Experts Debate Proton Therapy for Prostate Cancer

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Editor's Note: *A commentary by Dr. Gerald Chodak published earlier on Medscape questioned the relative value of proton radiation therapy (PRT) for prostate cancer compared with standard treatment using intensity-modulated radiation therapy (IMRT). Below, Dr. Carl Rossi offers a different perspective and challenges Dr. Chodak on key issues.*

Dr. Rossi: The Value of Proton Therapy

Dr. Chodak's thought-provoking editorial regarding the use of PRT in the treatment of prostate cancer concentrates solely on the negative while failing to reference -- or even acknowledge -- the very substantial body of peer-reviewed research that supports the use of protons in prostate cancer.

Here are 2 brief examples:

• The Proton Radiation Oncology Group (PROG) 9509 trial[1]

This was a prospective, phase 3, randomized trial of proton beam-based dose escalation in organ-confined prostate cancer. Just under 400 patients were randomly assigned to receive either 70.2 or 79.2 Gy. With a median follow-up of just under 9 years, there continues to be a substantial, statistically significant improvement in biochemical disease-free survival for those patients receiving the higher dose. In contrast with several x-ray-based studies, this improvement was achieved without an increase in grade 2+ gastrointestinal (GI) or genitourinary morbidity. The data from PROG 9509 are used by the National Comprehensive Cancer Network (NCCN) as a basis for the benefits of dose escalation in prostate cancer.

• Patient-reported quality of life in PROG 9509 patients[2]

A survey of patients who participated in PROG 9509 found no difference in quality of life between the 2 treatment groups.[2] Although this is at odds with the findings of Sheets and colleagues,[3] it probably reflects the difference between prospective evidence collection and retrospective reviews that did not consider differences in total radiation dose, treatment technique, or the use of surrogate endpoints (GI evaluations) to evaluate different treatment techniques.

Dr. Chodak decries the cost of PRT, which "could reach $100 million/year," yet he says nothing about the far greater cost of IMRT, which now exceeds $1 billion per year and was never tested in a prospective, randomized fashion before being introduced into clinical practice. The same is true of robot-assisted prostatectomy (which is touted on advertisements for greater efficacy and fewer side effects -- perhaps these should be banned as well?). In fact, very little of what we do in prostate oncology is based on prospective, randomized data. In the oft-cited NCCN guidelines for prostate cancer,[4] only 3% of initial treatment recommendations are based on Category I evidence.

Proton beam therapy is an evolutionary step in radiation oncology and is based on the same physical principles and clinical precepts that underlie every other major advance in this field, including IMRT (ie, there is no benefit whatsoever to irradiating normal tissue, and anything we can do to limit normal tissue radiation has been and always will be beneficial to the patient).[5] By virtue of their unique physical characteristics, protons will always spare far more normal tissue than any x-ray-based external-beam treatment method. As this technology

evolves and the capital costs associated with constructing proton therapy centers decrease, proton therapy likely will become the radiation therapy modality of choice in curative situations where concerns over late effects predominate.

The proton community is not standing still. There are currently 16 active prostate cancer proton beam clinical trials in which most, if not all, of the proton centers are participating. This degree of participation is far higher than that found in the x-ray therapy community, and it represents the level of commitment that those of us involved in proton beam therapy have made to try to optimize our treatment. This includes studies of reducing the overall treatment time, which will substantially reduce the per-patient cost of therapy. Rather than decrying the advance of proton beam therapy, I think Dr. Chodak should be lauding these efforts as a positive example to the rest of the medical community.

Dr. Chodak Responds

The PROG 9509 trial shows a biochemical benefit to dose escalation with protons, but overall survival still is similar between the 2 groups. Biochemical failure continues to be an inadequate method of assessing survival. Most importantly, the study did not compare dose escalation using photons, so there is no way to tell whether the benefit seen so far is due to protons or just a higher dose of any form of radiation. Furthermore, even if survival is improved, it does not prove that men will have a greater benefit from protons over photons for localized disease.

As for the companion questionnaire, the quality-of-life assessment is based on only 56 of the nearly 400 men enrolled in the study, and it is limited to an assessment of some GI toxicity. Regardless, this paper at best supports high-dose radiation but in no way proves that protons are superior to photons for the boost.

Dr. Rossi refers to false claims made by robotic surgery enthusiasts, which in no way justify similar claims by proton centers. The truth is that data are lacking to support either of them. As for cost, the patient expense for a full course of proton therapy greatly exceeds that for IMRT or 3D conformal radiation. With a limited number of proton centers, the added costs of patients' time away from work, travel expenses, etc., further weaken the cost argument in favor of protons.

Dr. Rossi also mentions the cost of proton therapy in comparison with the cost of robotic prostatectomy. He's right that robotic prostatectomy is more expensive than traditional surgery, but the government reimburses both methods at the same rate, so surgeons do not benefit from recommending one method over the other. That is not the case with proton therapy, which is reimbursed at a much higher rate than IMRT. One solution would be to pay the same amount for any form of radiation until studies prove the more expensive therapy is worth the added cost.

I take issue with Dr. Rossi's claim that more focused radiation necessarily will reduce side effects. Yes, proton therapy is evolving, but until good evidence is presented of either an improvement in survival or reduction in side effects as measured by validated surveys, it should be considered a work in progress and not ready for prime-time use. If the government stopped paying for it, everyone would be better off until proof of benefit is obtained.

I applaud the number of trials underway but must ask: Are any randomized trials comparing PRT with other forms of treatment?

Dr. Rossi: "Not so Fast"

While Dr. Chodak may not consider biochemical failure an adequate method of assessing treatment outcomes, it is the measure employed in virtually all radiation therapy and surgical studies of prostate cancer. As yet there is no overall survival advantage seen in the PROG 9509 trial, but the risk of subsequently receiving androgen ablation therapy is twice as high in the low-dose vs high-dose arm (22 vs 11 patients), which strongly suggests that as the data continue to mature (median follow-up of last analysis was 8.9 years), we will see a survival difference. This is similar to what has been seen with post-radical prostatectomy radiation therapy, in which initial reports of decreased biochemical failure in the radiation therapy arm eventually translated into an overall survival advantage after about 10 years.

Dr. Chodak is wrong in his conclusions about the quality-of-life report, which we performed. The study included data on 283 of the 393 patients treated in the randomized trial, or 83% of patients known to be alive. It used a validated patient questionnaire based on the Prostate Cancer Symptom Indices Response Score, which assessed urinary, bowel, and sexual function. It demonstrated no difference in urinary incontinence, bowel problems, or sexual dysfunction between the treatment arms. In contrast, several other prospective randomized trials that employed x-rays alone for dose escalation revealed increases in GI morbidity. The probable reason for this difference is that the use of protons for the boost dose exposed less of the rectum to low-moderate radiation doses than patients who were treated with x-rays.

The current higher reimbursement rate for PRT reflects the fact that (unlike x-ray treatment) PRT is still in a relatively early phase of development, and, like other maturing technologies, its equipment costs will decrease over time, as will reimbursement rates. Similarly, when IMRT first appeared, it was reimbursed at a much higher rate than 3D-CRT for similar reasons, with reimbursements now dropping (although still quite a bit higher than 3D-CRT). Please note that these "higher fees" are purely on the technical side; the physician reimbursement for proton therapy is no higher, and in many cases lower, than that for administering IMRT.

The history of radiation therapy is replete with studies demonstrating the positive impact of more focused radiation therapy on reducing side effects; in fact, virtually every technical advance in this field (including IMRT) was developed and introduced primarily for this reason. There is no advantage whatsoever to irradiating normal tissue to any radiation dose. I remind Dr. Chodak again that IMRT was introduced into clinical practice without first being "proved" in *any* prospective randomized trial; it came about because it is a method for reducing normal tissue dose, and if the "government had stopped paying for it until proof of benefit was obtained," it would have never gone into widespread use.

There is a prospective, randomized IMRT-PRT study underway. But if we relied only on prospective, randomized studies to guide our way, very little of what we currently do in prostate oncology (or oncology in general) would be supported. In the widely cited NCCN guidelines for prostate cancer, a whopping 4% of all treatment recommendations are based on "Level I evidence."[4] Like it or not, we are "stuck" with nonrandom studies in adult oncology, and to ignore their contributions to our body of knowledge is to denigrate most of what has been learned and most of what our practices are built on.

Dr. Chodak is wrong about reimbursement for robot-assisted prostatectomy being the same as for surgery using open techniques; it is actually 30% higher for robotic surgery. The evidence can be seen in the CPT codes:

• CPT 55840-Prostatectomy, retropubic, radical with or without nerve-sparing; CMS National Rate (from Find A CPT Code) -- $1242.24

• CPT 55866-Laparoscopy, surgical prostatectomy, retropubic radical including nerve sparing, includes robotic assistance, when performed. CMS National Rate (from Find a CPT Code) -- $1613.09

Likewise, the reimbursement rate per fraction for IMRT is *270% higher than for 3D-CRT* -- again, is this based on the existence of prospective, randomized data supporting the additional cost of IMRT? No, for that data did not exist before this technology was introduced; it was introduced purely because it provided a better degree of normal tissue sparing than 3D-CRT.

Here are the billing codes:

• APC 0301 for CPT Codes 77408-77416 3D are paid $179.52/per fraction

• APC 0412 for CPT Code 77418 IMRT are paid $483.70/per fraction

The current "cost" of proton therapy reflects the cost of a developing technology; I have no doubt that the cost will decrease as the technology matures, which is precisely what has happened with other high-technology radiation therapy methods. Like it or not, if you are unwilling to pay for technological development, you will not have innovation, and not just in radiation therapy.

Dr. Chodak: We'll Have to Agree to Disagree

The problem with using biochemical disease-free survival as an interim endpoint is that many randomized studies fail to show a survival benefit despite this short-term outcome. The fact that many studies use this outcome when reporting results is not a valid justification. Neither the US Food and Drug Administration nor the US Preventive Services Task Force nor the Agency for Healthcare Research and Quality accept prostate-specific antigen as a valid way to assess a therapy. So, until we have proof that overall survival is improved, the benefit of PRT will remain uncertain. Even if this study does show a survival benefit, it is not associated with PRT but rather with a higher dose. A comparative study would be needed to show that a higher dose with protons is better than a higher dose with photons.

Why should the government pay more for a new technology just because it is new? Drug companies are not reimbursed for research and development to get their drug to market, so why should a device company be any different?

The mess we have of new therapies coming along without proper studies needs to stop. If a randomized study had been conducted before PRT was offered, we would know if was better or not, and that applies to all therapies. The fact that it wasn't done before is no reason to avoid doing it now. The treatment of prostate cancer has 14 options, and only 2 have been compared, showing little or no improvement in survival. It is time to be more scientific about treating this disease.

Again, the fact that so little Level I evidence exists does not justify using less valid studies in their place. We will never know for sure if a treatment is worthwhile without Level I studies, with survival as the measure of success.

References

1. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. J Clin Oncol. 2010;28:1106-1111. Abstract

2. Talcott JA, Rossi C, Shipley WU, et al. Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. JAMA. 2010;303:1046-1053. Abstract

3. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012;307:1611-1620. Abstract

4. Poonacha TK, Go RS. Level of scientific evidence underlying recommendations arising from the National Comprehensive Cancer Network clinical practice guidelines. J Clin Oncol. 2011;29:186-191. Abstract

5. Suit H, Goldberg S, Niemierko, A, et al. Proton beams to replace photon beams in radical dose treatments. Acta Oncol. 2003;42:800-808. Abstract

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