Proton Radiation Therapy for Lung Cancer: Is There Enough Evidence?

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Proton radiation for cancer offers the ability to conform the high-dose region of radiation therapy to the tumor while reducing the dose of radiation to adjacent normal tissues. In lung cancer, this equates to greater sparing of uninvolved lung, heart, esophagus, and spinal cord. Sparing these normal tissues permits the delivery of higher-radiation doses to the tumor. Studies that compare the distribution of radiation doses for lung cancer show that proton radiation is superior, even when factors such as respiratory motion are considered. Clinical experience confirms the feasibility of proton radiation for early-stage non-small-cell lung cancers, and clinical trials are being conducted in locally advanced tumors: To date, evidence indicates that proton radiation should be further explored.

Lung cancer remains a leading cause of cancer death in North America.[1] Non-small-cell lung cancers (NSCLCs) predominate over the small-cell variant of lung cancer, and are usually associated with a poor prognosis, owing to locally advanced or metastatic presentations. The only NSCLC subgroup that has a better than 50% five-year survival is that comprised of patients with peripherally located T1 or T2 tumors without evidence of nodal or distant metastases.[2] However, unfortunately more than 80% of patients present with stage III or IV disease.

The goal of definitive radiotherapy is to eradicate intra-thoracic disease while respecting the radiation tolerance of nearby normal structures by minimizing the dose to such structures. Various photon radiation techniques have been tried in order to effect a therapeutic advantage, among them hyperfractionation (multiple treatments per day), accelerated fractionation (shorter treatment periods), and dose escalation.[3-6] Most innovative techniques have focused on conformal treatment delivery with computer assisted three-dimensional therapy planning and, in some cases, intensity-modulated radiotherapy in which more complex treatment planning and delivery can allow the radiation oncologist to have better control of doses to healthy tissues.[7-8] Here, the goal has been to deliver higher doses to target volumes in an effort to improve local tumor control within the constraints of surrounding regions of normal tissues such as the heart, lung, esophagus, and spinal cord. Tumor control rates with photon radiation therapy, however, continue to be disappointing, in part because of the dose-limiting constraints associated with these normal structures.

![Percent dose deposited per depth in tissue for photon beams of various energies, and a broton beam (shown in red).](image)

**Physical Characteristics of Proton Beams**

Because of their their mass (about 1800 times that of an electron) and charge, proton beams can be controlled in three dimensions so that radiation doses can be more accurately deposited within target volumes while the dose to surrounding non-targeted tissues is often minimized—or even eliminated. This ability to spare normal tissues is an important consideration: The greater the extent to which the physician can reduce or eliminate the radiation dose to normal tissues, the lesser the likelihood that treatment will need to be compromised because of unacceptable side effects. In other words, the reduced lateral scatter and sharp dose fall-off of the proton beam not only allows delivery of the total needed dose but also affords opportunities to deliver higher doses without increasing...
side effects.
The importance of reducing the volume integral dose to normal tissues has been noted for years. In studies spanning more than four decades, Rubin and several collaborators identified the clinicopathologic courses of radiation injury in organs and tissues throughout the body and identified tolerance doses for those organs. Tolerances were identified in ranges of total doses in which severe or life-threatening complications were likely to occur within five years of therapeutic radiation; i.e., severe sequelae would likely occur in 5% of patients treated at the lower end of the range (TD5/5) and in 50% of patients treated to the dose at the top of the range (TD50/5).[9] Although organs and tissues were separated into categories according to their importance for survival,[10] no “safe” dose (TD0/5) was identified for any organ; rather, in a classic series of graphs, Rubin and Casarett demonstrated that sublethal doses of radiation initiate a course that can eventuate in clinical manifestations of radiation injury, some of which progress further to lethality.[11]

In later studies of relevance to lung cancer treatment, Rubin and colleagues demonstrated early and persistent elevation of cytokine production following pulmonary irradiation. The temporal relationship between elevation of specific cytokines and histological and biochemical evidence of fibrosis illustrated the continuum of response which, the authors speculated, underlies pulmonary radiation reactions and supports the concept that a perpetual cascade of cytokines is produced immediately after radiation treatment and persists until pathologic and clinical late effects are expressed.[12]

The fact that protons display a Bragg peak is what enables proton radiotherapy to offer a means of reducing the volume integral dose. In the Bragg peak, the deposited dose from a single beam is relatively low upon entrance and increases slowly until the desired depth in tissue is reached; at that point the bulk of the dose is deposited within the targeted volume, while no dose is deposited in distal tissues. The Bragg peak can be spread out to encompass the target volume while still retaining a relatively low entrance dose and sparing tissues distal to the direction of travel (Fig. 1). In non-small-cell lung cancer, and in contrast to treatment of similar target volumes with photon beams, these properties afford a great deal of sparing to the treated lung, opposite lung, heart, esophagus, and spinal cord, in turn allowing for safe dose escalation.

Because local tumor control is insufficient with conventional photon radiation treatment, and because evidence exists to indicate that higher doses may improve tumor control, investigators have anticipated a role for proton radiation therapy in patients with lung cancer. Fowler analyzed the potential use of proton radiotherapy in such cases and, using biological modeling, estimated that significant improvements in local tumor control and survival likely are possible.[13] Owing to the normal-tissue-sparing properties of proton beams, not only is there clear potential to achieve effective disease control without increased normal-tissue complications, it also may be possible to decrease the severity of toxicity seen in comparable treatments with photons. Accordingly, clinical investigations into the use of proton and other heavy-charged-particle therapies for lung cancer are being conducted at centers around the world.

Planning comparison of a single lateral with photons (left) and proton beam (right).

Dose-distribution for a stage I lung cancer treated with proton beam shown in axial (left) and sagittal view (right). Beams include a right lateral, right posterior oblique arrangement. Colored contours represent the percentage of the total prescribed dose.
Dose distribution for a patient with stage III lung cancer treated with proton beam. Contours represent the lung tumor and involved nodes (red) and sub-clinically involved mediastinal nodes (light blue). Distribution shows the percent of the total dose. Beam arrangement includes a left lateral and posterior to the CTV (46 CGE) and a left posterior oblique to the GTV (30 CGE).

**Treatment Planning: Considerations and Comparisons**

As noted, proton beams exhibit a Bragg peak effect, which yields normal-tissue sparing not possible with photon beams. This capability exists despite the special dosimetric circumstances that exist for lung cancer treatment with protons. For example, lung cancers are invariably surrounded by aerated pulmonary parenchyma; an essentially water-density-equivalent tumor is surrounded by substantially less-dense lung tissue. Aerated lung tissue has reduced stopping power compared to other soft tissues, and this affects the stopping distance or distal edge of a spread-out Bragg peak; this can cause proton beams to travel some distance beyond the distal edge of the target volume, which is not typically true of tumors located in other parts of the body. Additionally, when lung targets are selected for treatment, one must consider physiologic internal target motion, which is highly dependent on the region of the lung in which the tumor resides; i.e., tumors near the diaphragm will show the largest respiratory excursion. The simplest method to account for such motion is to measure the three-dimensional excursion of the tumor and expand the treatment volume to encompass all possible tumor positions. For small tumors (with motion parameters of less than 1 to 2 centimeters), this method is adequate—the technique has been used for patients with peripheral lung tumors of one to four centimeters in size at Loma Linda University Medical Center for more than a decade with an excellent safety profile and a low incidence of radiation pneumonitis.[14] For larger tumors and when motion parameters are greater, respiratory monitoring with beam gating, or respiratory control or compensation (perhaps via a patient-positioning device that moves the patient during treatment in a way that allows the target to remain still relative to the treatment beam) may be employed to significantly reduce dose to normal lung tissue. A report by Engelsman and colleagues compared computerized treatment plans using various techniques to account for respiratory motion in planning proton treatments.[15] Target expansion utilizing 4D treatment planning, in which the planning CT data set included multiple phases of the respiratory cycle, was found to provide the most reliable target coverage. Intrinsic pulmonary or treatment-related factors, such as pleural effusion or atelectasis, may also cause uncertainties in the stopping region of the Bragg peak, and these need to be accounted for in therapy planning. If the radiation oncologist feels that such changes may occur during the treatment course, it may be necessary to repeat chest imaging and create a new plan of treatment for any significant anatomic changes; a practice referred to as adaptive treatment planning.

Even allowing for potentially confounding factors such as these, proton-beam dosimetry is an improvement over the use of photon beams (Fig. 2). The tissue-sparing capability of the proton beam is most apparent in the treatment of early-stage non-small-cell lung cancer (Fig. 3), but significant sparing also is achievable when protons are used to treat locally advanced disease (Figs. 4 and 5).

Chang and colleagues have published a formal comparison between proton and photon treatment planning.[16] They analyzed ten patients with inoperable stage I lung cancer, comparing proton treatment plans to 3D conformal photon plans at two dose levels (66 Gy and 87.5 Gy). Analysis revealed an approximately 50% reduction in non-target lung dose when protons where used. The normal lung tissue-sparing effect seemed to be increased with the high-dose plans, indicating an additional benefit for dose escalation when proton beams are used. Fifteen patients with stage III lung cancer were also analyzed, comparing 3D photon, IMRT, and proton beam plans at two doses (63 Gy and 74 Gy). Again results showed a substantial reduction in the non-target lung dose, and again, the proton benefit seemed to be more evident with the higher dose plans. Doses to the heart,
esophagus, and spinal cord were also found to be significantly reduced. This study suggests that protons can achieve higher target doses, with more significant normal-tissue sparing, than 3D conformal radiation therapy or IMRT.

Considerations in Beam Delivery

Today, most heavy-charged-particle-beam treatment facilities utilize a beam scattering system and passive beam-shaping devices (for example an aperture to shape the perimeter of the particle beam and a tissue compensator to shape the distal edge or Bragg peak region in order to contour it to the distal edge of the target). These devices are carefully designed so that they avoid unnecessarily over-radiating pulmonary tissue while allowing for factors such as altered stopping power in aerated tissue and physiologic motion.[17] Scanning-beam technology is under development at several treatment centers; most authorities believe this will provide enhanced target coverage and normal tissue protection not currently achievable with the passive beam-shaping methods that are commonly used today. However, the application of this technology for treating intra-thoracic targets presents a significant challenge due to physiologic internal motion and potentially unreliable radiologic path lengths. Until we have a thorough understanding and reliable control of these variables, it is likely that scattered beams will continue to be utilized for lung cancer treatment.

No standardized treatment techniques or beam arrangements exist for using heavy-charged-particle beams in patients with lung cancer. The most extensive experience in this area comes from Loma Linda University Medical Center, where proton beams have been utilized since the mid 1990s. For patients with solitary pulmonary nodules, the beam arrangements employed have been relatively simple, typically consisting of lateral, posterior, and posterior oblique beams. Frequently the lateral beam is preferred, as it typically provides the lowest volume of normal lung tissue exposure. This is in distinct contrast to photon beams, which will continue through the mediastinum into the contralateral lung. Lateral proton beams, however, are very useful for lung cancer treatment, as the Bragg peak allows the beams to stop distal to the tumor, frequently at the mediastinal pleural surface, thus completely sparing the mediastinum and contralateral lung. Multiple treatment beams per day have been utilized; hypofractionated treatment courses have been common. Treatment techniques in patients with locally advanced lung cancer can be significantly more challenging when mediastinal lymph nodes are targeted, other sensitive normal-tissue structures come into play, such as heart, esophagus, and spinal cord. In a recent clinical trial at Loma Linda University Medical Cancer, these patients are being treated with protons and chemotherapy. Typically, the patients are treated using anterior beams (which stop short of the spinal cord), along with lateral and posterior oblique beams. When beams are designed to limit the dose to the esophagus or spinal cord, it is generally preferred that the edge of the aperture be used to protect these structures. If a beam is designed to stop short of a critical normal tissue region, great care is taken to account for physiologic motion and the presence of inconsistent tissue densities within the chest.

Dose-volume histograms for treatment plan shown in Fig. 4. Histograms shown for the total lung (top), esophagus (center), and spinal cord (bottom).

Clinical Results

Protons have been the most commonly used particle beam for treatment of patients with lung tumors. At Loma Linda, patients with clinical stage I non-small cell lung cancer who are either medically inoperable or refuse a recommended surgical intervention, have taken part in a clinical trial that involves the use of proton particle beams. The latest report includes 68 patients treated...
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with either 51 CGE or 60 CGE in ten fractions over a two-week course.[18] The area targeted for treatment includes the gross tumor volume as well as a PTV that includes additional margin for respiratory motion. Typically, two to four beams are utilized for treatment, with at least two fields being treated each day. Various beam weightings have been utilized, generally with preference given to lateral beams to minimize lung exposure (Fig. 3). The therapy has been exceptionally well tolerated, with a low incidence of grade-one pneumonitis and no reported grade three toxicities. Disease-specific survival at three years was 73%. Patients with T1 tumors have achieved local control in 87% of cases; those with tumors larger than three cm (T2) have had local failures up to 50% at three years, which has led to a third dose escalation: the current regimen delivers 70 CGE in ten equally divided fractions over two weeks. Although no survival or local control data are yet available at this dose level, after treating nearly forty patients at this escalated total dose there does not appear to be any difference in tolerance. Additionally, no decline in post-treatment pulmonary function (FEV1 or PO2) has been observed.[14]

In Japan, Nihei reported on 37 patients with stage I non-small-cell lung cancer treated with proton beam therapy.[19] Most patients received between 80 and 88 Gy equivalent, utilizing fraction sizes ranging from 3.5 to 4.9 Gy. The reported two-year local-regional relapse-free survival rate for T1 tumors was 79%; for T2 tumors the rate was 60%. They identified six cases of grade 2 and 3 pulmonary toxicity, with the majority of these seen in patients with larger tumors. Shioyama and colleagues have reported on 28 patients with stage I non-small-cell lung cancer treated with proton beams to a median dose of 76 Gy at 3 Gy per fraction.[20] Patients with T1 tumors had a 70% overall survival at five years, while patients with T2 tumors had a significantly lower survival (approximately 16%). Pulmonary toxicity was reported as minimal.

Studies are underway at Loma Linda that utilize proton beam radiotherapy in conjunction with chemotherapy for the treatment of locally advanced lung cancers. Neo-adjuvant and concurrent chemotherapy is administered with proton therapy, which is given as a concomitant boost. The dose to the sub-clinically involved mediastinum is 46 CGE in two CGE fractions with a GTV, BID boost of 30 CGE during the last three weeks of treatment. Despite the much larger target volumes in such cases, significant sparing of normal tissues still is achieved (Figs. 4 and 5). In the most recent evaluation of ongoing results in 19 patients, no Grade 3 or 4 esophageal toxicities were observed; Grade 3 leukopenia was seen in two patients, and Grade 3 thrombocytopenia occurred in one individual. Two phase II clinical trials are currently underway that test the use of proton radiotherapy in combination with concurrent chemotherapy for locally advanced (Stage III), inoperable non-small-cell lung cancer. Studies at the University of Florida (ClinicalTrials.gov identifier: NCT00881712) and the University of Texas M.D. Anderson Cancer Center (ClinicalTrials.gov identifier: NCT00495170) are currently evaluating proton radiation in combination with Paclitaxel and Carboplatin. These safety/efficacy studies are similar, yet differ in some details. In the Florida study, the primary outcome measure is to determine whether there is a reduction in acute toxicity from combined concomitant chemotherapy and radiotherapy, compared to previous cooperative group trials. In this trial, disease control, median overall survival, and five-year survival are identified as secondary outcome measures. In the M.D. Anderson study, median survival time is the primary outcome measure, with local control, progression-free survival, disease-specific survival, and disease free survival as secondary outcomes. The M.D. Anderson study also seeks to determine whether grade 3 and higher toxicities are reduced; whether pre- and post-treatment PET/CT are useful in predicting clinical outcome; and whether a biomarker can be used for predicting treatment response and toxicities. Patients in the Florida study receive 80 CGE at two CGE per fraction to PET-positive deposits of gross primary disease and PET-positive deposits of gross nodal disease measuring more than 15 mm; 60 CGE at two CGE per fraction to PET-positive deposits of gross nodal disease measuring less than 15 mm; and 40 CGE in two CGE per fraction to full nodal stations containing foci of PET-positive gross disease, or anatomically adjacent to nodal stations containing PET-positive gross disease.

**Conclusion**

Strong evidence exists showing that dose escalation can provide improved local tumor control in non-small-cell lung cancer, and that it can be delivered safely when the radiation delivered to healthy pulmonary tissue is minimized with conformal delivery via proton beams. To date, clinical results have demonstrated that lung cancer treatment is feasible and that severe treatment-related toxicity has been minimal in both early and locally advanced cases, thus allowing for further dose escalation if clinically indicated. Historically, new technology that was proven to improve dose delivery to the intended target and/or decrease dose to surrounding healthy tissues has made its way into common clinical practice; it
would make sense that the use of proton beams in treatment would follow this path. Some would contend that randomized, controlled Phase III trials that compare proton therapy to photons are needed to first establish “evidence” that proton therapy is indicated for treating non-small-cell lung cancer. However, the only testable therapeutic variable in such trials would be the volume of normal tissue irradiated; both conformal IMRT and proton therapy encompass the targeted region similarly, but proton beams yield a significantly smaller volume integral dose to normal tissues. Some have questioned the wisdom of designing such trials, positing that data supporting the benefits to normal tissue dose reduction already exists.[21] In any case, there appears to be enough evidence to warrant the continued exploration of proton therapy, which most likely has not yet reached its full potential in the treatment of cancers of the lung.

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