. For example, Manzar, et al 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 found that symptom burden (5 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) vs. IMRT (N=46) of oropharyngeal cancer. While these are examples of small studies, a phase III randomized IMPT vs. IMRT trial for stage III-IVB oropharyngeal cancer (NCT01893307) just completed accrual (N=518), the results of which are awaited and may be more convincing.

The non-randomized among the clinical studies 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 vs. 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 utilization of IMPT increases, it is reasonable to expect that further improvements in clinical outcomes compared to IMRT and VMAT will be made. Moreover, 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

Protons are considered to have an advantage due to their physical characteristics in that they deposit lower dose outside the target volume and that they have lower integral dose

in the body as a whole. On the other hand, because of their scattering characteristics, they have a wider penumbra. While a large volume of tissue away from the target may receive considerably lower dose, the dose to volumes of normal tissues immediately surrounding the target volume may be higher for protons. It is possible to reduce the penumbra of beams incident on the patient using apertures and minimizing the scanning beam 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.[21,22] Continued further enhancement of such systems is expected in the future.

Furthermore, as stated above, IMPT dose distributions are highly sensitive to setup variability, inter-fractional anatomy changes (tumor/nodal regression, weight loss, etc.) and intra-fractional motion. The variations in anatomy in the path of protons during a single fraction and over the course of proton therapy can impair the conformality of dose distributions. Moreover , it is not just the motion of the tumor but also of the anatomy in the path of the proton beam that can have a significant effect on dose distributions within the volumes of target as well as normal tissues.[67,68] 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, i.e., 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 Section 5.5.

For interfractional changes, verification CT images are acquired more frequently for protons than for photons. If suggested by the visual inspection of 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 is generated for the remaining fractions.

Another physical issue is the accuracy of computed proton dose distributions. Since they are used to make treatment decisions, to establish the associations between dosimetric parameters vs. observed tumor and normal tissue responses and to develop response models, the accuracy of dose distributions is important. Approximations and assumptions in algorithms and formalisms used for computing dose distributions and the process of converting CT numbers to proton stopping power ratios lead to suboptimal treatment decisions and introduce additional uncertainty in treatment outcomes and the results of response analyses. Monte Carlo techniques (or their abridged or accelerated variations) are necessary to overcome the limitations of the current dose computation models. These are now being developed and implemented for clinical use.

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.[11,12] 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 the LET,

dose per fraction, tissue type, end point, inter-patient variation in sensitivity (e.g., due to DNA repair defects),[69] etc. If the region of low RBE happens to be in the tumor volume or the region of high RBE is in a normal tissue, the presumed advantage of protons may be lost or may even lead to unanticipated recurrences or toxicities. Numerous models for estimating variable RBE have been proposed[70–76] that can reasonably predict the trend of nearly linearly rising RBE up to the Bragg peak but not in the region of high LET beyond. To our knowledge, these models are not commonly used clinically. In any case, being based on limited measured data and because they ignore some of the important dependencies (e.g. inter-patient sensitivity variation), these models also have significant shortcomings.

An alternative that has gained acceptance recently is the incorporation of a function of LET in the criteria of IMPT optimization.[77,78] 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. A function such as Dose * (1 + λ * LET), where λ is an empirical tissue dependent parameter, may be used in the optimization process. 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 is ongoing to improve our understanding of biological effects using experiments and computer simulations to develop novel more accurate RBE models. The issue, 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 simplistic 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) prediction 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, etc. would improve the accuracy of the data that these models depend upon. More accurate estimation response using advanced imaging, including multi-modality imaging, and biomarkers is also key to improving the models. Another important step would be to develop “personalized” models that consider a 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 the Robustness of Dose Distributions for IMPT

There are significant differences in the planning approaches between photons and protons. This is in part because of the finite range of protons and the fact distal and proximal margins depend more on range uncertainty than on inter-and intrafractional anatomy variations. Moreover, the use of margins does not prevent anatomy variations from impacting dose distributions within the target volume and normal anatomic structures. Thus, the concept of planning target volume in the traditional sense is no longer appropriate; however, it still continues to be used commonly due to lack of alternatives. Ideally, for IMPT planning, robustness evaluation and robust optimization approaches (see next section) should be employed.

A simple strategy for robustness evaluation of IMPT dose distributions, regardless of whether they are designed using conventional margins or using robust optimization, is to examine individual dose distributions for each of a set of uncertainty scenarios.[79–83] These scenarios may, for instance, include shifts along the orthogonal axes, range uncertainty, end-inhale and end-exhale phases, etc. The magnitudes of shifts may be chosen to be the same as the margins for CTV to PTV used for designing photon plans. Such reviews would reveal 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 each anatomic structure of interest. The band of DVHs for a given structure represents the range of possible dose distributions the patient would receive. Band width at the critical dose-volume points on the DVH (e.g., at volume receiving 20 Gy (RBE) or higher for lung) may be used as a quantitative measure of robustness.

5.5 Robustness Improvement and Robust Optimization

Despite our best efforts to minimize uncertainties through such techniques as image-guidance, respiratory gating, adaptive replanning to accommodate anatomy changes from fraction-to-fraction, etc., residual uncertainties remain. It is important to account for them in treatment planning so that there is high confidence that the target remains covered by the prescribed dose and normal tissues are adequately spared in the face of uncertainties.

The robustness of proton dose distributions depends on many factors. Plans with larger numbers of beams tend to be more robust. The passage of beams through highly heterogeneous anatomy increases uncertainty and reduces robustness. For dose distributions

affected by respiratory motion, the magnitude of the effect of motion often depends on the beam direction. To overcome the high vulnerability of IMPT to motion and positioning uncertainties, “robust optimization” techniques have been developed and continue to evolve further and be tested for their potential.

A typical robust optimization process would simultaneously consider multiple uncertainty scenarios of the type mentioned in the previous section, and optimize intensities in the face of all scenarios. As an example, it may consider (a) the nominal dose distribution, (b) six dose distributions obtained by shifting the patient image by, for instance, ±5 mm (equal to the CTV-to-PTV margin) along three orthogonal directions, and (c) two additional dose distributions incorporating uncertainty in the range of, for instance, ±3%. The optimization algorithm computes the score (i.e., the value of the objective function to be minimized) in each iteration by selecting the worst dose in each voxel from among the nine scenarios. For the target volume, the worst 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[84–91]. Alternate approaches have been proposed and have different strengths.[92–94] Robust optimization has also been extended to four dimensions to make dose distributions resilient in the presence of respiratory motion.[68]

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 (RT), relies on an intact immune system.[95] However, RT suppresses the immune system through the killing of lymphocytes traversing the radiation field. Lymphocytes are highly radiosensitive (LD_{50} <2 Gy)[96,97] and are killed in much greater numbers than other cells by RT, resulting in radiation-induced lymphopenia (RIL), which has been shown to be associated with inferior RT outcomes.[98–104] Preservation of lymphocytes through mitigation of radiation damage to lymphoid organs and circulating lymphocytes is crucial for advancing RT.

Approaches for the mitigation of RIL are being investigated. A recent discovery of another potential benefit of proton therapy, because of its smaller dose bath, is the sparing of the immune system.[105] However, significant further sparing may be possible through 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 has an additional degree of freedom, that of energy, making it more probable that IMPT can succeed in achieving a significant reduction in RIL without compromising standard 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 that 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, i.e., 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 between the two modalities. However, there have been a small number of studies to date specifically for IMPT exemplified by the works of Cao, et al [106,107] and Gu, et al [108–111]. BCO remains an open area for further research.

5.8 Technological Limitations and ongoing advancements

Other challenges and obstacles that inhibit achievement of the maximum effectiveness of proton therapy are related to the technologies of treatment planning and delivery systems. 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, respiratory gating, etc. 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.[21,22]

Another concern about proton therapy has been its high cost. Current proton therapy facilities with three to four treatment rooms cost of the order of $100 – 200 million. A single room facility costs in the neighborhood of $30 million. These costs are an order of magnitude higher than the cost of a high-end photon treatment unit. Numerous efforts are underway to develop novel, lower cost compact accelerators and gantries based on innovative designs and super-conducting magnets. In addition, numerous studies are being conducted to determine the cost effectiveness of proton therapy.[112–114] 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. Furthermore, the cost effectiveness may vary significantly from patient to patient, and it may be important to identify patients for whom proton therapy will have the greatest benefit. A normal tissue complication model-based approach for the selection of appropriate modality for each patient is being used increasingly.[115–118] For the success of such an approach, it is important that the models are highly reliable.

6 Summary

The primary rationale for the use of proton therapy is its exquisite physical dose deposition characteristics. The expectations have been that such dose distributions will allow significant sparing of normal tissues surrounding the target volume or target dose escalation, or both. However, despite the high promise of proton therapy, and despite the fact that more than 170,000 patients have been treated with protons to date, the clinical evidence for protons so far has not been unequivocally clear and broad enough to alleviate concerns, particularly for the third party payors, in the face of the high cost of proton therapy. Possible reasons, are many, and include the still maturing technology and limited experience with proton therapy; the greater uncertainty in delivered biologically-effective dose distributions due to such factors as inter-fractional changes, intra-fractional motion and setup variability; the approximations and assumptions of dose computation methods; the assumption of constant RBE of 1.1; 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 passively scattered proton therapy, 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 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 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 use of accelerated MC techniques to improve the computed dose accuracy; 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 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 likely to reduce the cost of proton therapy. Thus, despite the current limitations of proton therapy, its future is very promising!

Acknowledgement:

This work is supported in part by the P01 CA261669 and the Cancer Center Support Grant P30 CA016672 from the NCI of the NIH to The UT MDACC

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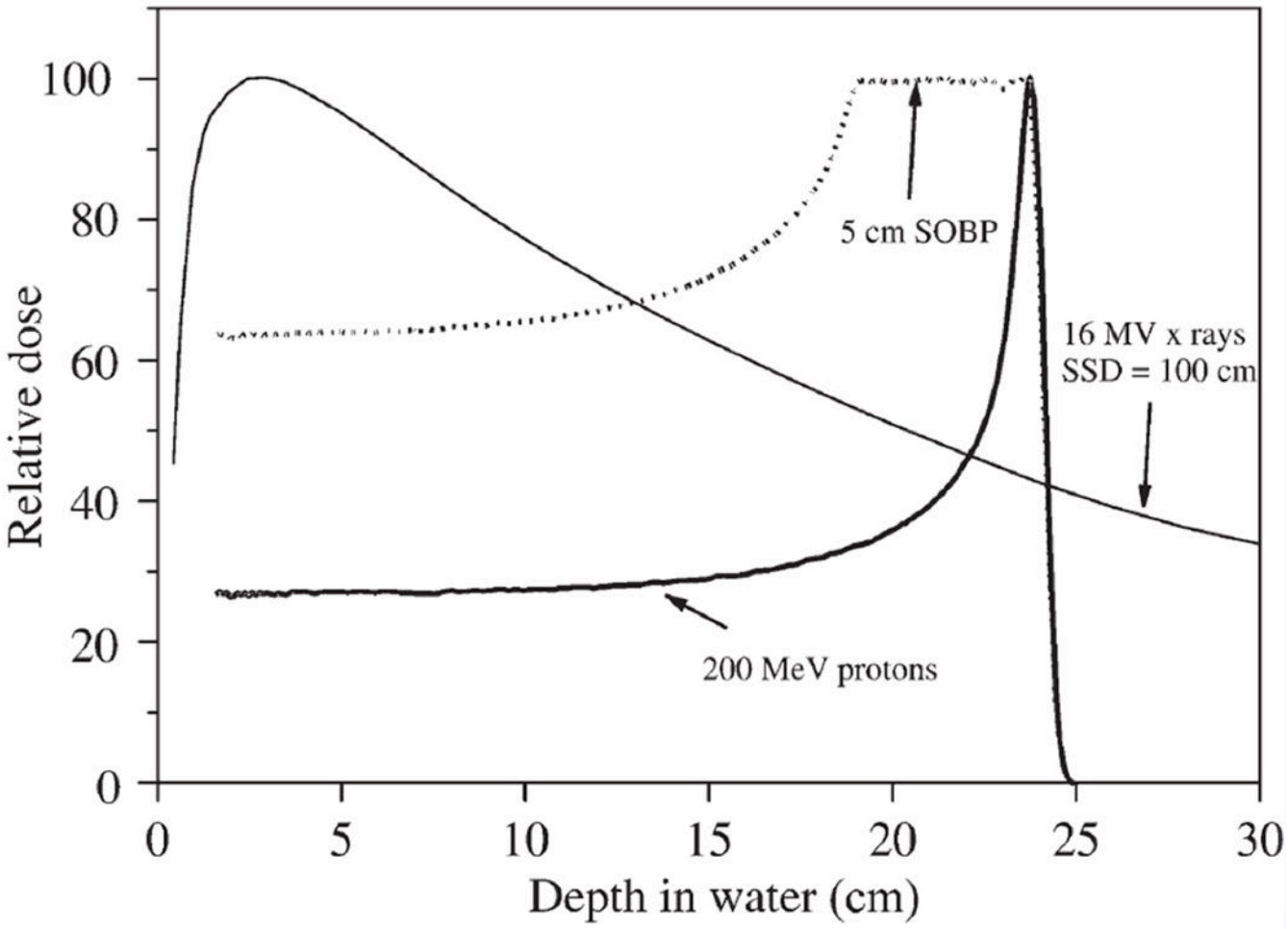

Figure 1.

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 x10 cm^2 fields). The curves are normalized in each case to 100 at maximum dose. (Adapted from Jones, reproduced with permission).[8]

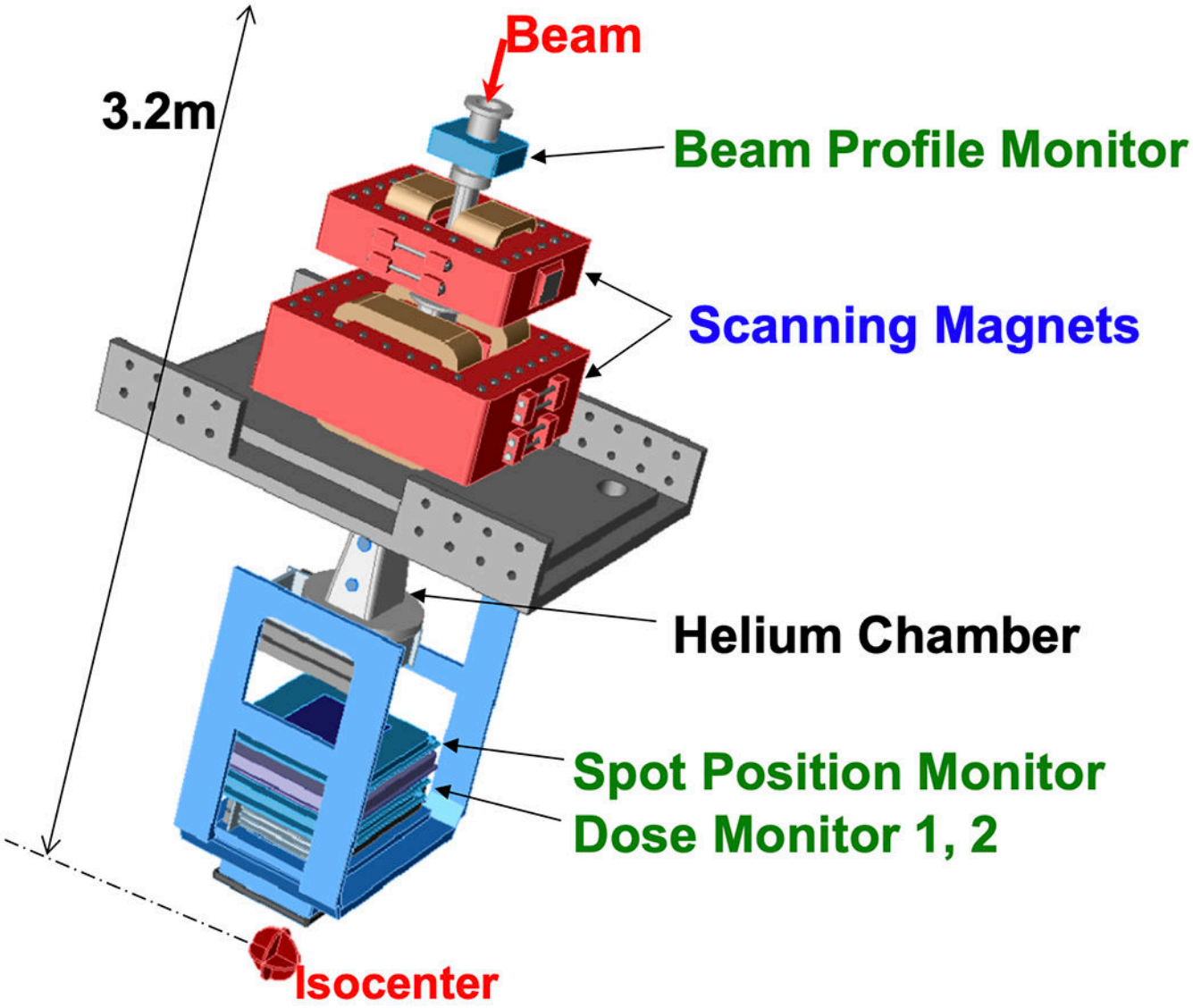

Figure 2.

Scanning beam nozzle (Hitachi system at MDACC). The thin beamlets of a sequence of energies entering the nozzle are spread laterally by a pair of x- and y-magnets to create a three-dimensional pattern of dose distribution. Magnet strengths are adjusted to confine the Bragg peaks of beamlets (“spots”) to within the target volume. Intensities of beamlets, computed using a treatment planning system, are optimized in order to conform the high and uniform dose pattern to the target volume and appropriately spare critical normal tissues. Various monitoring systems ensure that the characteristics of the proton beam are within specifications and that the requisite dose is accurately delivered. Part of the path from the beamlet entry position to the isocenter is replaced with a helium chamber to reduce lateral dispersion of the scanning beamlet in air.

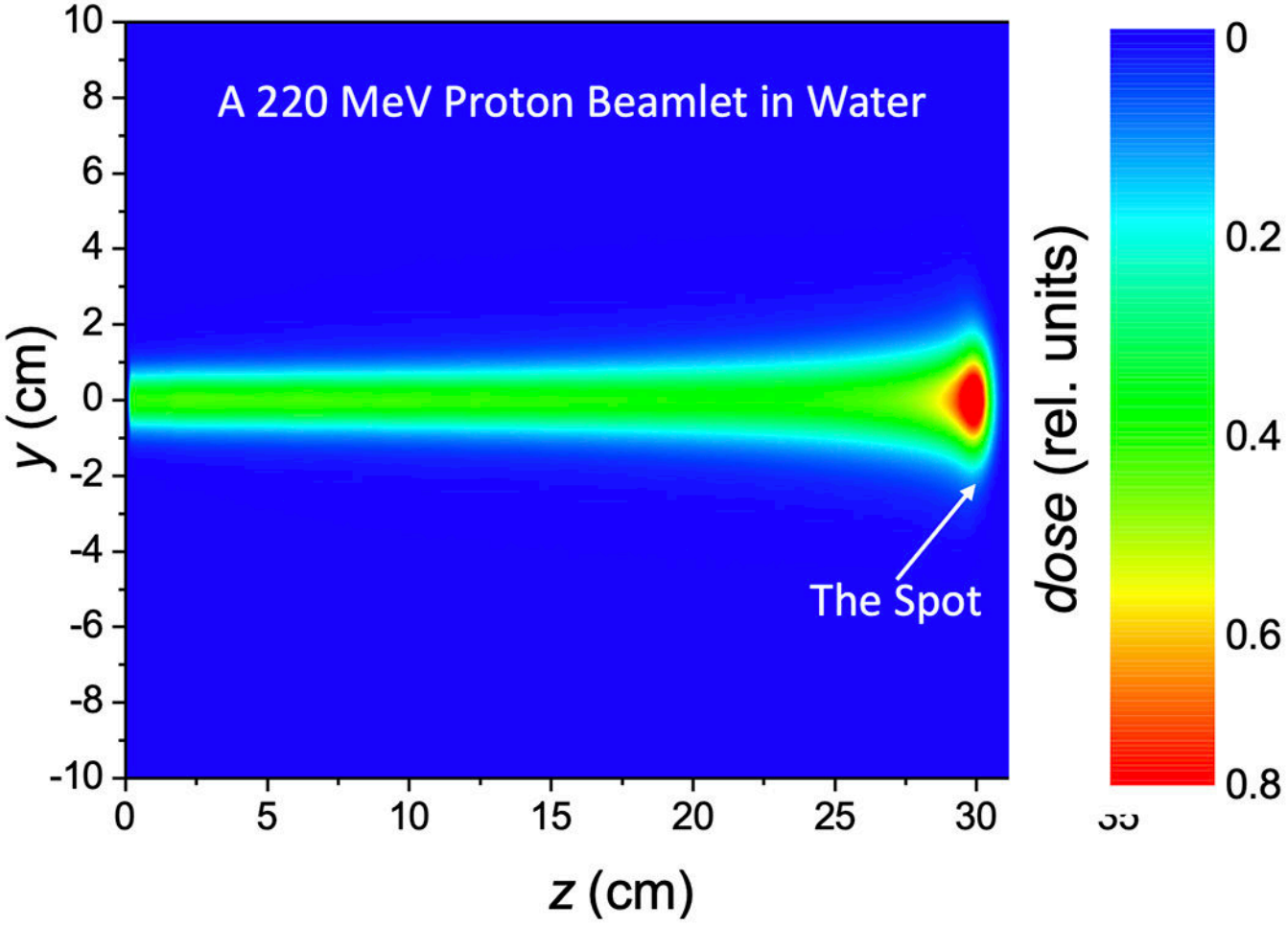

Figure 3.
Monoenergetic 222 MeV beamlet with FWHM of ~13 mm at the entrance to the water phantom and ~30 mm at the Bragg peak.

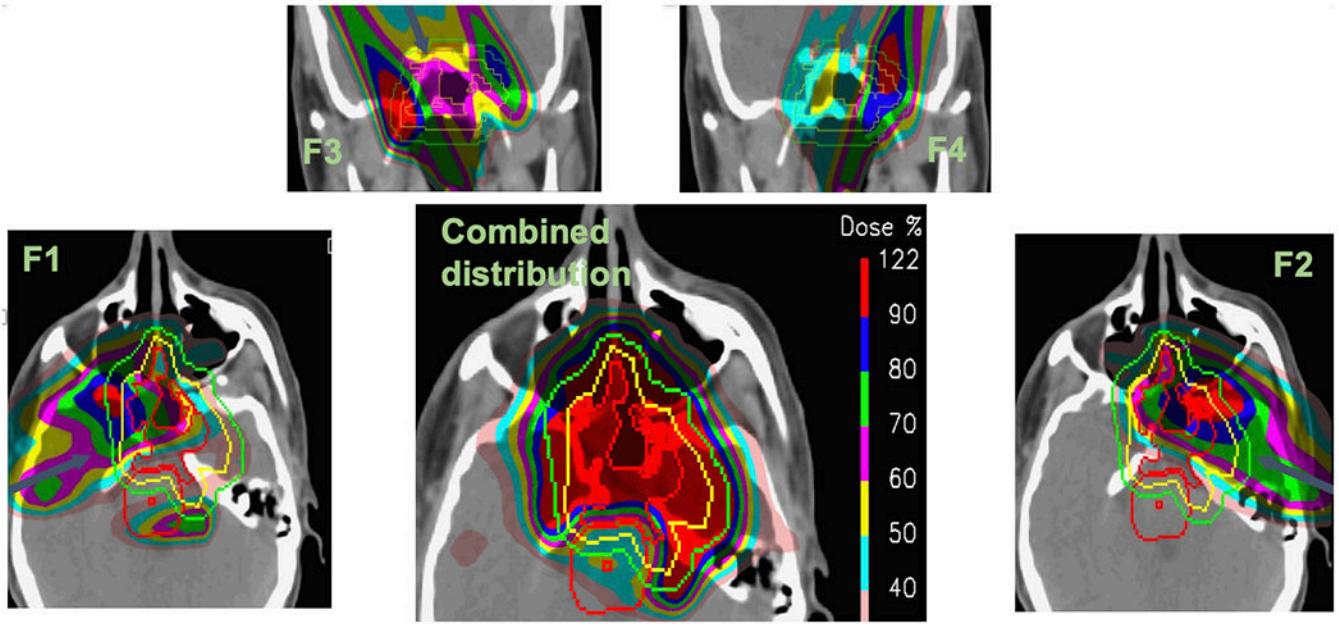

Figure 4.

Inhomogeneous individual field IMPT target dose distributions (F1, F2, F3, F4) and a homogenous combined dose distribution for a head and neck case. (Adapted from a figure provided by A. Lomax, PSI, private communication.)