The Proton Beam Debate: Are Facilities Outstripping the Evidence?

By Merrill Goozner

A recent report from the Agency for Healthcare Research and Quality (AHRQ) found no evidence to support claims that cancer patients undergoing pricey proton beam radiation therapy (PRT) achieve better outcomes or experience fewer side effects than patients receiving traditional photon radiation.

In the report’s wake, proton therapy practitioners are pushing for the first trial comparing the two approaches for prostate cancer, which is the fastest growing use of PRT. The hope for PRT is that it will cause less collateral damage to surrounding nerves and tissue than intensity-modulated radiation therapy (IMRT), the most advanced form of traditional photon radiation.

“It hasn’t proven itself to be superior,” said Anthony L. Zietman, M.D., professor of radiation oncology at Harvard Medical School in Boston, whose affiliated Massachusetts General Hospital runs one of seven operating proton beam cancer treatment centers in the U.S. “We’ve applied for a comparative-effectiveness grant to do a head-to-head trial with IMRT with the same radiation dose,” he said. The primary endpoint is quality of life.

Even if funded, it will be years before the results of such a trial are known. With dozens of facilities already built or in development worldwide (see Stat Bite), use of the technology and the controversy surrounding it are bound to grow. In the U.S., where at least three new $100 million-plus proton beam facilities are either under construction or in the planning stage, the costly treatment could dramatically increase Medicare spending on prostate cancer care alone.
The AHRQ technical brief, published last November, identified 243 published articles based on clinical trials using PRT. Fully 220 of the trials were single-arm studies and 185 of those were retrospective analyses. Just eight comparative, randomized, controlled trials involving PRT have taken place, and most of those compared use of the technology to itself at different doses of radiation. They did not compare groups who received similar doses of radiation by different methods.

“No trial reported significant differences in overall or cancer-specific survival or in total serious adverse events,” the report said. The study also identified nine nonrandomized comparative studies but said that none used advanced statistical analyses to adjust for confounding variables and none found PRT “significantly better” than alternative treatments.

“The few randomized trials that were performed ask interesting questions, but not the ones that can inform us what happens in most common cancers,” said Teruhiko Terasawa, M.D., of the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center, which performed the analysis for AHRQ. He wrote in an e-mail that the trials “tend to research comparisons that are not pertinent to our basic question: They do not compare proton/particle beam treatment to contemporary alternatives, and they do not deal with common cancers.”

The only one of the eight randomized trials that showed a statistically significant difference between proton and photon therapy compared PRT to brachytherapy (inserting a radioactive source inside or adjacent to the tumor) for eye melanoma. The study “found better local control rate of eye melanoma in helium [proton] therapy compared to a more ‘conventional’ type of radiation therapy,” Terasawa said in an e-mail. “Note that eye melanoma is a relatively rare disease,” he added.

One of the larger trials highlighted in the report did involve prostate cancer patients,
some of whom have become vocal advocates of PRT because of its promise to reduce side effects such as impotence and urinary incontinence. However, the trial, which originally appeared in 2005 in the *Journal of the American Medical Association*, wasn’t designed to answer those questions. It involved 393 prostate cancer patients treated by radiologists at Loma Linda University Medical Center in California and Massachusetts General Hospital, the two oldest proton treatment centers in the U.S., between January 1996 and December 1999. Patients were randomized to receive either low or high doses of proton therapy after photon radiation. At 5 years, there was no difference in overall survival rates between the treatment groups (97% versus 96%). Ten deaths occurred in the conventional-dose group (two related to prostate cancer) and eight in the high-dose group (none related to prostate cancer).

However, those receiving higher doses of PRT had twice the incidence of acute urinary and rectal complications, 2% versus 1% of patients in the low-dose arm, suggesting that proton therapy’s side effects were dose dependent. A 10-year follow-up, recently published in the *Journal of Clinical Oncology*, showed no change in the original findings. “It showed few side effects, but not fewer than any other therapy,” Zietman, the study’s primary author, said.

The idea that PRT would be a more benign form of radiation therapy had an appealing theoretical basis when first introduced in the 1970s. Positively charged hydrogen or helium particles, generated by huge cyclotrons, enter the body with a relatively low level of ionizing energy. They deposit a dose along their path but do not reach a peak until just before they come to a rest at the tumor site. This late-blooming characteristic of ion radiation is called the Bragg peak, after the physicist who discovered the phenomenon in 1903. Also, the power behind the protons determines their travel distance once they leave the beam line and enter the body. By adjusting the starting point, PRT radiologists could, in theory, minimize the damage caused both before and beyond the Bragg peak point.

However, practical limitations come into play when clinicians deploy ion radiation. Tumors are not a point in space. They have depth. That means that PRT radiologists have to stagger the starting and arrival points of the proton beams in order to hit the entire tumor. “Once we stagger those Bragg peaks, we get multiple levels of dose at the entrance area,” said Indra Das, Ph.D., director of medical physics at the Midwest Proton Radiotherapy Institute at the Indiana School of Medicine in Bloomington. Surface and adjacent tissue areas can receive doses “as high as 80%” of the maximum dose delivered to the tumor site, he said.

**Photons Versus Protons**

Photon therapy, in contrast, gradually loses energy along its journey, so the beam at the entry point must have considerably higher energy than at the tumor site. The earliest forms of photon radiation caused substantial collateral damage to healthy tissues and carried an increased risk of developing new cancers.

However, advances in technology have reduced those effects. Radiologists now have machines with multiple beams, using multiple entry points, that concentrate their energy at the tumor site. This approach reduces the amount of radiation absorbed by healthy tissues along any individual beam pathway. Radiologists can also modulate the level of radiation along a single beam (IMRT), which further minimizes the damage. And in recent years, they have begun taking computed tomography scan images of the cancer site just prior to radiation treatment, which allows more precise positioning of the patient, and they can implant markers inside tumors that allow for precise image-guided radiation therapy.

These advances have allowed radiologists using traditional photons to reduce side effects compared with earlier iterations of the technology. “IMRT for prostate cancer was associated with significantly reduced incidence of rectal bleeding after radiation, lowering the rate to 3% from a general range of 15%–20% when using [prior forms of] high-dose radiation,” said Michael J. Zelefsky, M.D., professor of radiation oncology at Memorial Sloan–Kettering Cancer Center in New York. “When we recently looked at those results after 10 years, the low risk of rectal bleeding remained very, very low.”

These advances have also allowed radiologists to use photon radiation against some of the hard-to-treat cancers for which PRT was initially thought ideal, such as head-and-neck cancers where the tumor wraps itself around the spine at the base of the skull. “Now we can give 400–500 beams and break each one up to a hundred parts,” said Theodore Lawrence, M.D., chairman of the department of radiation oncology at the University of Michigan and a proponent of traditional photon therapy. “These techniques allow us to treat the doughnut and not the hole.”

PRT proponents remain convinced that protons are a superior form of radiation despite the absence of comparative proof, especially for tumors in sensitive areas where damage to adjacent tissues can be life altering. “Most of the tumors I treat are relatively rare tumors for which the need to do dose escalation is well established,” said Allan Thornton, M.D., medical director of the Midwest Proton Radiotherapy Institute. He highlighted ocular melanomas, skull-based sarcomas, paraspinal tumors, parapharyngeal tumors. “These tumors were all treated with regular radiation over the years with suboptimal results,” he said.

**Pediatric Cancers**

Thornton also pointed to the advantages of using PRT in pediatric cancer cases. Young
patients run a heightened risk of developing other cancers later in life from the radiation exposure. Long-term developmental issues also exist for using radiation against head-and-neck tumors in children, including intelligence deficits and hormone imbalances. “We can treat with much less of the frontal lobe and hypothalamus being hit, which control the pituitary gland,” Thornton said. With traditional photon radiation, “you have to replace the hormones, like thyroid and growth hormones, and it is a lifelong thing. With protons, we still have to replace them but only in a one-in-three amount.”

Even proton skeptics see the value in the technology’s use in children. “This is probably the best case for proton therapy even though there are no hard data,” said Lawrence of the University of Michigan. “Certainly the theoretical argument is the strongest in treating kids.”

However, rare pediatric cancers are not the reason for the proton treatment center mini-building boom that is now under way. Proton therapy can cost up to $90,000 for a course of treatment under established Medicare reimbursement policies. That’s more than double the cost of conventional photon therapy. “Many of the new centers have no plans for treating pediatrics and spine tumors,” said Zietman. “Their business model is entirely prostate based.”

No debate exists about which approach produces better outcomes for burning out tumors. “If you get the same dose, the outcome is going to be the same,” Thornton, a proton proponent, said. “But if you treat the rectum to a higher dose, the end result is a higher incidence of rectal complications, from 1% with protons over 5 years to 3%-5% with regular photons.” No randomized trials to back that claim are available.

“I’m more than happy to do a randomized, controlled trial in prostate cancer,” Thornton said, “as long as there are good patient-reported outcomes tools to really measure the quality-of-life outcomes.”