Proton-Beam vs Intensity-Modulated Radiation Therapy

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External-beam radiation is a highly effective curative treatment option for men with localized prostate cancer.[1,2] Over the past several decades, efforts have been made to improve the “therapeutic ratio” of radiation by increasing dose to improve cure rates without causing a substantial increase in side effects. Due to its potential to create superior dose distributions, proton therapy is considered by many to be the best available form of external radiation therapy. Here we will critically examine the evidence supporting the use of protons in the treatment of prostate cancer.

Photon beams deposit their dose continuously as they traverse tissue so that the volume in the beam’s path beyond the primary target also receives a measurable amount of falloff dose. Proton beams, on the other hand, deposit a large share of their dose in the “Bragg peak” over a relatively short distance close to the end of the particle’s track in tissue. Beyond the Bragg peak, the position of which is determined by the beam energy, protons deliver almost no additional exit dose. This property has allowed proton beams to effectively spare critical structures that are located very close to the target, and thus, this modality has been used successfully in the treatment of certain optic tumors, central nervous system tumors, base-of-skull diseases, and pediatric malignancies.[3] In theory, the superior depth-dose characteristics should always give protons a clear advantage over photons if the photon beams are replaced one-by-one with proton beams. However, localization of the dose in the Bragg peak also makes the proton dose distributions highly sensitive to uncertainties in the particle range in tissue, which affects different treatment sites and beam directions to a varying degree. Additionally, using the same beam configuration for the proton and photon treatments is usually not practical. Thus, the extent to which the theoretical advantage of the proton dose can be engaged and realized differs among disease sites.

In the treatment of prostate cancer, the day-to-day variation in the patient setup, as well as rectal and bladder filling, may significantly affect the range of protons in tissue.[4] This makes some of the beam directions commonly used in photon therapy (eg, posterior-anterior) less suitable for proton irradiation. To minimize the effects of the range uncertainties, prostate patients are typically irradiated using opposed lateral proton beams, which generally forces at least a portion of the dose-limiting anterior rectal wall into the high-dose region. Therefore, demonstrating the potential advantage of protons is not as clear-cut in prostate cancer as in some other sites, and requires careful clinical and dosimetric studies, several of which are described below.

Dose Escalation Improves Cancer Control

There is currently ample evidence from five randomized controlled trials demonstrating that dose escalation can improve prostate cancer-specific outcomes, particularly for those with intermediate-risk disease based on prostate-specific antigen (PSA) level, clinical T category, and biopsy Gleason score. The earliest evidence comes from the M.D. Anderson Cancer Center, where 301 patients with T1-T3 disease were randomized to 78 vs 70 Gy (prescribed to isocenter). After a median follow-up of 8.7 years, the investigators found that the higher dose improved freedom from biochemical or clinical failure (78% vs 59% at 8 years, respectively; P = .004), with the greatest benefit seen in those with an initial PSA greater than 10 ng/mL (78% vs 39% at 5-years, respectively; P = .001).[5]
Similarly, a Dutch trial by Peeters et al randomized 669 patients with T1b to T4 prostate cancer to 78 vs 68 Gy (to isocenter) and detected an improvement in freedom from failure at 5 years (64% vs 54%, respectively; P = .02). On subgroup analysis, however, the investigators found that the benefit was limited to patients with intermediate-risk disease.[6]

A study from Ontario randomized 104 patients with intermediate- and high-risk disease to 75 Gy in 6.5 weeks delivered by external-beam radiation therapy (EBRT) plus implant vs 66 Gy in 6.5 weeks by EBRT alone and found that dose escalation reduced biochemical failure (29% vs 61%, respectively; P = .0024).[7]

More recently, a Loma Linda University/Massachusetts General Hospital (MGH) study of 393 mainly low- and intermediate-risk patients randomized to 79.2 vs 70.2 Gy-equivalents (GyE) used a mix of photons and protons and prescribed to the target volume. These investigators found that all risk strata of patients experienced a significant improvement in freedom from biochemical failure with the higher dose.[8]

Finally, Dearnaley et al have published their randomized trial from the British Medical Research Council showing that among men who all received short-course hormonal therapy, treatment with 74 vs 64 Gy resulted in improvements in 5-year outcomes for all patients.[9]

While none of the trials published to date has been powered to detect a difference in overall survival, the Radiation Therapy Oncology Group (RTOG) 0126 study is currently attempting to do just this by accruing over 1,500 patients to a large randomized trial of 79.2 vs 70.2 Gy.

**Protons for Dose Escalation: Evidence From Clinical Trials**

No randomized trials have directly compared the efficacy of protons and photons in the treatment of clinically localized prostate cancer. Clinical experience with the use of protons in dose escalation comes from the combined Loma Linda/MGH trial mentioned above. In this study, all patients received 50.4 Gy in 1.8-Gy fractions to the prostate and seminal vesicles using conformal photon therapy in a four-field configuration. The randomization was to either a 19.8-GyE or 28.8-GyE prostate boost via protons in 1.8-GyE fractions, to a total dose of 70.2 or 79.2 GyE. Overall, treatment to the higher dose with protons was tolerable, but came at the cost of an increase in late grade 2 rectal morbidity (8% vs 17%; P = .005).[8]

However, new preliminary data from an analysis of patients in this trial who received a detailed validated quality-of-life questionnaire suggest that there is no significant difference in long-term patient-reported quality of life between the high-dose and conventional-dose arms.[10] This evidence is a clear proof of principle that protons can be used to escalate dose without causing a significant difference in patient-reported quality of life, which is more relevant than physician-reported measures of toxicity.

The randomized trials using photons from the UK and the M.D. Anderson Cancer Center also had quality-of-life components, and it will be interesting to see whether they find additional patient-reported morbidity. It is currently unknown whether the use of protons for the entire course of treatment, rather than just the boost, could improve toxicity profiles further and allow for an even greater increase in dose. This is the subject of an ongoing Loma Linda University/MGH prospective study treating patients to 82 GyE with protons only.

**Physical Comparison of Protons and IMRT**

To have a fair assessment of the dosimetric trade-offs between protons and photons, one must compare proton therapy to the most conformal type of photon therapy currently available, which is intensity-modulated radiation therapy (IMRT). With IMRT, more beams are used than in conventional three-dimensional (3D) radiation therapy, and the fluence of each beam is modulated to create a highly target-conformal dose distribution capable of bending around critical normal structures such as the anterior rectal wall. In the United States, IMRT is becoming the dominant method of delivering external-beam radiation to the prostate.

Trofimov et al recently performed a dosimetric comparison of 10 patients whose treatment was planned with both protons (using the currently available 3D conformal proton planning methods) and photon IMRT to a total dose of 79.2 Gy (or GyE).[11] The proton therapy was planned using two lateral parallel opposed beams, while the photon IMRT was planned with seven coplanar beams (Figure 1). This study found that IMRT actually yielded better dose conformity (defined as the ratio of the prescription isodose volume to the volume of the corresponding target), reflecting the fact that a greater volume of nontarget tissue received the prescription dose of 79.2 Gy with proton therapy than with IMRT. Correspondingly, the V70 of the bladder (volume of bladder receiving more
than 70 Gy) was 50% higher with proton therapy than with IMRT, although the V70 of the rectum was not significantly different. FIGURE 1

Protons vs Photons

In the low-dose range, however, IMRT had worse performance characteristics than proton therapy due to the fact that IMRT spreads out the dose over several beams. The rectal V30 was reduced with protons by between 16% and 53% compared to IMRT.[11] Additionally, the total volume of normal tissue exposed to low and moderate doses of radiation was significantly higher with IMRT than with protons. Figure 2 illustrates the difference between the dose distributions from representative IMRT and proton plans on a single axial slice. For this same patient, the total volume of tissue irradiated to a dose of at least 10 Gy was 1.7 × 103 cm3 with proton therapy compared to 3.5 × 103 cm3 with IMRT. FIGURE 2

Dose Difference Between IMRT and Proton Plans

For the typical patient who receives these treatments, the concern is whether these differences in dosimetric profile between protons and IMRT might translate into differences in acute and late toxicity. Cheung et al from M.D. Anderson recently published the results of normal tissue complication probability modeling to predict bladder toxicity after prostate irradiation. These investigators found that those in whom the hottest 2.9% of the bladder received 78 Gy or more had a significantly higher risk of delayed grade 2 or higher genitourinary (GU) toxicity than those in whom the hottest 2.9% received less than 78 Gy.[12] This raises the possibility that conventionally delivered protons may therefore be no better than (or potentially even worse than) IMRT in terms of GU toxicity.

Similarly, given that rectal doses in the high-dose region appear comparable with IMRT and protons, there is concern that protons, as conventionally delivered, will not allow for dose escalation beyond what will be possible with IMRT. In the future, however, intensity-modulated proton therapy may allow for even more conformal boosting, as described below.

Finally, epidemiologic evidence suggests that hip fractures are associated with both pelvic irradiation and antiandrogen therapy, and given that many patients receive both treatments, and that opposed lateral proton beams deposit a significant amount of dose in the femoral heads, there is concern that proton radiation may result in more hip fractures than IMRT. Unfortunately, these types of questions can only be answered definitively in a randomized trial, for which there is currently an urgent need.

Controversies in the Use of Protons for Prostate Cancer

Second Malignancy Risk

Because IMRT exposes a greater amount of normal tissue to low-dose radiation than conventional 3D conformal photon therapy, it is believed to be associated with a higher risk of secondary malignancies than conventional photon therapy. For example, Hall et al have estimated based on data from atomic bomb survivors that patients who receive IMRT for prostate cancer would have a secondary malignancy risk of 1.75% at 10 years compared with 1% at 10 years for those who receive conventional photon therapy.[13] Since protons appear to expose less normal tissue to radiation than IMRT, they might be expected to confer a lower risk of secondary malignancies than IMRT. Miralbell et al assessed the potential
influence of improved dose distribution with proton beams compared to photon beams on the incidence of treatment-induced secondary cancers in pediatric oncology.[14] Two children, one with a parameningeal rhabdomyosarcoma and a second with a medulloblastoma, were considered. The investigators found that proton beams have the potential to reduce the incidence of radiation-induced secondary cancers for the rhabdomyosarcoma patient by a factor of > 2 and for the medulloblastoma case by a factor of 8 to 15, compared with either IMRT or conventional x-rays. However, these results are for treatments delivered with scanned proton beams, in which the secondary neutron dose component was limited to the neutrons produced within the patient’s body, and in the range shifter plates close to the patient’s skin surface. Although the difference is facility-dependent, neutron production will typically be higher in proton therapy using broad scattered beams and field-shaping devices such as apertures and range compensators (which is the method currently employed by most proton centers in the United States and abroad).

Hall has suggested that this method of passively scattering proton beams against a foil to produce a useful field size may result in an increase in the total body dose to the patient from neutron scatter beyond the acceptable limits, and actually lead to a higher risk of second malignancies than IMRT.[15] However, the data shown by Hall for neutron doses to be expected in proton therapy do not represent a typical scenario.[16]

Other investigators have shown experimentally that the actual amount of neutron leakage with scattered-beam proton therapy is likely much lower than suggested by Hall.[17,18] Wroe and colleagues at Loma Linda University used a microdosimeter to record the body surface dose out-of-field for an anthropomorphic phantom receiving a typical prostate proton treatment, and found overall very low doses outside of the field. At a distance of 60 cm from the field edge, the dose-equivalent for the patient-specific setup was 0.176 mSv/Gy, which would give a dose equivalent to that point of about 14 mSv over the total course of a typical 80-Gy treatment.[18] At MGH, a similar neutron dose measurement for a typical prostate treatment with protons found out-of-field dose levels that were highly concordant with the Loma Linda results. Recent investigation using Monte Carlo simulation has confirmed that the cumulative neutron dose for proton treatment was significantly lower than the scattered photon dose in IMRT, providing empiric evidence that the risk of secondary malignancies from protons is unlikely to be higher than the risk from IMRT.[19] However, one must keep in mind that experimental as well as theoretical results on neutron equivalent doses in proton therapy are subject to considerable uncertainties in the weighting factor reflecting the relative biologic effectiveness of neutron radiation.

It should also be noted that while second malignancies may be a major concern in younger populations and especially in pediatric populations, the issue has less of an impact on the treatment of older patients. Due to the protracted latency period of secondary malignancies (10–20 years), and due to the advanced age of many patients with prostate cancer, the absolute risk of developing a secondary malignancy from radiation during their lifetime is relatively small.[20,21]

Are Protons Cost-Effective?

The typical cost of a new proton facility at an academic center in the United States has ranged from about $100 million to $150 million, and while it may be possible to build scaled-down proton centers for significantly less money in the future, the question can reasonably be raised of whether proton therapy is worth the cost, particularly in a disease such as prostate cancer where the cure rates are so good and the complication rates are overall modest.

To help answer this question, Konski et al recently published a cost-effectiveness analysis incorporating Markov models to determine the incremental cost per quality-adjusted life year (QALY) of treatment with proton therapy vs IMRT for a man with intermediate-risk prostate cancer.[22] The model assumed a cost of $58,610 for protons vs $25,846 for IMRT. In addition, it assumed that IMRT would be delivered to 81 Gy and result in an 83% 5-year freedom from biochemical failure, whereas the proton therapy was modeled as being given to 91.8 GyE and it was assumed that this would result in a 93% 5-year freedom from biochemical failure without any increase in toxicity over IMRT. These assumptions were quite favorable to proton therapy, as prostate doses to 91.8 Gy have not yet been attempted, and it is unlikely that there would be no increase in toxicity at that dose, but even with these favorable assumptions, the authors were unable to show that proton therapy would be cost-effective. Specifically, they found an incremental cost-effectiveness ratio of $63,578 per QALY for a 70-year-old man and $55,726 for a 60-year-old man, both of which are above the $50,000 per QALY threshold that is typically used as a benchmark for a cost-effective intervention.

While the introduction of lower-cost, single-gantry proton facilities in the near future could change the results of this analysis, proton treatment for prostate cancer cannot be considered cost-effective.
Future Novel Uses for Proton Therapy in Prostate Cancer

Partial Prostate Boosting

FIGURE 3

Example of a Partial Prostate IMPT Boost

While prostate cancer is typically considered a multifocal disease, not all foci are of the same volume within any individual prostate. Some may be small and require only modest conventional radiation doses for control, whereas others may be more bulky and clearly need higher doses.[23] At present we are treating the entire prostate to the highest possible dose, but there may be a smarter way of using technology to focally modulate dose according to tumor bulk. Increasingly high-resolution, dynamically enhanced or spectroscopic magnetic resonance imaging is being used to identify dominant lesions.[24] This has led to interest in the strategy of treating the entire prostate to a conventional dose to control microscopic disease and then employing a partial prostate boost to the dominant lesion to a much higher dose than could safely be delivered to the entire gland. The rationale is that this might improve local control without causing a measurable increase in toxicity. The feasibility of this technique has been explored at a few centers in planning studies employing IMRT.[25-27]

Intensity-modulated therapy with protons (IMPT) allows one to create dose distributions that are more target-conformal than those achievable with photon IMRT[28] This technology may become available in the United States within the next few years and should make it possible to deliver highly conformal boosts to portions of the prostate without significantly increasing the dose to surrounding tissue. An example of what a partial prostate IMPT boost might look like is shown in Figure 3. Issues such as organ motion and proton range uncertainties will become absolutely critical when “sharp-shooting” such small lesions.

Real-Time Dosimetry With PET

FIGURE 4
Comparative Doses for Proton Treatment of a Pituitary Adenoma

An interesting property of proton therapy is that positron emitters are produced within the body along the proton path that can be detected on a positron-emission tomography/computed tomography (PET/CT) scan taken after the fraction is delivered. As recently reported by Parodi et al.[29] PET scans produced images that were highly concordant with the actual dosimetry of the proton therapy. Figure 4 shows the calculated doses for a pituitary adenoma treatment using orthogonal beams in the top panels compared to the measured and Monte Carlo–calculated doses from posttreatment PET scans in the bottom panels. The same are shown for a proton treatment with a single lateral field to the prostate in Figure 5. The dosimetric agreement between the PET measurements and the planned dose are not as good for the prostate as for the pituitary adenoma, likely due at least in part to motion and bladder filling. While there is further work to be done to account for these problems, this raises the possibility that PET/CT could be used to provide real-time dosimetric verification of prostate treatments in the future. This noninvasive method of verifying the delivered dose represents a form of quality control that would be quite unique in radiotherapy.

Conclusions

FIGURE 5

Comparative Doses for Proton Treatment of the Prostate

While there is growing enthusiasm for the use of protons in the treatment of prostate cancer, a review of the literature suggests that there is so far no clear evidence to show that proton therapy would be superior to highly conformal photon treatments. As the use of protons in prostate cancer will no doubt become more widespread in the coming years, there is urgent need for a randomized trial of IMRT vs protons to provide us with concrete clinical data about the relative merits and potential risks of each type of therapy. The possibility of launching such a trial is currently being explored by the RTOG. Until results from such a trial are available, we continue to view protons in prostate cancer as a modality with tremendous promise. As it comes with a relatively high price tag, however, proton therapy must remain under scrutiny until it has proven itself against the best possible alternative. This article is reviewed here:

Proton-Beam vs Intensity-Modulated Radiation Therapy: Too Soon for a Randomized Trial
References


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