Proton Therapy for Prostate Cancer: Show Me the CER!

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Hoppe et al present an excellent review of the physics relevant to an understanding of proton therapy—and of the available literature assessing the use of proton beams in the management of prostate cancer. This subject has generated a great deal of discussion in both scientific and health policy circles over the past few years, and some context and commentary seems appropriate. It is particularly noteworthy that, as the authors point out, this technology that has existed for half a century in many ways can still be considered a new and emerging technology.

While it is not my intent to extensively debate the physics and clinical studies supporting the use of protons in prostate cancer, it is important for readers who may be just now learning about these issues to understand that many of the underlying assumptions supporting proton therapy are still the subject of intense debate. The physics of the Bragg peak is well described. However, the question of how to give a full description of the dose ultimately delivered to the prostate remains problematic, on account of the inhomogeneity and uncertainty in the penumbra, and also because of organ motion.[1]

Levin et al[2] reviewed the role of proton therapy across a spectrum of adult and pediatric cancers, and suggested that it is likely to be most valuable in the treatment of tumors “located next to critical structures such as the spinal cord, eyes, and brain, as well as for pediatric malignancies.” They concluded that randomized clinical trials are still required in prostate cancer. Others have argued that randomized clinical trials are neither feasible nor appropriate given the clear presumed superiority of protons based on their physics.[3] But one must ask, will the clear benefit we believe proton therapy enjoys in an idealized dosimetry plan always translate into a clinically meaningful difference? Some have reported that many real world plans are no better with protons, and occasionally inferior, depending on whether one is looking at the high-dose region or the low-dose region.[4] Mohan et al,[5] in an abstract, found that despite the widespread assumption that proton therapy would spare more normal tissue, the low-dose region in normal lung was paradoxically worse after proton therapy than after standard treatment with intensity modulated radiation therapy (IMRT).

It is, however, the health policy implications of the authors' discussion that I would like to focus on. No reader of this journal will be surprised that the cost of medical care is driving a national conversation on health policy. As of 2010, Medicare spending alone represented 3.5% of the gross domestic product (GDP)—and all health care spending, a staggering 17% of GDP.[6] Without change, Medicare spending alone is projected to more than double over the next 30 years. Roughly 12% of this increase represents physician services, and it is from this pool of dollars that many new large outpatient proton facilities, both planned and completed, will be funded.

Hoppe et al rightly point out the importance of comparative effectiveness research (CER) in their report. However, the experience here is sobering. Oncology is still grappling with the way in which new treatments are integrated into clinical practice. There is a well-documented history of the adoption of newer, fancier, and often more expensive technologies in advance of CER—and often in advance of clinical trial results. Brachytherapy for prostate cancer, for example, was pioneered by a relatively small group of practitioners and fueled by patient demand long before any CER data were published. Recent reports from the Institute for Clinical and Economic Review (ICER) looked at the clinical benefit, cost, and economic value for a variety of treatments for early prostate cancer.[7] Starting with a systematic literature review, their analysis showed, with a high degree of confidence, that brachytherapy was both effective and cost-effective. However, this report was released in 2009, roughly two decades after widespread acceptance of brachytherapy.

More recently, Nguyen et al[8] described the rapid adoption of IMRT for the management of prostate cancer, based on an analysis of the Surveillance Epidemiology and End Results (SEER) database for
the years 2002 to 2005. During that period, the utilization of IMRT went from 29% to 82% without benefit of any CER data supporting its use. (One such study, subsequently published by Konski et al[9] in 2006, showed that an increase in Quality Adjusted Life Years [QALYs], resulting from a reduced risk of late rectal toxicity, supports the use of IMRT in this setting.)

This problem of early adoption of new technology is not unique to radiation oncology. Similar trends have been seen in the rapid adoption of minimally invasive prostate surgery, specifically robotic prostatectomy. In the same report, Nguyen[8] showed a jump in the less invasive surgery from 1.5% to 28.7% during the same 2002-to-2005 interval. Arbash and Glied[10] report a 75% growth in the availability of robotic prostatectomy in the years 2007 to 2009, and it may be assumed that this trend has only continued. Still, CER data supporting these choices are lacking.

Hoppe et al discuss the CER work by Konski et al,[11] which found that despite highly favorable projections, proton beam therapy for prostate cancer was not cost effective. Clearly, innovations such as hypofractionation can be expected to reduce the cost of future proton therapy; however, any anticipated reduction must be weighed against the reality that hypofractionation is being actively studied in photon therapy as well.[12] So as the cost of one treatment changes, so too do the costs of other interventions. Thus, it is impossible to assume, a priori, what the comparative effectiveness of a given treatment will be.

So how can we ever resolve this conundrum? Clearly, new research is called for, which may include randomized clinical trials. Realistically, such research may also include creative and innovative trial designs; pragmatic clinical trials; adaptive trials; and observational studies, including registries.[13] As with new surgical therapies, randomized clinical trials are unlikely to be completed before these therapies become widely available. Nonetheless, we look forward to the CER that is required to inform future treatment choices. If the promises of protons are to be realized, then their value to both the patient and the health system must be proven.

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