The Promise of Protons in Cancer Therapy

By Norra MacReady

The sobering economic climate has not stopped some cancer centers from pouring money into cutting-edge therapies that may have many enticing benefits but scant long-term evidence of superiority. In a move that seems audacious given today’s money-saving ethos, the Mayo Clinic is building proton beam facilities for its Minnesota and Arizona locations. The estimated cost of each: $180 million.

The decision is controversial: In the Jan. 3 New York Times, Steven D. Pearson, M.D., and Ezekiel Emanuel, M.D., noted that Medicare pays about $50,000 for proton beam therapy to treat prostate cancer, roughly twice what it reimburses for conventional radiation treatment. They described this as “crazy medicine and unsustainable public policy.” Essentially, they posed the question: Is it wise to pay so much for something that offers little if any improvement over less costly treatments?

More Energy, Fewer Side Effects

Proton beam therapy, at least in theory, irradiates tumors while leaving adjacent healthy tissues unscathed. Conventional x-rays, by contrast, are much less precise and often damage healthy as well as cancerous tissue, said Thomas Kroc, Ph.D., head of the Accelerator Division of the Neutron Therapy Facility at Fermilab in Batavia, Ill.

Protons deposit less energy during their passage through the body, Kroc explained. “They have a definite range, and as they get to that distance, they deposit the major portion of their energy at that particular spot. So, for example, if you were to take a cross-sectional slice of the body from a computed tomography scanner and superimpose on it computer simulations of how the energy will be deposited by these beams, you see that with proton therapy, you can get very precise geometric distribution of the dose, and much less dose to the surrounding healthy tissue, than with [conventional radiation]. And that’s the main attraction of proton beam therapy.”

That is the key to successful radiation therapy: delivering a dose sufficient to kill the tumor while sparing the surrounding healthy tissue, added Jerry D. Slater, M.D., chairman of the department of radiation medicine at Loma Linda University Medical Center in Loma Linda, Calif., home of the nation’s first hospital-based proton therapy facility. “With x-rays, you can control only the size and shape of the dose. With protons, you can control the beam in the third dimension, as it goes into the patient, so you can control where it gives off the maximum amount of radiation, and you can stop it in the patient within a matter of a few millimeters. So it allows you to miss more normal tissue and, in some situations, to increase the dose to try and improve the cure rate.”

In fact, said Slater, the cure rate associated with proton therapy sometimes exceeds that of conventional radiation, and the technology is always improving. “Even though we’ve been using this treatment for 20 years, we’ve made dramatic changes in how we deliver proton therapy. We’ve expanded what we’ve been able to do and are learning, through new technology, how to treat some cancers that we couldn’t treat this way 10 years ago. So it’s kind of an evolving technology.”

However, randomized trials have not yet compared proton beam therapy and conventional radiation therapy. So far, proton therapy has come closest to fulfilling its promise in the treatment of childhood cancers and in cancers located in hard-to-reach parts of the body. “We think the people who are most likely to benefit will be young children, adolescents, and young adults with cancer, who have a very good chance of being cured and living into adulthood and having a long life, but who are very sensitive to the long-term effects of radiation because their organs are still developing,” said Robert L. Foote, M.D., chairman of the department of radiation oncology at the Mayo Clinic in Rochester, Minn.

“There are certainly some situations in which protons have a significant theoretical advantage,” said Joel E. Tepper, M.D., Hector MacLean Distinguished Professor of Cancer Research at the University of North Carolina School of Medicine in Chapel Hill, and a consultant on the New York Times article. “But there are other situations in which you wouldn’t expect protons to have much advantage at all, and where they might even have some disadvantages. The major argument I’ve made over the years is that protons should be studied formally to decide whether the theoretical advantages are clinically real and to determine what the proper usage of protons really is.”

Doctors already understand the physics underlying how protons act in the body, Tepper said. “Some would argue that if the calculations show a physics advantage, there almost has to be a clinical advantage. I agree that our understanding of the physics of how protons behave in tissue is extremely good, but the biological implications of that, and the impact on patients, are still not clear. I think time will tell to what extent the promise of proton therapy is real.”
Proton treatments are effective against many types of cancer, so it is appropriate for Medicare to pay for them, Tepper added. “The harder question is, should they be reimbursed at a greater rate than for x-rays? In other words, if it’s not shown that protons are better than x-rays, should society pay more to use something that’s not clearly any better?”

“People have been saying that for 20 years, so it’s nothing new,” Slater responded when asked about claims that few good data support the use of proton beam therapy. “You have to work your way through phase I and phase II studies before you get to phase III. The science of what protons can do is, I think, very well understood. The question that really needs to be answered is, how do we best optimize it?”

The Longer View
In Foote’s opinion, long-term data exist to show that proton beam therapy is cost-effective. He cited a study by Jonas Lundkvist and colleagues at the Karolinska Institute in Stockholm, which used a Markov simulation model to calculate the potential benefits of proton therapy for children with medulloblastoma. They determined that initially, proton beam therapy would be more than twice as costly as conventional x-ray therapy, but over time, the adverse effects of conventional radiation, such as growth hormone deficiency and reduction in IQ, would be far greater in economic as well as human terms—at least according to the statistical model.

These authors obtained similar findings in a study of breast cancer in women. Conventional radiation is associated with a high initial breast cancer cure rate, but after about 15 years, patients have an increased risk of esophageal cancers, heart disease, lung disease, and cancers in the other breast, Foote explained. The Swedish investigators asked whether preventing only the heart disease that the radiation caused would help offset the initial cost of proton beam therapy. Their findings: “The more risk factors a woman had, such as diabetes, hypertension, or a history of smoking, the more cost-effective it became to use protons in their model because of the lower dose to the heart and the lungs and the esophagus and the opposite breast. Had they accounted for the harm caused to the lungs and the radiation-induced cancers [associated with conventional radiation], that would have made it appear even more cost-effective to use proton beam therapy.”

He believes such findings help justify the enormous costs associated with proton treatment. “We need to take into account not only the initial costs but also the costs associated throughout the patient’s lifetime in treating the cancer if it recurs, or with treating the side effects and complications related to radiation therapy. These patients have an excellent chance of being cured and living a long time, so we think the initial up-front costs will pay dividends over their lifetime.”

The Race for Patients
Some clinicians worry about using proton therapy in situations where it has no clear advantage, most notably for prostate cancer. Some facilities claim that proton therapy provides similar if not better cure rates than conventional radiation, without the side effects. Medicare is convinced, but the evidence to support this practice is rather thin. In fact, data presented at the recent Genitourinary Cancers Symposium in San Francisco showed that proton therapy was no more effective than intensity-modulated radiation therapy for treating prostate cancer and was associated with more toxic effects of the bowel.

Why the push for protons? Some believe it is part of a “medical arms race,” in which leading institutions compete for patients through the latest advances in technology. Others say it is a simple question of business. As a 2009 article in Forbes noted, the company behind many of the new facilities is the privately held ProCure, which raises money from investors and sells minority stakes to hospitals and oncology practices. Thus, medical centers must aggressively market these facilities so they can make money for the investors.

Not all centers have chosen that route. “We avoided that model because we didn’t want the financial pressure,” said Foote. Federal funding, grants, and donations pay for the Mayo facilities. However, private funders may exert pressure to keep costs down and develop more efficient machines, said Krocz. “If you look at cosmetic surgery, dental surgery, and laser eye surgery, which are predominantly paid for out of pocket, those technologies have shown tremendous improvements in results and customer satisfaction over the years. So there is something to be said for the pressures of the free market in that.” Whether proton beam therapy will follow a similar trajectory remains to be seen.

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