

Proton radiotherapy in the treatment of lung cancer

Heath Devin Skinner, Ritsuko Komaki

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding to: Heath Devin Skinner. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 97, Houston, TX 77030, USA. Email: hskinner@mdanderson.org.

Abstract: Radiation therapy for lung cancer often leads to treatment-related pneumonitis or lung fibrosis, especially when given with concurrent chemotherapy. These side effects can impair quality of life and negatively affect treatment outcomes. With the advent of proton radiotherapy comes the possibility of reducing these toxicities by minimizing the amount of non-target tissue that is irradiated. Protons have significantly different physical characteristics that can make their use advantageous over standard photon radiotherapy. Multiple retrospective reviews and phase I/II studies have linked the use of protons with fewer side effects in at least some patients with lung cancer, and randomized trials comparing proton therapy with photon treatments are ongoing. Technologic advances may allow for even further minimization of toxicity associated with radiation therapy. In this review, we discuss the current state of proton therapy for the management of lung cancer as well as challenges and opportunities for further development of this treatment modality.

Key Words: Radiation therapy; lung cancer; protons



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Introduction

Ever since the first attempts to treat malignancy with radiotherapy were made in the early 1900s, delivering a tumorcidal dose of radiotherapy while minimizing toxicity to nearby normal tissues has always been a challenge. Initially, tumors could be targeted only via direct or near-direct contact with a radiotherapy source. With the advent of Cobalt-60 radiation sources and, later, linear accelerators, therapeutic radiation could be delivered to virtually any site in the body. However, the dose that can be delivered to the tumor continues to be limited by normal tissue constraints. Fundamentally, this is determined by the physical characteristics of standard photon or electron radiotherapy. Photons, which include standard X-rays, and electrons deposit the radiation dose over the entire track of the beam; after peaking at a physically determined depth in water (or tissue), the deposited dose decreases slowly. For example, as shown in *Figure 1*, the maximum dose of radiation delivered by a standard 6 MV photon beam is at a depth of 1.5 cm in

water. For electrons of similar energies, the depth at which maximum dose is delivered (D_{max}) is even less. This dose distribution is reasonable for superficial tumors, but for tumors more than 1.5 cm below the surface of the skin, for one radiation beam, the normal tissue proximal to the tumor will be treated to a higher dose than the tumor itself. This physical reality is compensated for in standard radiotherapy by the use of multiple beams that converge at the level of the tumor. With more advanced planning techniques, such as intensity-modulated radiotherapy (IMRT), the intensity of each beam can be altered by using a computer-determined “best solution” for all beams to maximize tumor dose while sparing surrounding normal tissue. Despite these significant advances, standard radiotherapy continues to be limited by the generally inalterable physical characteristics of a photon (or electron) beam. This has led to interest in other forms of radiotherapy with different beam characteristics. Here we focus primarily on proton radiotherapy, the most common charged particle therapy in clinical use for lung cancer in the United States.

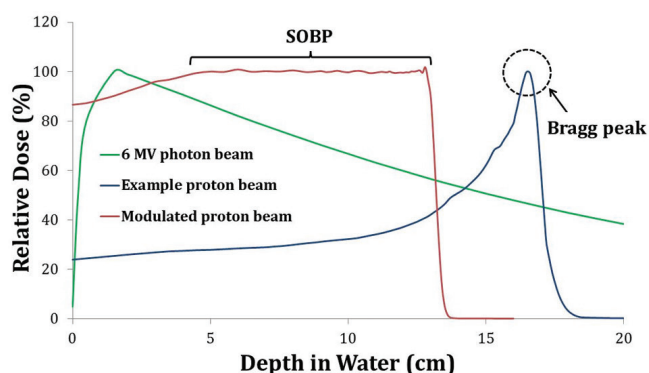


Figure 1 Depth-dose characteristics of proton and photon beams. The example proton beam is of a higher energy than the SOBP for clarity

Physical characteristics of proton beams

As previously stated, photon beams reach their maximum dose (D_{max}) at a known depth in tissue, a known physical property determined by the beam energy. Higher photon energies lead to greater D_{max} at the expense of increased fall-off dose as well as increased possibility of neutron scattering. However, charged particles such as protons have minimal ionization along their beam path, meaning that the dose delivered to any point along the beam path is minimal and the entrance dose for any particular proton beam is less than that for a comparable photon beam. Instead, the vast majority of dose in a charged particle beam is deposited near the end of the beam path, when the particles have nearly stopped (*Figure 1*). This phenomenon was initially observed as early as 1904, and has been dubbed the “Bragg peak” for its discoverer William Henry Bragg (1). By modulating the proton energy, the depth of the Bragg peak, or point of maximal radiation dose delivery, can be altered. However, the area of the Bragg peak for any one proton energy is too narrow for clinical use, requiring the use of a summed proton beam of multiple energies, resulting in the so-called “spread-out Bragg peak” (*Figure 1*).

A concept useful in comparing forms of radiotherapy is that of relative biologic effectiveness (RBE). Simply stated, this is a ratio between a standard dose of radiation (typically 250 kVp X-rays) and the dose of the test radiation required to produce the same biologic effect. Although the concept is fairly simple, derivation of the RBE is a complex process, depending upon a number of variables including the type of tissue being studied, the degree of hypoxia within the tissue, the type of radiation being used, the dose delivered, and the energy lost over the beam path (linear energy transfer or

LET). Historically, the RBE for a variety of different types of radiation has been determined primarily by *in vitro* and preclinical studies. For clinical use, the RBE for a proton beam (within the Bragg peak) is generally assumed to be 1.1 (2,3), meaning that for every 1 Grey (Gy), the biological effectiveness of a proton beam is similar to what is seen with 1.1 Gy of standard X-rays. This has led to the use of the term cobalt-Grey equivalent (CGE) when describing doses or proton therapy. Thus 74 CGE is equivalent to 67.3 Gy delivered by protons. Although the RBE/CGE concept provides a clinically useful value, several caveats must be borne in mind. The RBE is thought to vary slightly over the breadth of a Bragg peak. Specifically, the experimentally determined RBE values within a proton beam generally increase over the Bragg peak and are highest in the final millimeters (4-8). This effect is recognized in the course of routine clinical treatments by the recommendation that no proton beam should terminate in a critical normal structure. RBE also varies as a function of the tissue irradiated; *in vivo* preclinical models have predicted average values ranging from 0.7 to 1.6 (2). Examination of this variation in the RBE of a proton beam has led to attempts to integrate this factor into treatment planning (9-11).

Clinical use of proton therapy in lung cancer

The use of proton radiotherapy has grown substantially, particularly over the past decade, with 10 facilities using this modality in the United States alone. The unique characteristics of proton radiotherapy has led to its use being championed to allow both sparing of normal tissue and increasing the radiation dose delivered to targets heretofore limited by proximity to adjacent normal surrounding structures. Particular interest in proton radiotherapy has been expressed for the treatment of lung cancer. The standard therapy for locally advanced lung cancer involves a combination of radiation and chemotherapy delivered concurrently, typically to radiation doses of 60-70 Gy. However, treatment in this dose range can be quite toxic, leading to significant pulmonary injury (mainly pneumonitis and fibrosis) as well as esophagitis and other toxic effects (12). Any damage to the lungs in patients with lung cancer tends to be exacerbated by a lack of pulmonary reserve, as many patients present with some form of chronic obstructive disease from cigarette smoking and many require supplemental oxygen even before radiotherapy. The findings regarding the value of dose-escalation in these patients is somewhat conflicting (13,14).

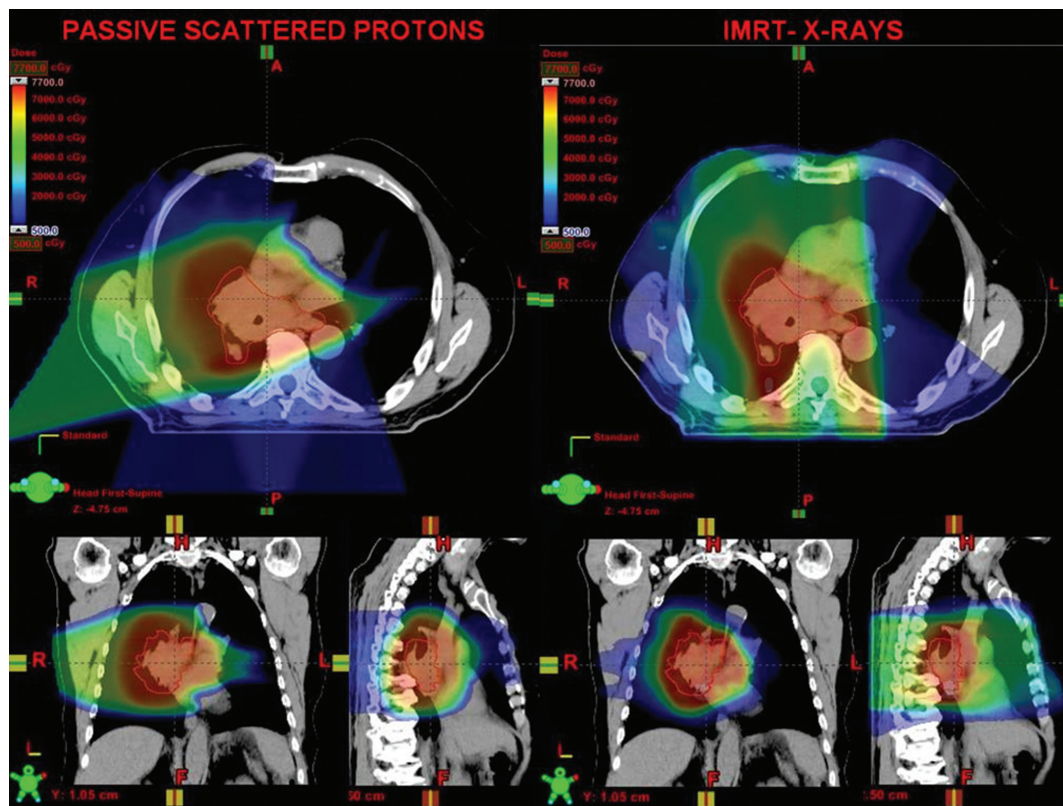


Figure 2 Example of comparison plans for the treatment of lung cancer between passive scatter proton radiotherapy and IMRT

One possibility for this disparity could be treatment-related toxicity; in other words, although tumor control may be increased in patients treated with higher radiation doses, the commensurate increase in toxicity and toxicity-related death can mask any potential benefit. Hence the desire for a radiation treatment modality that can minimize radiation dose to critical structures (e.g., the lungs) while allowing the possibility of dose escalation to the target. One such modality that attempts to achieve this goal is proton beam therapy.

Several planning studies have been done to compare the dose to normal surrounding structures associated with either photon or proton radiotherapy. Generally, in these studies, proton beam therapy has shown benefits over standard conformal radiotherapy; specifically, the dose to the uninvolved lung can in some cases be superior to that provided via conventional radiotherapy (15-17) or IMRT (15,17). Examples of a typical plan for passive scatter proton radiotherapy and one for IMRT are shown in *Figure 2*. Proton radiotherapy may also have advantages over photon-based stereotactic radiotherapy for smaller tumors in terms of sparing normal tissue (15,18-20). However, the benefit

from the use of protons from the dosimetric perspective is not universal. Because of the uncertainty of the exact range of the Bragg peak, particularly in hypodense tissues such as lung, the use of additional margin of high-dose radiation may be required, leading to a higher dose to critical structures, particularly when they are close to the target (21). Further, because many tumors have irregular borders and involve the mediastinum, highly conformal IMRT may provide an advantage in regard to normal tissue sparing compared with the traditional passive-scatter approach to proton radiotherapy (22).

Dosimetric studies aside, a growing body of literature details the clinical experience of using charged particle therapy for lung cancer. Several institutions have generated significant data from the use of proton radiotherapy as monotherapy. One of the earliest published studies reported the investigators' experience in treating mainly early-stage non-small cell lung cancer (NSCLC) with a proton boost after traditional photon radiotherapy. In that study of 37 patients, the local control rate was 87%, and only 2 patients developed symptomatic pneumonitis (23). Studies of stereotactic or hypofractionated proton-based radiotherapy

for early-stage lung cancer have shown similar local control rates for small, peripheral lesions (24-27). However, in the same studies, local control rates for larger lesions have been less favorable, falling in the range of 40% to 60%. Toxicity in these studies has been minimal; in a phase I/II trial recently completed at MD Anderson Cancer Center involving a dose of 87.5 CGE, the rates of symptomatic pneumonitis and esophagitis were 11% and 6% (27).

Less information is available regarding combinations of proton radiotherapy with concurrent chemotherapy for locally advanced lung cancer. The guiding principle for radiotherapy to the lung has been to increase the dose to the point of maximum tolerability, as a radiation dose-response relationship has been observed for locally advanced lung cancer (13). However, any dose escalation must take into account the significant toxicity associated with thoracic radiotherapy. In fact, the most recent national trial of dose-escalated thoracic radiotherapy initiated by the RTOG led to the premature closure of the high-dose treatment group (74 Gy) because of the absence of any observed survival benefit (14). Although the final toxicity data from this trial were not available when this review was written, it is worth noting that 7 patients died in the high-dose group versus 3 in the control group (treated to 60 Gy). Thus, it seems that significant caution should be observed in attempting dose escalation of thoracic radiotherapy when that therapy involves conventional methods. However, a recent retrospective review of concurrent platinum-based chemotherapy and proton radiotherapy noted particularly low rates of pneumonitis (2%) and esophagitis (5%) compared with those rates in a similar group of patients treated to a lower dose (63 Gy) by either 3-dimensional conformal radiotherapy or IMRT (28). Further investigation of these results in a phase II trial showed similarly positive results, with local control rates of close to 80% and pneumonitis and esophagitis rates of around 2% and 11% (29). These results are also being evaluated further in a Bayesian randomized trial of image-guided proton radiotherapy compared with photon radiotherapy for patients with locally advanced lung cancer.

Despite the dosimetric evidence and some clinical data supporting the use of proton radiotherapy for the treatment of lung cancer, significant challenges remain. First, treatment planning using proton radiotherapy is complicated by the inherent motion of the lung. Unlike photon radiotherapy, protons are drastically affected by the material through which they pass. Thus tissue densities must be accounted for during treatment planning. However

the motion of the lung - and consequently the motion of the tumor - during the respiratory cycle can make this challenging, particularly in light of the finite range of protons. Although proton radiotherapy is appealing in the context of sparing normal structures, any changes in the path of the beams during respiration could change the range of the proton beam significantly, leading to marginal misses of the target or increased dose to surrounding normal structures. This problem has been addressed in several planning studies [reviewed in (30)], and a variety of different approaches are being used to minimize this problem. In one such approach, "smearing" the target volume artificially increases the volume targeted in an attempt to ensure good coverage despite small changes arising from motion during the respiratory cycle. This problem of appropriate targeting is further amplified by changes in the tumor itself during radiotherapy: tumors can shrink or become more cavitory in response to radiotherapy, which again changes the density of the tissue traversed by the proton beam and altering its range. At MD Anderson Cancer Center, we have tried to minimize this problem by obtaining images throughout the course of the radiotherapy and modifying the plans ("adaptive planning") if the tumor responds significantly.

Further difficulties arise from highly irregular targets. As noted previously, IMRT can in many cases provide more conformal treatment for large irregular lesions. In an initial dosimetric comparison between IMRT and proton radiotherapy as part of the above-mentioned randomized protocol, IMRT was found to have a dosimetric advantage in many cases (31). One possible solution to the problem of conformality is the use of some form of modulated proton radiotherapy. Conventional proton radiotherapy ("passive scatter") uses material to scatter the beam over a large area, with a rotating wheel placed in the beam path to allow generation of a spread-out Bragg peak. This approach basically delivers a uniform dose over the extent of the target, but does not allow generation of irregular contours for the dose to be delivered. The concept of "pencil beam" proton radiotherapy is being investigated to improve upon this dose distribution; in this technique, the dose can be "painted" over any particular target by the use of pencil beams of protons directed at small segments of an individual target. Although this approach can improve the conformal coverage of irregular targets, in some situations it can be less robust than use of a passive scatter beam, because the accuracy of scanning beam proton radiotherapy is affected to an even greater extent by organ motion (32). Studies of the use of scanning beam technology for the treatment of

lung cancer are ongoing.

Finally, cautions have been raised regarding the problem of unintended neutron dose when using proton radiotherapy. The production of secondary neutrons may be of particular concern for passive scatter beams, in which a physical component is placed in the beam path, because these scattered neutrons may themselves be carcinogenic. Although this could be of significant import for younger populations, patients with lung cancer tend to be older, and risk estimates for carcinogenesis are highest for young patients (33). Further, the magnitude of neutrons generated by passive scatter beams is debated in the literature (34). Regardless, the advent of scanning beam technology has greatly reduced the possible risk of neutron scatter in the use of proton beam radiotherapy (33).

Future challenges and opportunities

The advent of proton radiotherapy for lung cancer brings with it an opportunity to minimize the toxicity of current standard-of-care therapy. At present, this possibility is being investigated in at least one randomized trial in which the benefits of passive scatter proton radiotherapy are being compared with those of IMRT. Further prospective studies are also ongoing to compare the benefits of stereotactic proton radiotherapy with those of standard 3D-conformal stereotactic radiotherapy. So, what further challenges and opportunities remain? One major criticism of proton radiotherapy for the treatment of lung cancer is its cost. The development of proton radiotherapy capability requires a significant cost outlay for any institution. Moreover, a treatment course of proton radiotherapy is significantly more expensive at the current time than is a comparable course of IMRT. Although this cost will likely decrease with time, proton radiotherapy remains an expensive treatment option. However, the costs of proton radiotherapy for lung cancer must be weighed against the costs of toxicity associated with therapy. In fact, in one cost-effectiveness model involving only recent studies, proton radiotherapy was found to be cost-effective for the management of selected cases of lung cancer (35). This finding underscores the idea that merely calculating treatment costs does not completely measure the value of any particular therapy.

With regard to technology, the current “cutting edge” in proton radiotherapy delivery is the development of intensity modulation. As noted previously, one of the disadvantages of passive beam proton radiotherapy is the inability to conform to a highly irregular target or to allow dose-painting within

the irradiated field. Scanning beam technology removes this disadvantage. Moreover, one could conceivably generate treatment plans that take advantage of the increased RBE at the Bragg peak by deliberately encompassing a radioresistant area of a tumor (e.g., an hypoxic area) within the Bragg peak of each scanning beam. Theoretically, this approach would lead to improved response without incurring any toxicity associated with dose escalation. However, as noted previously, scanning beam technology for proton delivery is highly dependent on precise planning software and improved motion management. As these technologies improve, true intensity modulation of protons in the treatment of lung cancer will become a reality.

In summary, the current state of proton beam radiotherapy or intensity-modulated proton beam radiotherapy for lung cancer is one of optimism. Prospective trials of proton radiotherapy are ongoing, and those findings, as they mature, will be valuable in further clarifying the role of proton radiotherapy for the management of this deadly disease.

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Footnote

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