CCR New Strategies

Clinical Cancer Research

New Strategies in Radiation Therapy: Exploiting the Full Potential of Protons

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Abstract

Protons provide significant dosimetric advantages compared with photons because of their unique depth–dose distribution characteristics. However, they are more sensitive to the effects of intra- and intertreatment fraction anatomic variations and uncertainties in treatment setup. Furthermore, in the current practice of proton therapy, the biologic effectiveness of protons relative to photons is assumed to have a generic fixed value of 1.1. However, this is a simplification, and it is likely higher in different portions of the proton beam. Current clinical practice and trials have not fully exploited the unique physical and biologic properties of protons. Intensity-modulated proton therapy, with its ability to manipulate energies (in addition to intensities), provides an entirely new dimension, which, with ongoing research, has considerable potential to increase the therapeutic ratio. *Clin Cancer Res; 19(23); 6338–43. ©2013 AACR.*

Background

Research and development in the last three decades has led to considerable improvement in our understanding of dose and dose–volume response to radiotherapy. Radiation, with and without cytotoxic and targeted chemotherapy, affects a variety of molecular pathways in normal and tumor tissues (1). Moreover, increasingly powerful tools to target tumors more precisely with higher radiation doses while sparing normal tissues have been developed. These tools have included 3-dimensional conformal radiation therapy (3D-CRT) in the 1980s, intensity-modulated (photon) radiotherapy (IMRT) in the 1990s, and proton therapy in the last decade.

High-energy photons are the most common radiation modality used for external beam radiotherapy. They have well-described and understood physical characteristics and biologic effectiveness. As shown in Fig. 1 (green curve), high-energy photons deliver a dose that increases at very shallow depths and then decreases exponentially as they pass through the body. This results in unwanted dose to normal tissues proximal and distal to the tumor.

In the modern practice of photon radiotherapy, intensities of small subdivisions of beams known as "beamlets" are optimally adjusted to balance the dose requirements of the tumor versus normal tissues and the normal tissues among themselves. This mode of photon treatments is known as IMRT. However, even with such advancements, the physical characteristics of photons limit the ability to escalate dose because normal tissues in their path receive significant doses of radiation.

Protons provide dosimetric advantages compared with photons. This advantage stems from their unique depth–dose distribution characteristics. As protons enter the body and slow down on their way to the target, the dose deposited per unit path length increases, initially slowly and then progressively rapidly, until the energy of the protons is fully depleted and they come to a complete stop. This results in a dose deposition pattern with a peak (called the "Bragg peak") and a sharp drop off in dose at the end of the range of the protons as depicted by the red curve in Fig. 1. Protons, in contrast with photons, deliver no dose beyond the end of this range.

The biologic effectiveness of protons relative to photons (i.e., "relative biologic effectiveness" or RBE) has simplistically been assumed to have a generic fixed value of 1.1. RBE is defined as the ratio of the physical dose of a reference photon radiation to the physical dose of protons required to achieve the same biologic effect. This assumption of generic RBE of 1.1 is based on an average of the results of numerous *in vitro* and *in vivo* experiments conducted under limited conditions and which have large error bars (2–4). Most commonly, these experiments were conducted at high doses per fraction (e.g., 6–8 Gy) and in the middle of the spread-out Bragg peak (SOBP, defined later and in Fig. 1). The spectrum of proton energies in the middle of the SOBP is rather broad and depends on the SOBP width. There is a paucity of proton RBE data because experiments to determine proton RBE by proton energy are challenging to design and require large datasets. An accurate estimation of biologic effectiveness of protons as a function of energy has not been reported. Furthermore, the RBE data have been acquired for only a limited number of cell lines, tissues, and endpoints.

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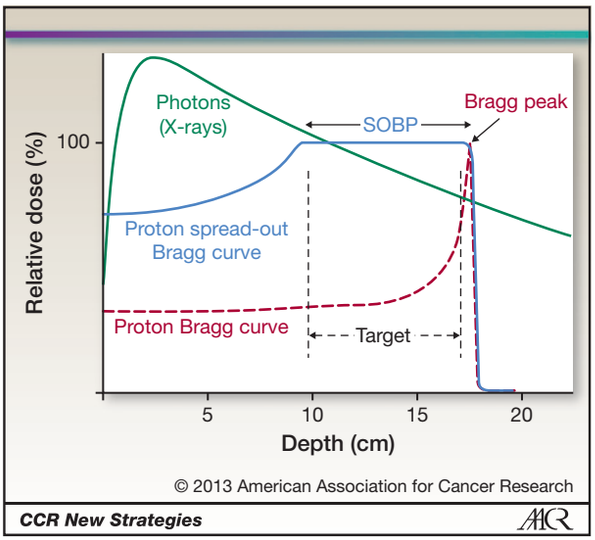

Figure 1. The green curve shows the depth dose data of a typical 15-MV photon beam. The red curve shows the depth dose curve of a monoenergetic proton beam. The maximum dose point of this curve is termed the Bragg peak. Scanning thin monoenergetic proton beams are used for intensity-modulated proton therapy. The blue curve is obtained by electromechanically spreading the monoenergetic proton beam laterally and longitudinally and is used in passively scattered proton therapy. The top flat portion of this curve is called the spread-out Bragg peak. The potential advantages of proton versus photon dose distributions are clear.

Increasing evidence suggests that the RBE is a complex function of multiple variables including but not limited to dose deposited per unit path length ("linear energy transfer" or LET), dose per fraction, and tissue or cell type being treated (2–4). At a more fundamental level, the biologic effects of protons differ significantly from those of photons because of the differences in the patterns of ionization and molecular excitations between the two modalities. Such events are densely concentrated along the path of protons and increase as the protons slow down in the medium, reaching a peak at the end of their range. In contrast, with photons these events are sparsely spread across the irradiated field. These differences lead to significant differences in the biologic effects of the two modalities. Examples include greater complexity of DNA damage and greater production of free radicals with protons. Furthermore, the two modalities modulate different signaling pathways involved in apoptosis, and data are available to suggest that protons have a greater proficiency in inducing apoptotic cell death. They also regulate gene expression differently, leading to distinctly different transcriptome profiles. Girdhani and colleagues provide a comprehensive overview of current knowledge of biologic effectiveness of protons relative to that of photons (5).

Most of the routine practice of proton therapy and the vast majority of proton-based clinical trials have used "passively scattered proton therapy" (PSPT). In this mode of proton therapy, in which a thin initial beam of protons is electromechanically modulated longitudinally and spread laterally to produce a "spread-out Bragg peak" (Fig. 1, blue curve), the advantage of the dose distribution characteristic of protons is exploited to some degree to reduce the low-dose bath associated with IMRT in the normal tissues surrounding the target. However, as discussed in the On the Horizon section of this article, the clinical practice and trials to date have not fully exploited the unique physical and biologic properties of proton therapy. This is true, in part, because of the sensitivity of protons to changes in anatomy. These variations result from day-to-day differences in treatment position, intrafractional motion (e.g., because of respiration), or interfractional changes such as tumor shrinkage or weight loss. The steep fall-off in dose at the end of the range of protons that makes them attractive for radiotherapy, unfortunately also makes them more sensitive to anatomic variations leading to uncertainty in the dose actually delivered. This uncertainty, combined with uncertainty in RBE, often inhibits the use of optimal treatment strategies such as reducing the treatment margins or utilizing beams aimed directly at certain normal critical anatomic structures. It should also be noted that, although protons reduce the low-dose bath, the conformality of the high-dose region immediately adjacent to the target is superior for IMRT compared with what is achievable in the current state of the art of protons.

Furthermore, potentially the most effective form of proton therapy, intensity-modulated proton therapy (IMPT), is still in its infancy. IMPT, with its ability to manipulate energies (in addition to intensities), has the power to shift the clinical paradigm to an entirely new dimension to maximize the therapeutic ratio. As explained below, in addition to exploiting physical properties of protons to a greater extent than PSPT, IMPT has the ability to take advantage of variable RBE to further increase the differential between tumor dose and normal tissue doses.

Clinical Trials

There is general acceptance of protons in the management of pediatric cancers because the reduction in normal tissue dose will result in a reduction of acute and late toxicities, including the risk of secondary malignancies, without compromising tumor control. Published data, however, are limited to small single-institutional reports for a limited number of indications (6–15). Randomized trials in pediatric cancer comparing proton versus photon therapy are not feasible, and for this reason a national registry has been created (16). Additional areas of interest are gastrointestinal and breast cancers, lymphoma, and recurrent cancers (15, 17–21). For example, for patients with breast cancer, proton therapy may provide a practical, safe, and better alternative for management of deep internal mammary lymph nodes, or other anatomic situations in which conventional radiation approaches are limited by normal adjacent structures (17–19). Proton therapy is also an attractive alternative for selected patients with recurrent disease in or near a previously irradiated site (22, 23).

Phase I and II clinical trials (nonrandomized) are examining the role of proton radiation in adults. The clinical sites

being studied include skull base chordomas and chondrosarcomas (14, 24), ocular melanomas (25), prostate cancer (26–28), paranasal sinus tumors (29), nasopharyngeal carcinomas (12, 30), spine sarcomas (24, 31), non–small cell lung cancer (32–36), and hepatocellular carcinomas (37, 38). Overall, these trials have demonstrated two major advantages. First, dose escalation with protons is potentially achievable. For example, the treatment of the reduced dose bath allows for a higher prescription dose for protons and, therefore, would lead to superior local control versus photons (39, 40). Second, protons reduce the normal tissue integral radiation dose with the potential to significantly lower rates of normal tissue toxicity.

There have been four published randomized trials utilizing protons. Clinical sites include locally advanced prostate cancers (41, 42), chordomas and skull base chondrosarcomas (43), and choroidal melanoma (25). In these trials, protons were used as a boost, and the randomization was between two proton doses. Currently, over 50 active phase II and III trials are being conducted in the United States, specifically evaluating proton therapy in a variety of clinical sites. Of these, phase II and III randomized trials comparing photons and protons are ongoing in oropharyngeal cancer, esophageal cancer, lung cancer, glioblastoma, and prostate cancer. The primary endpoints are toxicity, functional outcome, and quality of life. An additional 18 observational/registry studies are actively collecting data (16).

On the Horizon

IMPT is an innovative technology that is inherently more powerful than both PSPT and IMRT because of its ability to modulate energies as well as intensities. In contrast, IMRT modulates intensities only and PSPT modulates neither (44). IMPT offers the ability to exploit the physical as well as biologic potential of proton radiotherapy to a considerably greater degree. However, IMPT is more sensitive to uncertainties than PSPT and even more so compared with IMRT (45). Considerable research and development is needed and is being undertaken to realize the full potential of IMPT. Even in its current relatively immature form, IMPT has been used in a few institutions to confirm feasibility and identify potential benefits over PSPT and highly conformal x-ray–based technologies, such as IMRT and its variants (VMAT and tomotherapy; refs. 46–49). Patients have been treated safely and effectively with IMPT for tumors of the prostate, head and neck, central nervous system, spine, and lung.

IMPT utilizes thin scanning beamlets of protons to "paint radiation dose" onto the target volumes. The energy of the 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 determined using computer-aided mathematical optimization methods to balance the tumor dose versus the limits of normal tissue tolerances. Because of its ability to control proton energies, IMPT dose distributions are, in general, vastly superior not only to the corresponding photon-based techniques such as IMRT but also to PSPT. Figure 2 shows an example comparing IMPT with IMRT dose distributions.

IMPT aims to achieve a homogeneous dose to the tumor target. To optimally balance target and normal tissue doses, the optimization process would, in general, lead to highly

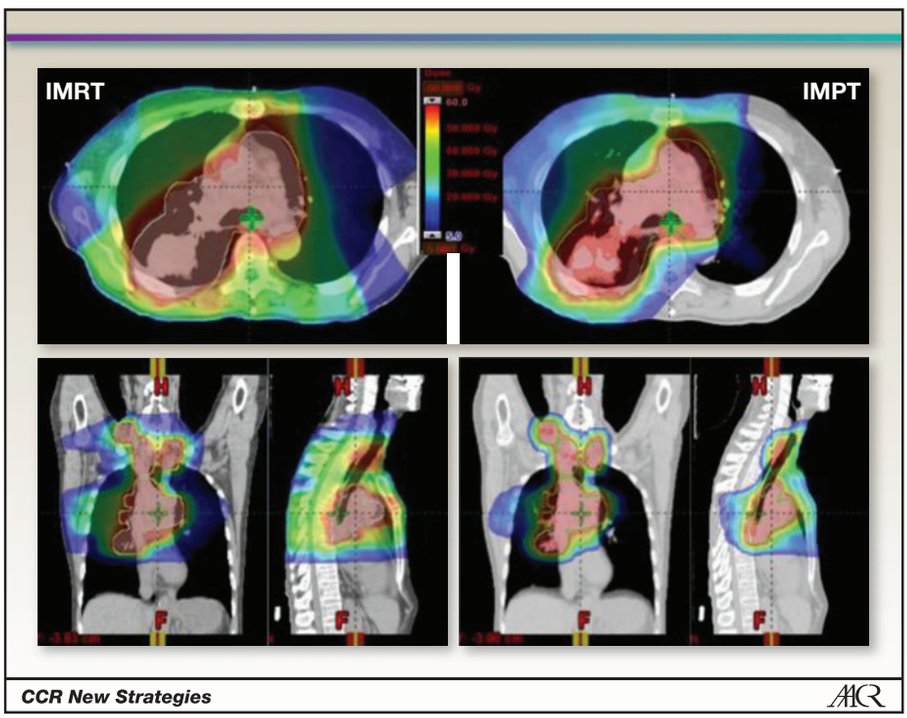

Figure 2. Comparison of IMRT and IMPT dose distributions in a thorax treatment plan. The large "low dose bath" in IMRT (left) is considerably reduced in IMPT dose distributions (right). (Courtesy J.Y. Chang, PTCOG 47 presentation)

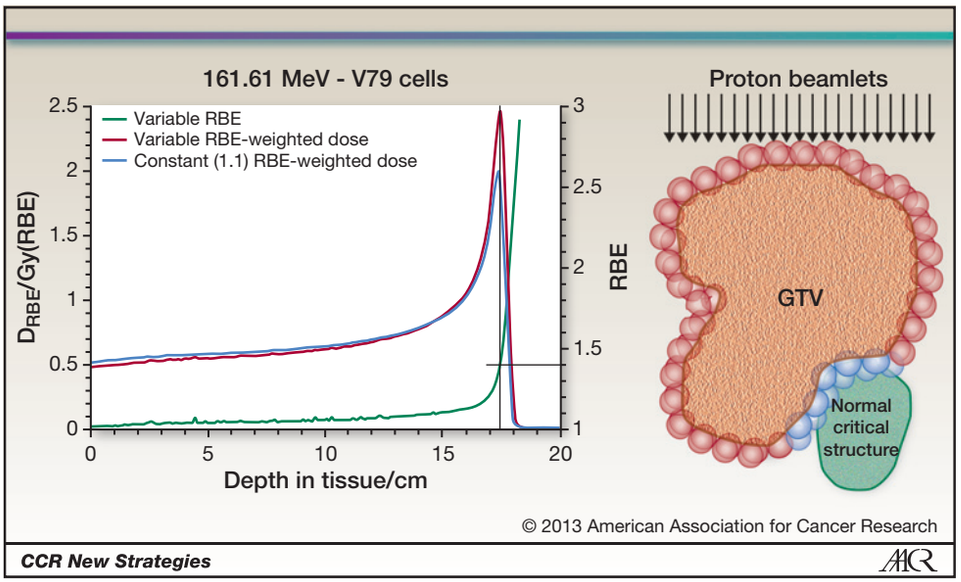

Figure 3. Optimization of IMPT taking advantage of the physical and biologic characteristics of protons. The panel on the left shows illustrative Bragg curves for variable RBE (red) and fixed RBE of 1.1 (blue). It shows that, over and above the dose advantage, the use of variable RBE may lead to an additional 40% differential (more in some cases, less in others) between normal tissue and tumor dose. A goal of current research is to selectively place the high RBE portions of the Bragg curve (represented by small translucent red and blue circles, or "spots," right) within the gross target volume (GTV). If there is a normal critical structure present adjacent to the distal edge of the target volume along the beam direction, the intensities of spots (blue translucent circles) at the distal edge are set to zero. The underdosing in the target volume thus created at the distal edge is compensated by beamlets of beams from other directions.

inhomogeneous target dose contributed by each of the individual beams. The inhomogeneous dose patterns from individual beams are presumed to be perfectly matched to produce a homogeneous target dose. However, because of uncertainties in dose distributions, mismatches can occur, and the actual target dose patterns delivered may be quite inhomogeneous.

Therefore, a multipronged approach is needed to maximize the potential of IMPT. In-room volumetric image guidance is essential to minimize the uncertainty in daily positioning, and respiratory gating or breath-hold delivery is critical to minimize the effect of respiratory motion of the anatomy on dose distributions. Repeat imaging (typically weekly) is necessary to examine the changing anatomy and its impact on dose distribution. If an anatomic change would result in inadequate treatment, a new treatment plan will be designed to adapt to the changed anatomy. To account for residual uncertainties, "robust optimization" methodology is used to make dose distributions more resilient (45, 50). These methods have been used in other fields, such as statistics, operations research, finance, and engineering to achieve robustness against uncertainties. The initial application of robust optimization to IMPT has been limited to uncertainties in patient positioning and in the range of protons. Additional research is needed to include uncertainties in inter- and intrafractional anatomic variations. Although these measures would benefit both IMRT and PSPT, they are critical for IMPT (50–53).

Although the robust optimization of IMPT dose distributions based solely on the physical properties of protons would lead to substantial gains, the incorporation of the variable nature of RBE will yield maximum dividends (54, 55). As shown in Fig. 3, the RBE at the top of the Bragg peak may be as high as 1.5 instead of the assumed value of 1.1. Methods are being developed to selectively place the high RBE portions of the Bragg peak within the target volume and far enough away from critical normal tissues. This would lead to an increased biologically effective dose within the target and reduced doses to normal tissues. In one such strategy, called "distal edge avoidance," the beamlets of a beam contributing the distal-most portion of the target would be omitted. Any low-dose regions thus created would be compensated for by beamlets from other beam directions. An example of this is seen in Fig. 3. However, as pointed out earlier, significant gaps remain in our knowledge of RBE data and, therefore, a major effort needs to be mounted to conduct *in vitro* and *in vivo* experiments to acquire biologic effects data and also to derive them from clinical response data.

Summary

In summary, the state of the art of radiotherapy has considerably and continually improved over the last three decades. The most recent development is proton therapy, which is still evolving. However, even in its current form, it has reduced dose to normal structures, helped reduce acute toxicities, and has been proved to be safe and effective. Continued research and development and the use of IMPT provide the opportunity to exploit the full physical and biologic potential of proton therapy and to demonstrate its superiority over the most advanced photon-based techniques currently used.

Disclosure of Potential Conflicts of Interest

R. Mohan has received commercial research support from Philips. A. Mahajan has received commercial research support from Varian Medical Systems. B.D. Minsky is employed on a consulting basis as co-chair of the GI Steering Committee of NCI.

Authors' Contributions

Conception and design: R. Mohan, A. Mahajan, B.D. Minsky
Development of methodology: R. Mohan, A. Mahajan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Mohan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Mohan
Writing, review, and/or revision of the manuscript: R. Mohan, A. Mahajan, B.D. Minsky
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Mohan, B.D. Minsky

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