The Heated Debate

ACCELERATING PROTONS COULD CONQUER CANCER, BUT AT WHAT PRICE?

By Kristen Georgi

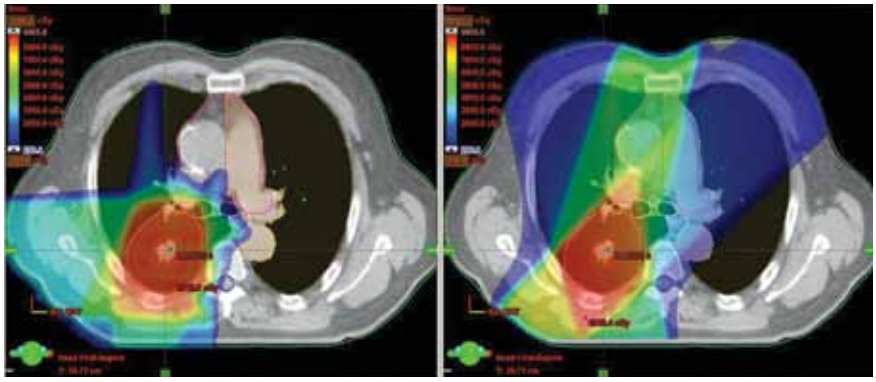
In 2008, on the border between France and Switzerland, the Large Hadron Collider sent two protons on a collision course deep within the Earth. Scientists hope that tracing the protons' trajectory will provide insight into the laws of nature that rule everything from the miniscule atom to the vast universe.

Today, in a growing number of proton therapy centers across the United States, medical scientists are using particle accelerators to intensively direct protons at targeted velocities within the bodies of patients. They aim to delve into the nature of cancer, to damage the DNA of cancer cells.

Experiments with protons that began in the 1950s led to the world's first hospital-based proton therapy center at California's Loma Linda University Medical Center in 1990. Now, seven centers are in operation across the country, with more under construction and in development (see sidebar on centers).

Additionally, RTOG® is considering allowing protons in a number of its protocols, including:

- RTOG 0539 – Phase II Meningioma
- RTOG 0930 – Somatostatin Receptor Scintigraphy Pituitary Adenoma (in development)
- RTOG 0815 – Phase III Low/Intermediate Risk; Androgen Deprivation Therapy vs. No Androgen Deprivation Therapy
- RTOG 0924 – Phase III Intermediate/High-Risk Prostate With or Without Pelvic Radiotherapy (in development)
- RTOG 0922 – Phase II Proton Beam and Androgen Suppression in Locally Advanced Prostate Cancer (in development)



Courtesy University of Pennsylvania Health System

Much less radiation is delivered to healthy tissues that surround a patient's lung tumor when treated with the precision of proton therapy.

Bringing Down the Cost

But some question whether the rewards of accelerating protons is worth the high price tag. Factoring in a cyclotron, multistory gantries, and multiple treatment rooms, the cost for an average-sized 90,000 square-foot proton center can be between $140 million and $200 million.

More questions arise about the cost of using proton therapy and which cancers to treat. "At Loma Linda, the most common cancers we treat are prostate cancers, along with brain cancers, cancers of the eye and neck, benign disease around the base of the skull and spinal cord, and most recently, cancers of the lung," says Jerry D. Slater, M.D., professor and chair of the Department of Radiation Medicine at Loma Linda University.

Slater points out that Medicare, which covers proton therapy, sets the standard for payment. "Proton therapy is still a developing technology, and we're proud to say we've been able to bring the cost down over the last decade, while conventional therapies, which are 30 to 40 years old, are getting more expensive," he says. "We have to separate out what people are asking as payment for proton therapy and what is being paid.

"Medicare is a major player in this," Slater continues. "Right now, the differential between intensity-modulated radiation therapy and proton therapy is running about 30 percent, with an average cost of treating prostate cancer with proton therapy in the vicinity of $30,000 to $40,000."

Sparing Patients Side Effects

Numerous studies are underway to determine proton therapy's benefits in terms of side effects and outcomes. What is already certain is that proton therapy's ability to precisely and intensively target areas of cancerous activity at a desired degree of tumor penetration spares underlying tissues from radiation exposure and results in fewer side effects than other forms of radiation therapy.

"To be clear, there *are* side effects with proton therapy, but this must be put in perspective," says Slater. "Side effects occur when we hit normal tissue that doesn't need radiation. With proton therapy, for a typical course of therapy, we reduce the radiation [in normal tissue] by a factor of three or four times. We're finding that when we grade toxicity using RTOG/EORTC[1] Late Radiation Morbidity Scoring Schema, we're seeing severity in less than one percent of cases, and we're using higher doses."

This favorable side-effect profile makes it easy to speculate about when the benefits outweigh the cost. A case in point includes a clinical study to evaluate the use of proton therapy in treating children with rare brain cancer, a collaborative effort between St. Jude Children's Research Hospital and the University of Florida Proton Therapy Institute in Jacksonville.

"With proton therapy, one rarely has to sacrifice target coverage to protect adjacent critical organs, such as the

brainstem or optic chiasm," says Nancy P. Mendenhall, M.D., FACR, University of Florida professor and associate chair of the Department of Radiation Oncology. "The types of side effects from proton therapy are similar to conventional therapy and depend on the location of the tumor in the brain," she continues. "However, the ability of proton therapy to decrease unnecessary radiation to normal CNS tissue should translate to an overall decreased incidence of severity of any given side effect," Mendenhall adds.

Addressing the Skeptics

A long-term benefit may be the reduced risk for secondary cancer occurrence, as demonstrated in research of 1,591 patients with epithelial tumors, sarcomas, and cancers of the brain, head, neck, and prostate who received proton therapy, compared with 503 patients with similar cancers who underwent photon therapy[2]. In the study, researchers found that 6.4 percent of the proton therapy patients developed a second cancer, compared with 12.8 percent of those who underwent photon radiation treatment.

"We tend to look at how to control costs right now, while secondary cancers may be 10 years out," says Andrew K. Lee, M.D., M.P.H., director of the Proton Therapy Center at The University of Texas MD Anderson Cancer Center in Houston. "Endpoints only focus on what is occurring during the two months of treatment, not amortized over the lifetime of the patient. We may do well to look at comparative costs of different radiation therapies in terms of side effects, recurrence, lost wages, and the cost of care given by family members," he notes.

In spite of the benefits, proton therapy has its skeptics. A 2009 technical brief issued by the Agency for Healthcare Research and Quality maintains that there is not enough evidence from long-term outcome studies about the safety of proton therapy compared with conventional radiation or brachytherapy[3]. Other than for head and neck cancers, the brief says, data from comparative studies are insufficient to formulate a conclusion about the therapy's cost and effectiveness.

In response, Lee feels that the question about safety is odd, given the number of patients treated with proton therapy in the United States, and the fact that it has been FDA-approved. "It is difficult to assess a new technology by doing a MEDLINE search and without visiting a proton therapy center," he says. "I didn't see one *p* value in the brief, and while new studies are coming out every month, some of the research quoted in the brief was not even done in this decade."

In terms of outcomes, Lee is a supporter of proton therapy. "Let me add that overall, the death rate for breast, prostate, and other cancers is declining[4]. The nation wanted these numbers to be lower, and as a result of advancements in cancer therapy, the trend is going downward." //

Courtesy University of Pennsylvania Health System

Stephen M. Hahn, M.D., chairman of the Penn Medicine Department of Radiation Oncology, and James M. Metz, M.D., vice chair for clinical operations in the Department of Radiation Oncology, stand in front of one of the four gantries in the Roberts Proton Therapy Center. Each gantry is a 90-ton rotational machine that delivers a therapeutic beam to the patient's tumor at precise angles.

ENDNOTES

1. EORTC = European Organisation for Research and Treatment of Cancer
2. Chung, C., et al. "Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy," *International Journal of Radiation OncologyBiologyPhysics*, September 2008:S8.
3. Agency for Healthcare Research and Quality. "Particle beam radiation therapy is promising, but unproven for treating cancer." Available at www.ahrq.gov/research/nov09/1109RA.pdf. Accessed Jan. 8, 2010.
4. Jemal A., et al. "Cancer Statistics, 2009," *CA Cancer J Clin.* 2009;59:225-249.

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U.S. PROTON THERAPY CENTERS

Operating Centers

- Francis H. Burr Proton Center at Massachusetts General Hospital, Boston
- James M. Slater, M.D. Proton Treatment and Research Center at Loma Linda University Medical Center, Loma Linda, Calif.
- MD Anderson Cancer Center's Proton Therapy Center, Houston
- Midwest Proton Radiotherapy Institute at Indiana University, Bloomington, Ind.
- ProCure Proton Therapy Center, at the INTEGRIS Cancer Institute, Oklahoma City
- The Roberts Proton Therapy Center at University of Pennsylvania Health System, Philadelphia
- The University of Florida Proton Therapy Institute, Jacksonville, Fla.

Centers Under Construction

- CDH Proton Therapy Center, a ProCure Center, Warrenville, Ill.
- Hampton University Proton Therapy Institute, Hampton, Va.
- Northern Illinois Proton Treatment and Research Center, West Chicago, Ill.

Center In Development

- South Florida Proton Center at University of Miami, Miami

SOURCE: The National Association for Proton Therapy (**www.proton-therapy.org/**)