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Does Proton Therapy Offer Demonstrable Clinical Advantages for Treating Thoracic Tumors?

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The finite range of proton beams in tissues offers unique dosimetric advantages that theoretically allow dose to the target to be escalated while minimizing exposure of surrounding tissues and thus minimizing radiation-induced toxicity. This theoretical advantage has led to widespread adoption of proton therapy around the world for a wide variety of tumors at different anatomical sites. Many treatment-planning comparisons have shown that proton therapy has substantial dosimetric advantages over conventional radiotherapy. However, given the significant difference in cost for proton vs conventional photon therapy, thorough investigation of the evidence of proton therapy's clinical benefits in terms of toxicity and survival is warranted. Some data from retrospective studies, single-arm prospective studies, and a very few randomized clinical trials comparing these modalities are beginning to emerge. In this review, we examine the available data with regard to proton therapy for thoracic malignancies. We begin by discussing the unique challenges involved in treating moving targets with significant tissue heterogeneity and the technologic efforts underway to overcome these challenges. We then discuss the rationale for minimizing normal tissue toxicity, particularly pulmonary, cardiac, and hematologic toxicity, within the context of previously unsuccessful attempts at dose escalation for lung and esophageal cancer. Finally, we explore strategies for accelerating the development of trials aimed at measuring meaningful clinical endpoints and for maximizing the value of proton therapy by personalizing its use for individual patients.
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Introduction

Thoracic malignancies such as non-small cell lung cancer (NSCLC) and esophageal cancer are complex and challenging to treat. Often they are diagnosed at a locally advanced stage and are not amenable to surgical resection. In such cases, radiation therapy, given with either concurrent or sequential chemotherapy, is often the treatment of choice. Unfortunately, most patients with locally advanced lung or esophageal cancer die of the disease; the median survival times are only 16-28 months, and local recurrence accounts for 40%-50% of failures.

Although radiation dose escalation has been tested as a strategy to improve tumor control and patient survival, recent phase III randomized studies investigating dose intensification of thoracic irradiation showed no benefit from higher radiation doses for locally advanced NSCLC or esophageal cancer.[1,2] No differences were found in local control between the standard-dose and high-dose arms, and the higher-dose radiation had a detrimental effect on patient survival. The fact that the cancer-related death rates for standard-dose and high-dose groups in both studies were similar suggested that the higher death rate in the high-dose group was from noncancer-related reasons, specifically treatment-related toxicity. The results of RTOG 0617 showed that radiation dose to the heart was an independent predictor of survival, confirming that exposing larger portions of the heart to higher thoracic radiation doses contributed to higher death rates in the high-dose arm.[1]

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Several current reports have also linked therapy-induced lymphopenia during chemoradiation with poor survival for many types of tumors, including lung cancer, esophageal cancer, head and neck cancer, gastrointestinal cancers, and cervical cancer.[3-6]

The relevant organs at risk (OARs) in the treatment of thoracic malignancies are the esophagus, lung, heart, and bone marrow; other important structures or tissues include the brachial plexus, spinal cord, skin, and chest wall. In principle, the most effective strategy to reduce toxicity would be to reduce unnecessary irradiation of OARs by using advanced technology, 1 example of which is proton beam therapy. Proton therapy offers substantial potential advantages over conventional photon therapy because of the unique depth-dose characteristics of protons, which can be exploited to reduce irradiation of normal tissues proximal and distal to the target volume so as to allow escalation of tumor doses while simultaneously sparing greater amounts of normal tissues; the expectation is that these effects would improve local tumor control and survival as well as reducing toxicity and improving quality of life.

However, particle therapy (including proton therapy) is significantly more expensive than the best available photon technology, and evidence demonstrating clinical benefit after proton therapy is increasingly demanded to justify the higher financial burden on the healthcare delivery system. Despite the high capital costs associated with charged particle therapy and the lack of level I evidence of clinical benefit from direct comparisons, the demand for improved technology in cancer treatment, particularly proton therapy, is evidenced by the numbers of facilities being built worldwide. Currently, 76 particle therapy centers are operating worldwide, 25 of which are proton centers in the United States, and many more are being planned (Particle Therapy Cooperative Group, https://www.ptcog.ch/index.php/). By 2015, more than 154,000 patients worldwide had been treated with charged particle therapy (https://www.ptcog.ch/index.php/). Parallel with this increase in numbers of facilities and the clinical use of particle therapy is the accumulation of knowledge about the physical uncertainties of particle therapy and methods of counteracting these uncertainties to ensure accurate planning and precise delivery of particle therapy.

In this review, we summarize the rationale for and challenges of using charged particles to treat thoracic cancers; we review the clinical experience to date on use of proton therapy for locally advanced lung cancer and esophageal cancer; and we discuss future directions for use of proton therapy.

Dosimetry and Radiobiology of Charged Particle Therapy

The radiobiology and dosimetric characteristics of charged particle therapy have been reviewed in depth elsewhere.[7] Briefly, charged particle radiotherapy involves the use of charged particles such as protons or carbon ions to treat cancer. The depth-dose characteristics of charged particles are well understood and described by others.[8] When a "fast" charged particle moves through matter, it interacts with the electrons within atoms and causes ionization, which deposits energy and dose along its path. The energy loss per unit path length is relatively constant until it reaches a peak (the so-called Bragg peak), where energy deposition occurs at a depth that is a function of the energy and nature of the charged particle. Beyond the Bragg peak, very little dose is delivered. In passively scattering proton therapy (PSPT), the Bragg peak is spread both longitudinally and laterally to create a spread-out Bragg peak, which provides a uniform dose to cover the entire volume of a target. Conformal coverage of the tumor is achieved by using range modulation wheels, compensators, and beam apertures. Pencil beam scanning proton therapy, on the other hand, uses magnetic scanning of thin beamlets of protons of a sequence of energies, delivered from different directions, to produce the desired pattern of dose distribution. The tumor is "scanned" layer by layer, with 1 layer per energy, until the entire target is covered. This technique provides greater flexibility and control for ideal dose distributions and allows delivery of intensity-modulated proton therapy (IMPT), to date the most advanced form of proton therapy.[7] Many treatment-planning comparison studies have demonstrated dosimetric advantages of IMPT over intensity-modulated photon radiation therapy (IMRT) (Fig. 1).

The biological interaction of ionizing radiation with matter (ie, tissues) is related to the amount of energy transferred to the matter over a specified path length (known as linear energy transfer [LET]). For particles such as protons and helium, the LET is thought to be nearly equivalent to that of photons, and therefore the relative biological effectiveness (RBE) is also nearly equivalent (the RBE for protons:photons approximately equals 1.1).[9,10] For heavier charged particles such as carbon ions, the density of ionization is greater at the end of their range, which causes greater damage to the DNA within cells at the end of that range. This results in carbon ions having a higher RBE (1.5-3). However, it is becoming increasingly evident that RBE is a complex, variable function of radiation dose per fraction, total dose, LET, cell and tissue type, choice of endpoint, and other factors.[11,12] Thus the RBE may be less than 1.1 at the entrance, may increase with depth, and may be highest at the distal edge of the beam.

These 2 physical properties of protons, that is, having a finite range in tissue and having a higher RBE at the distal edge of the beam, make proton therapy both appealing and potentially problematic. Proton therapy is exquisitely sensitive to changes in tumor position and differences in tissue composition; this sensitivity is particularly problematic for thoracic tumors, because the tumors move with lung ventilation and diaphragm motion, and because the tissues along the beam path are quite heterogeneous in structure and density. In PSPT, extreme care must be taken to consider the need to compensate for tumor motion, changes in lung density owing to respiration, and uncertainties in proton range with regard to respiration-induced tumor motion and lung density changes (Fig. 2). These variables should be assessed separately for each beam direction, and some amount of dosimetric uncertainty should be built into the planning of each beam.[13]