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PCa Commentary

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CONTENT

PROTON BEAM, A BETTER THERAPY FOR PROSTATE CANCER? - Where's the Beef?

In this era of burgeoning health care costs with the currently unfulfilled - and problematic - promise of cost control through programs of "comparative effectiveness", it is appropriate to examine the current state of knowledge of comparisons between proton beam with other forms of radiation regarding outcomes and toxicity in the treatment of localized prostate cancer.

WHAT IS KNOWN TO DATE:

1) There has never been a randomized prospective trial comparing proton therapy and other modes of radiation, but one will shortly open for registration.
2) In the last nearly ten years the preponderance of expert opinion is that there is *no significant difference* in outcome for these effective options.
3) Treatment side effects may be minimally different between therapy modes, but the differences are small, and all forms have low percentages of serious toxicities.

There is consensus between proton advocates and skeptics, however, on one basic point: a proper trial between protons and photons would provide data for an accurate comparison. Lacking that, we must manage as best we can with optimally constructed analyses of outcomes based on optimally balanced stratification of patient characteristics. Three recent reports fulfill this criterion.

THREE RECENT COMPARATIVE STUDIES WITH CREDIBLE STRATIFICATION

1) **"Comparison of High-Dose Proton Radiotherapy and Brachytherapy in Localized Prostate Cancer: A Case-Matched Analysis,"** Coen, Zietman, et al., *Int J Rad Oncol Biol Phys,* 2012*,* from Massachusetts General Hospital and Loma Linda University Medical Center.

The match compared long-term cancer outcomes of

- 141 men treated with a high-dose (79Gy) *combination* of protons and photons (P/P) with
- 141 men who received brachytherapy (BT) alone, either 125-Iodine or 103-Palladium at doses of 145 Gy or 115 Gy, respectively.
- Median follow-up was 8.6 years for P/P and 7.4 years for BT.
- Biochemical failure was calculated with both the ASTRO and the Phoenix definitions.

The patient characteristics of the 141 men were scrupulously matched.

Patient age was 67 v. 65 (P/P vs. BT).
Low risk was defined as T1c-T2a, Gleason score ≤6, PSA level <10 ng/ml.
Intermediate risk required a Gleason score 7 or Gleason score 6 with either a PSA level of >10 ng/ml or a T2b tumor.
For the analysis the Gleason score was 6 in 89%, and 7 in 11% for both arms.
The P/P cohort included 80% men with low risk and 20% with intermediate-risk cancer, and in the BT arm the distribution was 84% and 18%.

***"Comparison of High-Dose Proton Radiotherapy and Brachytherapy…"* continued**

Outcome: At 8 years, overall survival [combining data from both low and intermediate groups] was 93% vs. 96% for external radiation and brachytherapy, respectively (p=0.45).

In a subgroup analysis of outcome performed separately on the low-risk and the intermediate-risk cohorts "There were no significant differences observed ... ." For example at 8 years the biochemical failure rate (nadir+2 definition) was 7.5% (P/P) vs. 11.0% (BT), p=0.74).

A PSA nadir of ≤0.5 ng/ml was achieved in 92% of BT patients vs. 74% for the P/P arm. The median time to nadir was similar in both groups: 60 and 56 months" for P/P vs. BT. The proportion of patients with low PSA nadirs (≤0.5 ng/ml) at last follow-up was higher in the BT group, 91% vs. 66% for P/P.

This study likely offers the most stringent and meticulously matched comparison available to date.

Conclusion: "This case matched analysis did not show statistical differences between high-dose external-beam radiotherapy and prostate brachytherapy for the control of low- to intermediate-risk localized prostate cancer."

"A well-informed patient may reasonably chose either option on the basis of individualized assessment of morbidity risk and perceived quality of life."

2) A second detailed and credible comparison of permanent seed brachytherapy (BT) and proton beam therapy (PBT) was reported by Jabbari, Roach, et al. (*Int J Rad Oncl Biol Phys,* 2010).

The study focused on biochemical control and post-treatment PSA nadir in 206 BT patients treated at UCSF compared to 195 men in the high-dose proton/photon cohort referred to in article #1 (above).
- The median patient age for BT v. PT was 63 v. 66; initial PSA, 6.3 v. 6.2 ng/ml.
- In the brachytherapy group 65% were low-risk by D'Amico criteria; in the PT cohort, 60%.
- The median follow-up was 5.3 years. Biochemical failure was set by the Phoenix definition (PSA nadir+2ng/ml).
- Approximately one third of BT group received neoadjuvant androgen deprivation.

Outcome: The 5-year freedom from biochemical recurrence in the low-risk groups was 97% for protons v. 94% BT; in the intermediate-risk groups: 82%, protons vs. 90% brachytherapy.

The median time to PSA nadir was 43.2 months for BT and 39.6 months for protons.
A PSA nadir of ≤0.5 ng/ml was achieved in 91% of men receiving BT compared to 59% treated with protons. A nadir of ≤1.0 ng/ml was seen in 96% vs. 87%, respectively.

Conclusion: This study shows at least equivalent 5-year biochemical control rates for men with low- and intermediate-risk prostate cancer treated with brachytherapy or proton beam therapy. A greater proportion of men in the brachytherapy group achieved lower PSA nadirs.

3) The third comparative analysis addresses disease control and morbidity of proton therapy and intensity modulated external beam radiation (IMRT) for localized prostate cancer (Sheets, Chen et al, JAMA, April 2012).

It is a "Population-based study using Surveillance, Epidemiology, and End Results-Medicare-linked data from 2000 through 2009 for patients with non-metastatic prostate cancer."

Its focus was on gastrointestinal and urinary morbidity, erectile dysfunction, and hip fractures. The employment of additional therapy following primary treatment was used as an indicator of disease recurrence. Since the goal was to identify long-term morbidity, "diagnoses and procedures that occurred within 1 year of radiation therapy" were excluded.

For proton therapy there were 684 patients; for IMRT, 6666. The median follow-up was 46 months for IMRT and 50 months for protons.

Because of the nature of the data, the outcome information lacks the important nuances possible in prospective trials such as detailed baseline functional evaluation and severity grading of morbidity. However, the comparisons were weighted to adjust for major important baseline characteristics such as diabetes or anticoagulant therapy, and relied on the large numbers of patients to balance the comparisons.

Outcome: "There was no significant difference in proton therapy- vs IMRT- treated patients in urinary nonincontinence or incontinence diagnoses or procedures, erectile dysfunction, or hip fractures. The only difference was that proton treated men "were more likely to receive a diagnosis or gastrointestinal morbidity and undergo gastrointestinal procedures (rate/100 person years: 12.2 IMRT vs. 17.8 for PBT). "Rates of additional cancer therapy were no different between the two groups."

As expressed by Sheets, Chen et al. about their findings, but additionally reflective of other comparison studies, "Overall, our results do not clearly demonstrate a clinical benefit to support the recent increase in proton therapy for prostate cancer."

AN EVIDENCE BASED ASSESSMENT OF PROTON BEAM THERAPY FOR PROSTATE CANCER

The American Society of Radiation Oncology (ASTRO) convened a panel of experts to "evaluate the state of science of PBT and arrive at recommendations for the use of PBT." In their evidence based review (*Radiology and Oncology,* March 2012) they considered approximately 2000 prostate cancer patients treated with proton therapy.

Their conclusion: In prostate cancer "there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches."

AN EVIDENCE BASED ASSESSMENT OF PROTON BEAM THERAPY continued

A PROMISING TRIAL (to be opened in June, 2012): The Massachusetts General Hospital in association with the National Cancer Institute will open a $5M 5-year trial (NCT01617161):

"Phase III Randomized Clinical Trial of Proton Therapy vs. IMRT for Low or Low-Intermediate Risk Prostate Cancer." The trial description states "Both IMRT and PBT have been used in the treatment of prostate cancer and are thought to be equally effective at curing prostate cancer."

The **primary** trial outcome measures are efficacy and survival at 10 years.

Secondary outcome measures are patient-reported quality of life; cost effectiveness; radiation dose; bowel, urinary, and erectile function; and the development of late second cancers.

The trial will be accessible at a half-dozen centers across the country, locations yet to be determined.

Half of the expected 700 enrollees will be randomized between protons and IMRT. "The other half will receive whatever course of treatment they and their doctor have decided on, but also will be followed as part of the trial (Johnson, *Boston Globe,* May 14, 2012)."

The *Boston Globe* article offered some interesting perspective. At MGH between November 2010 and October 2011 814 patients received proton therapy. By treatment site the breakdown was brain, 41%; eye, 15%; bone/soft tissue 10%; prostate 8%; skull base, 7%; and liver, pancreas, lung for the remaining 8%. Currently in the US 10 proton facilities are operational; by 2015 there will be 20.

Although it is difficult to state the exact cost of the various modes of treatment for prostate cancer, it is generally understood that proton therapy (at about $50,000 - at one institution the "list" price was $75,000 - or considerably higher for a course of treatment) is approximately double that of currently standard methods. The cost of building a proton facility runs from $150,000 to $200,000.

Dr. Jason Efstathiou, professor of radiation oncology at Harvard Medical School and principle investigator for the study, raises the question: "Is the additional cost for proton beam therapy worth it? Ultimately, we need to figure out if these new emerging high-technology therapies being introduced into medical care provide benefit.... This trial will determine whether or not the more expensive therapy leads to a better quality of life."

BOTTOM LINE: Proton therapy for prostate cancer? The beef is still on the hoof.

POMEGRANATE EXTRACT FOR PROSTATE CANCER? - Surely You Will be Asked.

Over eons Nature, in its evolutionary chemistry laboratory, has been gradually constructing a bountiful offering of unique phytochemicals which shamans and medicine men of old up to today's research scientists have put to the service of medicine. The results are the many complex therapeutic molecules we now depend on: digitalis from the deadly nightshade, Foxglove; penicillin from the Penicillium notatum mould; Vincristine and the vinca alkaloids from the Madagascar periwinkle; and from the Yew, the taxanes, the backbone of our currently most useful chemotherapy drug for prostate cancer, Docetaxel - just to name just a few.

The pomegranate, its seeds and juices, fits into this long history. Its usefulness as a medicine has a history that winds back to its early therapeutic use in the ancient cultures of the Middle East. Today it is a contender for a role in cancer therapy.

Consider the full page advertisement in the New York Times, May 24th, loudly announcing that *POM Wonderful* "supports prostate health," "prolongs PSA doubling time," and promotes "erectile health and erectile function." Although the FTC charged the company with "false and misleading advertising on the ground the science did not support *POM's* health claims, nonetheless the Chief Administrate Law Judge (5/17/2012) did allow that "scientific evidence supports the conclusion that the consumption of pomegranate juice and pomegranate extract supports prostate health... ."

WHAT IS THE SCIENTIFIC EVIDENCE? RESULTS OF TWO CLINICAL TRIALS.

The **first clinical trial** of pomegranate juice in men with prostate cancer was reported in July, 2006, by Pantuck et al. (School of Medicine, UCLA) in *Clinical Cancer Research*: "Phase II Study of Pomegranate Juice for Men with Rising Prostate-Specific Antigen following Surgery or Radiation for Prostate Cancer."

As background and rational for their study they point out that the husks of the fruit contain high levels of antioxidant flavioids whose anticancer effects "include the inhibition of cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression, promotion of cellular differentiation, ... and inhibition of inflammation."

Patients were treated with 8 ounce of 100% pomegranate juice daily (POM Wonderful variety) until disease progression.

The 46 men studied were in the low-risk category: 96% had Gleason scores between 5-7; 63% had organ confined disease; 35% were locally advanced; and the median initial PSA value at the initiation of the study was 1.05 ng/ml.

POMEGRANATE EXTRACT continued

Results:

1) 35% of the patients showed a decrease in PSA values of a median of 18%, with 4 men decreasing >50%;

2) the mean PSA doubling time significantly lengthened from a mean of 15 months at baseline to 54 months posttreatment (P <0.001), with 83% of patients achieving an improvement in PSADT.

The authors concluded that "the pattern of achieving a slowing of PSA progression with significant PSA decline is consistent with a cytostatic rather than a cytotoxic effect."

A **second trial** was first reported at the 2011 ASCO GU Symposium and then published in June, 2012, in *Prostate Cancer Prostatic Dis.* by Paller, Carducci et al. from Johns Hopkins: "A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer." Intervention was one 1000 mg capsule daily. The randomization was between one capsule daily vs. three. The two arms showed equal outcomes.

In this study of 104 men the eligibility profile was *expanded to include a higher-risk population* and allowed any PSA level ≥0.4 ng/ml with no limit on Gleason score or PSA. The median patient Gleason score was 7, and 70% had a baseline PSADT of longer than 9 months.

Results:

1) The median PSADT lengthened from baseline 11.9 months to 18.5 months after treatment (P=0.001).

2) A *decrease* in PSA was seen in 13% of men. Most men had stable PSA values during the study, which was continued until disease progression or 18 months. However, of concern was the observation that 42% of patients discontinued treatment before 18 months "*primarily due to a rising PSA."*

3) The only side effect was diarrhea 1.9% of patients.

A discussant at the symposium cautioned that "A treatment-induced alteration in PSA doubling time has never been shown to confer a clinical benefit, even in animals."

At the ASCO Symposium Dr. Carducci said that there is an ongoing 200 man placebo-controlled trial (NCT00413530) of pomegranate extract, sponsored by M.D. Anderson Cancer Center. (Pomegranate "extract" is formulated as a 1000 mg capsule and said to be equivalent to 8 oz of the 100% pomegranate juice.) In Carducci's opinion, however, the extract (capsules) "controls the growth of prostate cancer more effectively."

In addition, clinicaltrials.gov lists 4 other placebo controlled trials sponsored by major universities studying men with rising PSA values after primary therapy.

POMEGRANATE EXTRACT AND ERECTILE FUNCTION:

The claim that Pom Wonderful improved erectile function was only weakly supported based on a single, randomized, controlled study of 53 men with mild to moderate ED *(Int J of Impotence Research*, 2007). The schema featured a 4 week period of 8 oz. POM vs. a control juice, a washout period of 2 weeks, then a crossover repeat test period of 4 weeks.

The biologic rational for the study built on the antioxidant properties of POM which have been shown to increased the bioavailability of nitric oxide to promote small vessel dilation.

Result: 25 men saw some improvement with POM vs. 17 with the placebo (p=0.058).

BOTTOM LINE: Pomegranate extract for prostate cancer and erectile function? Now you have the current facts. The outcome of future trials will be additionally informative.

Your comments and requests for information on a specific topic are welcome at **ecweber@nwlink.com**

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