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Finding Value for Protons: The Case of Prostate Cancer?

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The standard radiotherapy treatment for prostate cancer is intensity-modulated radiotherapy (IMRT). An alternative option is proton beam therapy (PBT). PBT is a safe and effective treatment, but does it add value over IMRT? We explore this controversial question by examining the available dosimetric and clinical evidence.
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Introduction

For men in the United States, prostate cancer is the most common malignancy.[1] When the disease is localized, it can be cured by radiotherapy.[2,3] This treatment is typically intensity-modulated radiotherapy (IMRT)[4]—an external beam of photons sculpted to closely fit the target. These photons are massless, uncharged quanta of electromagnetic radiation. They pass completely through the patient and deliver dose along their entire path.

An alternative treatment is proton beam therapy (PBT). Unlike photons, protons are heavy, charged particles. PBT stops within the body and delivers virtually no dose past the target, thus reducing radiation exposure to normal tissues (Fig).[5] PBT is a safe and effective treatment for prostate cancer[6–8]—but does it add value over IMRT? In the article that follows, we explore this controversial question.[9,10]

Value: A Two-Part Equation

First, we must define value. A common formulation is health care outcomes divided by cost.[11] This equation's denominator poses a challenge for expensive technologies. For example, prostate PBT costs ~$13,000-14,000 more than IMRT,[12,13] although this gap may shrink with cheaper PBT equipment[14] and shorter-course treatment.[15]

To provide value, PBT must therefore improve health outcomes relative to IMRT. This could mean either better cancer control or fewer side effects. It seems unlikely that PBT will improve cancer control: few men die from lower-risk prostate cancer,[2] and escalating the dose for higher-risk disease beyond current standards may not be safe.[16] Even under favorable assumptions—that further dose escalation is feasible and would enhance biochemical control—PBT may still be too expensive.[17]

Therefore, in our view, the value proposition for PBT rests on whether this technology can meaningfully reduce side effects. Otherwise, most cost-effectiveness analyses raise doubts about PBT.[18,19] According to 1 study, an improvement in composite toxicity of 41% may be necessary to reach traditional value thresholds.[20]

Radiotherapy Side Effects: Scope of the Problem

The principal potential side effects from prostate radiotherapy are bladder, bowel, and erectile dysfunction. The precise

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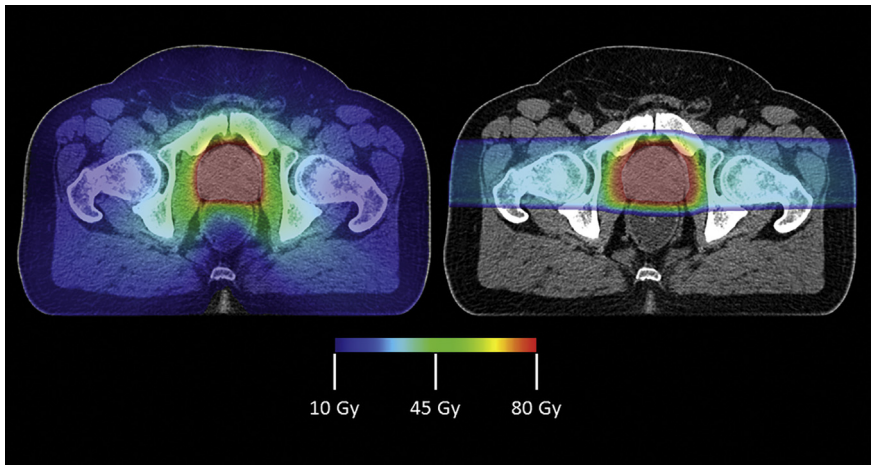

Figure Comparison of intensity-modulated radiation therapy (left) vs proton beam therapy (right) for intact prostate cancer. Gy, gray. Figure courtesy of Maura Kirk, MS, from the University of Pennsylvania. (Color version of figure is available online.)

frequency and magnitude of these toxicities is challenging to pinpoint,[21] but we can reach some general conclusions: in the short term, radiotherapy causes moderate rates of transient urinary and rectal irritation; in the long run, it causes moderate rates of erectile dysfunction and a smaller risk of rectal complications.[22–25]

One source of high-quality toxicity data is the Prostate Testing for Cancer and Treatment (ProtecT) trial, which randomly assigned men to active surveillance, surgery, or radiotherapy.[25] These data have 2 particular strengths. First, side effects were prospectively collected and recorded as patient-reported outcomes. Second, the active surveillance arm provides a strong comparator group, helping to distinguish radiotherapy effects from general aging. The data also have important caveats. Patients in this pragmatic trial could receive medical treatment for side effects, so the reported toxicities also reflect the effect of those interventions. Furthermore, men in the active surveillance arm could undergo radical treatment over time, potentially obscuring differences between the arms. This phenomenon was initially rare (11% at 6 months, 13% at 1 year) but eventually became more common (35% at 6 years).[25]

Men in the ProtecT trial reported the expected bladder, bowel, and erectile toxicities. For example, radiotherapy caused transient urinary irritation.[25] At 6 months, radiotherapy increased nocturia rates by 28% compared to surveillance (59% vs 31%). At 6 months, radiotherapy caused worse irritative voiding scores compared to surveillance (mean score 5.1 vs 3.8, on a 20-point scale[26]). Urinary side effects resolved by 1 year.

Radiotherapy also caused rectal toxicity,[25] as measure by the Expanded Prostate Cancer Index Composite (EPIC) score. At 6 months, more men reported that their bowel habits had a moderate-to-severe impact on quality of life after radiotherapy compared to surveillance (10% vs 3%). This difference faded over time. However, a long-term increase in bloody stools was seen. At 6 years, more men reported bloody stools half of the time after radiotherapy compared to surveillance (6% vs 1%).

Sexual side effects were also seen.[25] At 6 years, 73% of men treated with radiotherapy typically did not have erections firm enough for intercourse. However, normal aging also impacts erections. The effect of age was investigated in a subgroup of the active surveillance arm that never received any radical therapy. At 6 years, 62% of these untreated men reported erections that were not firm enough for intercourse. Therefore, radiotherapy increased long-term erectile dysfunction by about 10% in absolute terms.

Finally, radiotherapy can cause secondary cancers.[27] This endpoint was not assessed in the ProtecT trial, but several retrospective studies have examined the question.[28] The absolute risk may be about 0.3%-0.5%,[28,29] although it is challenging to exactly quantify.

Of note, the ProtecT trial used photon treatment delivered by an older technique called three-dimensional conformal radiotherapy. The current standard, however, is IMRT.[4] Two recent nonrandomized studies suggest that IMRT produces a similar pattern of toxicity, but the magnitude may be slightly less.[30,31]

The first study included about 550 men receiving radiotherapy or active surveillance between 2011 and 2013.[30] Radiotherapy treatments were IMRT with image guidance. Patient-reported side effects were measured prospectively using the Prostate Cancer Symptom Indices. Compared to active surveillance, IMRT caused urinary irritation at 3 months (12 points on a 100-point scale), bowel issues at 3 months and 2 years (5 points and 4 points on a 100-point scale, respectively), and sexual problems at 3 months and 1 year (14 points and 10 points on a 100-point scale, respectively).[30]

The second study included about 1,000 men receiving radiotherapy or active surveillance between 2011 and 2012.[31] Radiotherapy treatments were IMRT in 81% of cases. Patient-reported side effects were measured prospectively using the EPIC score. Compared to active surveillance, IMRT caused more bowel issues at 6 months (6 points on a 100-point scale). No significant increases in urinary irritation or sexual side effects was detected at any time point.[31]