Proton Radiotherapy for Prostate Cancer: How Did We Get Here, and Where Do We Go From Here?

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Despite the promise of proton therapy, comparative evidence has yet to definitively demonstrate its clinical benefit over other forms of contemporary radiation for prostate cancer.

Proton radiotherapy is an important technology for cancer treatment. By reducing and even eliminating unwanted radiation dose to surrounding tissue, proton therapy has the potential to lessen the toxicity of radiotherapy. The promise of precisely delivered radiation doses has led to the adoption of proton radiotherapy in selected centers across the United States.[1] Currently there are 11 proton centers in operation, with 8 centers under construction and 1 in planning. There are 11 additional smaller superconducting synchrocyclotron proton radiotherapy machines currently in development.[2] However, despite the promise of proton therapy, comparative evidence has yet to definitively demonstrate its clinical benefit over other forms of contemporary radiation for prostate cancer.

Following the first postulation by Wilson in 1946[3] that high-energy protons could penetrate into tissue to a depth that could potentially treat small volumes of tumor within the body, prostate cancer was one of the earliest organ sites to be targeted by proton radiotherapy.[4] In-silico studies comparing the theoretical distribution of radiation dose for prostate intensity-modulated radiotherapy (IMRT) and proton radiotherapy have suggested that the benefit from older 3-D conformal proton radiotherapy was limited to a reduction in low and moderate doses of radiotherapy to the bladder and rectum.[5-7] However, newer intensity-modulated proton radiotherapy (IMPT), currently in the earliest phases of adoption,[8] may allow for even more significant reduction of dose to surrounding normal tissue.[6]

Clinically, there have been multiple retrospective and prospective single-arm studies showing excellent outcomes for both proton therapy[9,10] and IMRT[11,12] in patients with prostate cancer. Comparative claims-based analyses[13-15] and retrospective quality-of-life studies[16] have shown mixed results for proton radiotherapy compared with IMRT. Certainly these studies have limitations—and randomized trial data are sorely needed. The definitive randomized trial of proton radiotherapy vs IMRT for prostate cancer, PARTIQoL,[17] led by Massachusetts General Hospital and the University of Pennsylvania, is now actively accruing.[18]

Because of the current lack of strong clinical evidence supporting the relative benefit of proton radiotherapy compared with IMRT in the treatment of prostate cancer, some private insurers have announced that they will no longer cover proton radiotherapy for prostate cancer.[19] Responding differently to the same circumstances, the American Society for Radiation Oncology (ASTRO), as part of the American Board of Internal Medicine's Choosing Wisely campaign, has recommended that patients who receive proton radiotherapy for prostate cancer enroll in a clinical trial or prospective registry.[20] Therefore, in contrast to insurers, who increasingly are not covering proton therapy for prostate cancer, ASTRO continues to strongly support coverage with evidence development,[21] recognizing that proton beam therapy is not a new technology, and that insurance coverage of prostate cancer patients treated on trials or within prospective registries is important to the gathering of comparative effectiveness data. The question thus arises: How did we get here?

Steinberg and Konski have outlined the historical, regulatory, and economic factors that have contributed to the proliferation of proton radiotherapy in the United States.[22] Beyond the practical reasons they offer for why proton radiotherapy proliferated for prostate cancer, another factor to consider is that innovation in radiation technology occurs at a fast pace, without a clear framework for investigating whether the innovations translate to incremental, as well as measurable and clinically meaningful, improvements in patient outcomes. One approach to determining Medicare coverage and reimbursement for new technologies was recently proposed. Medicare would assign new medical technologies to one of three payment categories based on comparative effectiveness evidence. The authors write: “After an initial 3-year period, if services with insufficient evidence do
not provide additional evidence demonstrating superior comparative clinical effectiveness, payment would drop to reference pricing levels.”[23] The authors highlighted the example of IMRT as a perfect setting for testing this approach. However, for clinical studies examining the effectiveness and toxicity of treatments, especially in prostate cancer, 3 years is simply too short. This proposal is only one of many such proposals under discussion. Clearly there is a need for intensive dialogue around how best to generate evidence for new technologies in radiation therapy. The problem of rapid innovation outpacing comparative evidence and broad consensus on best practice is hardly unique to radiation oncology,[24,25] or even to medicine.[26] It may be a hallmark of truly transformative technology that the implications of that technology are impossible to predict until it is adopted. Realizing this, where can we go from here? Will the continued cycle of innovation, investment, and adoption of new radiation technology always outstrip our ability to evaluate the technique clinically in a timely manner? At the very least, it is time for radiation oncology to strive to perform more timely and more widespread clinical investigations of new radiation technologies. Specific funding for evaluation of the clinical comparative effectiveness of new radiation modalities is sorely needed. Currently, only 1.6% of National Institutes of Health (NIH) funding supports radiation oncology research,[27] and of this amount, only 7.6% (less than 0.1% of overall NIH funding) supports clinical investigations, presumably the category of research into which the testing of the comparative effectiveness of new radiation technologies would fall. The importance of federal funding for research specific to radiation technology is crucial in the absence of industry-sponsored randomized controlled trials (RCTs) for radiotherapy (RCTs investigating radiation alone account for only 4% of all industry-funded trials in a recent survey[28]). Because radiotherapy affects roughly two-thirds of all patients with cancer,[29] funding of comparative effectiveness trials and prospective outcomes registries for radiotherapy is critical for all cancer patients. We are confident that the field of radiation oncology will continue to innovate. However, increasing funding for radiation-specific comparative effectiveness research and continued coverage of promising therapies that are being evaluated in a timely and rigorous prospective manner is critical if we are to balance innovation and promise with data and value.

**Financial Disclosure:** Proton radiotherapy is available at Massachusetts General Hospital (JAE) and at the Abramson Cancer Center at the University of Pennsylvania (JEB), but not at the Yale School of Medicine (JBY).

**References:**


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