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Review

Proton beam and prostate cancer: An evolving debate

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ABSTRACT

This paper evaluates the reasons behind the rise in the use of proton beam for prostate cancer, the economics drivers behind it, and the evidence that exists to support it. It concludes that clinical outcome data underlying the notion that this is a superior treatment remains sparse and discusses what is needed to fill in the gaps.

1. Introduction and rationale

The properties of the proton beam have been long recognized as having therapeutic potential. In particular, their singular property of slowing rapidly in tissue, depositing energy at depth, and without any dose beyond the target, were envisioned to have great clinical advantage. This was first recognized in the 1940s and has been the basis of its use ever since.[1] Early therapeutic facilities were merely physics laboratories at universities cleverly adapted to allow patient treatment. The beam energies were generally low and so treatment was limited to tumors at relatively shallow depth such as the eye, the spine, or the base of skull. In the realm of pediatrics where low dose, or indeed any dose, radiation to normal tissues can have disastrous consequences proton beam was used with enthusiasm. Luckily the lower energy beams then available had sufficient penetration to reach most pediatric sarcomas or CNS tumors and indeed tumors almost anywhere in a baby.

In the 1990s patient-dedicated proton facilities were developed and since then their use and establishment has greatly accelerated. Dozens of facilities now exist globally, ten of which are fully functional in the Unites States. Contracts have been signed on many more facilities and construction is underway. It is the wave of the future and, at current costs, a very expensive wave. The enthusiasm, based upon simple dosimetric studies, has actually preceded the results of prospective clinical studies designed to assess the outcomes of this therapy and, in some cases, has actually replaced it. Data is starting to emerge demonstrating clear advantages in terms of organ function and a reduction in second malignancies among the pediatric population.[2–4] This has retrospectively justified its use in an area where it was long presumed to be advantageous. The problem is that, in the USA at least, 80% of patients treated with proton beam have prostate cancer.[5] The reasons are simple. Between 3 and 5 prostate patients can be treated in the time it takes to treat a single complex pediatric case. The installation of a proton facility is so expensive that, at current rates of US reimbursement, a hospital can only begin to cover its debt with a high throughput of prostate cancer cases. This has lead to a dangerous distortion of patterns of care. Many centers that should be treating

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children treat prostate cancer cases, and many elderly patients with prostate cancer who should be having no treatment at all receive it unnecessarily. An "arms race" has begun with many centers taking a huge financial and moral risk investing in proton therapy to keep up with their competitors.[6] As prostate cancer is the US economic engine for proton therapy it is worth spending some time assessing the evidence supporting its use.

2. Uncertainties in the physics and biology

The Bragg Peak has a tremendous therapeutic appeal but in vivo the distribution of the proton beam is subject to many perturbations and uncertainties. The deeper the beam in tissue the less certain one is of its stopping point. This "end of range uncertainty" means that the beam has to be planned to overshoot the target to guarantee good coverage. In addition, at greater depths there is considerable lateral scattering resulting in a significant penumbra making the lateral margins of the beam less sharp.[7] Proton beam, like other forms of particle therapy, is highly subject to tissue inhomogeneities. Trofimov et al. have demonstrated the difference that small movements of the hips can make to a lateral beam delivered to the prostate.[8]

The Radio-Biologic Effect of the proton beam has been measured at 1.1 relative to X-rays yet this number may not be so precise. Just beyond the Bragg Peak it may be a little higher. Furthermore the RBE may differ slightly for different tissues. While this would not matter at lower doses when one is giving close to 80 Gy to a prostate, for example, small differences in RBE can be critical. A passively scattered proton beam, and this remains the prevalent delivery technique in 2013, also generates neutrons in the collimator with a very high RBE and a completely unknown contribution to the effect on normal tissues.

Many of these issues will either be clarified by future experimentation or modeling (RBE) or by moving to spot scanned beam techniques (neutrons) but, for now they may or they may not contribute to the morbidity of proton therapy or, at least, dilute the benefits.[9,10]

3. The clinical evidence

The management of localized prostate cancer has been controversial for decades. It has been difficult to decide whether or not any treatment is better than simple observation and, if so, which of the curative therapies is superior: surgery, external radiation, or brachytherapy. Among the radiation options new technologies have been readily adopted although there is remarkably little evidence of the benefit they bring. 3-D external radiation was shown to reduce rates of radiation proctitis over simple 2-D therapy.[11] In the early 2000s IMRT became extremely popular and is now almost exclusively the external beam strategy of choice in the US. A recent analysis of RTOG data suggests that the advantage of IMRT over 3-D in terms of morbidity and quality of life may be remarkably small.[12] It is impossible to turn back the clock but if this data had been available over a decade ago it is possible that the big switch to IMRT may have been slowed or, had there been no financial drivers, stopped altogether. New techniques of image-guidance may ultimately prove to be more significant than either the planning or beam delivery technique.

Convincing data now exists in the form of five randomized trials demonstrating that higher radiation doses are more likely to reduce the risk of prostate cancer recurrence and, in the case of high-risk tumors, the rate of metastases.[13,14] This now drives the use of high-doses in practice with the presumption that only IMRT or proton beam are adequate to safely them. High quality evidence demonstrating that that is the case is indeed rare. At the end of the day the highest radiation doses are delivered by brachytherapy, a low cost and thus high-value alternative. Quality of life studies have failed to show that patients receiving brachytherapy fare any worse than those receiving any form of high-tech external beam treatment.[15]

One randomized trial has compared proton beam with conventional radiation and showed no difference in any outcome. Interpretation of this study is, however, greatly limited by the fact that it treated advanced cases who would have been better served by the addition of hormonal therapy and because it took place in the pre-PSA era when many patients would have had occult metastatic disease at the time of presentation.[16]

The work of the Massachusetts General Hospital has tested a number of hypotheses:

Does proton beam produce superior dose distributions over IMRT for prostate cancer? The answer is mixed. There is undoubtedly less of a "dose bath" to the anterior and posterior tissues but more radiation passes through the femoral heads and, because of beam uncertainty, the high-dose volume is actually a little larger with protons than IMRT[17] Fig. 1. In addition, two regions associated with morbidities (the prostatic urethra and peri-prostatic nerve bundles) are treated equally with the two techniques. The volume of rectum treated likely depends more on image guidance, choice of margins, and the use or not of a rectal balloon than it does the delivery technique.

Does proton beam cure patients with prostate cancer? Indeed it does, as do all forms of radiation delivered in high dose. A prospective phase III study clearly shows that doses of 79 Gy can be delivered safely with protons and that over 90% of low-risk patients may be cured this way. The problem is that 79 Gy can also easily be delivered by IMRT and probably by 3-D therapy also.[18] A case-controlled study has also shown that the cure rates at 10 years from proton beam and brachytherapy appear to be identical[19] Fig. 2.

Can proton beam be used to dose escalate further? This has been tested in a phase II study of 90 patients. 82 Gy was delivered but unacceptable levels of rectal toxicity were reached implying that, for whole gland treatment using current techniques at least, 79 Gy is close to the practical limit.[20]

Can proton beam be used to escalate the dose further to part of the prostate gland? It is certainly appealing to imagine the entire gland being treated to one dose and a dominant nodule being treated to a higher dose. This could represent intelligent dose escalation without morbidity escalation and is theoretically possible using scanned beam techniques. The problem is that our imaging, although improving, rapidly, is currently insufficient to pick out a target within the prostate with great reliability. In addition our techniques of image-guidance and