Protons for Prostate Cancer: the Dream Versus the Reality

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Proton therapy has generated much excitement among physicians and patients. During the period from 2006 to 2009, the number of prostate cancer patients treated with protons nearly doubled (1) and use continues to rise. There are 11 operational proton facilities in the United States, opening at a rate of more than 1 per year over the past 6 years. Why is everyone so excited? There are at least three reasons. Two are clear, and one is complex.

First, protons are a new technology. Although, proton therapy has been around for more than 20 years, it is viewed as a new or advanced technology. Everyone in the United States wants new; it sells both breakfast cereal and therapies.

The second reason is reimbursement: The current method of reimbursement by Centers for Medicare & Medicaid Services (CMS) is based on cost and not effectiveness. Prostate cancer proton treatment is delivered quickly because it uses just a few beams (high throughput) and there are many men with prostate cancer (high volume). High reimbursement per case × High throughput × High volume = High profit.

References


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The third—and complex—reason is physics. Protons have some theoretical advantages over photons. Protons are charged particles that deposit only a low dose as they enter the body and deliver most of their energy over the last few millimeters of their range (the Bragg peak). Essentially no radiation passes this point. Therefore, protons have the potential to treat a tumor while giving less radiation to normal tissues, which is the holy grail of radiation therapy. Unfortunately, some “dragons” may keep the grail from being reached. First, because the Bragg peak of a single energy is too focused to treat a tumor, protons of different energies must be combined to broaden the peak. This increases the entrance dose. Second, because of uncertainty about how far these protons will travel, the high-dose region is typically extended several millimeters beyond the target. Third, protons are susceptible to changes in tissue density, so slight changes due to respiration or gas motion during a given treatment or tumor shrinkage or rectal filling over the course of several treatments can allow high doses to escape beyond the planned region into normal tissues or cause them fail to reach the far edge of the target. Intensity-modulated (photon) radiotherapy (IMRT), which has become the standard of care, conforms the high-dose region to the prostate better than current proton therapy. Thus, although 20 years ago it seemed clear that protons should be superior to photons, the superiority of current proton therapy over IMRT photons is no longer certain.

In this issue of the Journal, Yu et al. (2) examine the patterns of use, cost, and early toxicity of modern proton therapy for prostate cancer. They performed a retrospective study of all Medicare beneficiaries aged 66 years or older who received proton radiotherapy or IMRT during 2008 and 2009. They identified factors associated with the receipt of proton radiotherapy and its cost. They also compared early genitourinary, gastrointestinal, and other toxicities experienced by patients treated with each modality. Not surprisingly, patients who received proton therapy were younger, healthier, and of higher socioeconomic status than patients who received IMRT. With few proton centers across the country, patients must seek them out, often travel long distances, and stay for 7 to 9 weeks of therapy. Median Medicare reimbursement was $32,428 for proton therapy and $18,575 for IMRT. As alluded to, this differential is likely a key driver in the spread of proton centers, despite their high building cost of $125 to $200 million per facility.

So what was the outcome of treatments? Cancer control data will not be available for many years because of the relative indolent nature of prostate cancer, but it is unlikely that a difference will emerge (3,4). Was toxicity decreased? Six months after treatment, men treated with protons had slightly less genitourinary (GU) toxicity (6% vs 10%; P = .03), but this difference disappeared at 12 months. There was no difference in gastrointestinal or other toxicities at any time point. Proponents of proton therapy may argue that any reduction in toxicity is worthwhile. However, is this small transient difference enough to justify a 70% higher cost per patient? Also consider a recent Surveillance, Epidemiology, and End Results Medicare analysis of patients treated during the period from 2000 to 2009 (4), which found a lower rate of gastrointestinal toxicity in patients treated with IMRT than in those treated with proton therapy.

These studies have weaknesses. It is assumed that one can assess toxicity by evaluating billing codes, but toxicities are not well graded, and many could be missed. We have no dosimetric data evaluating the radiation delivery. These are all problems associated with retrospective, population-based studies, as the authors are aware. Therefore, a rigorous comparison of protons vs photons cannot yet be made.

Recently, the emerging technology committee of the American Society for Radiation Oncology published an evidence-based review of proton beam therapy, which concluded that, although proton therapy holds promise, there is insufficient evidence that it is superior or even comparable to photon radiotherapy in most cancer sites (5). The National Cancer Institute, Institute of Medicine, Agency for Healthcare Research and Quality, and Centers for Medicare and Medicaid Services have called for randomized studies. We should commit to running and encouraging patients to participate in randomized trials of photons vs protons because we are uncertain that protons, as they are delivered in 2012, produce a superior outcome to IMRT photons. In a recent survey study, 59% of patients stated they would either “definitely” or “probably” participate in a randomized study comparing IMRT and proton beam radiotherapy (6). Although it seems unlikely that proton therapy will be superior to IMRT photons for prostate cancer, protons may be superior for tumors in which the elimination of the low-dose regions might decrease normal tissue injury (eg, lung cancers, when combined with chemotherapy). However, this is a hypothesis that must be tested. Declaring that proton therapy is new, awarding it high reimbursements, and stating that it has theoretical dosimetric advantages over photons is not acceptable. We need prospective clinical trials directly comparing protons to IMRT photons.

References

Note
The authors have no conflicts of interest to declare.

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