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QUALITY OF LIFE: PROTONS vs. PHOTONS: How Do Their Toxicities Compare?

This article, as with so many in this Commentary, arose from a question to me by a man contemplating his choice of primary therapy for his biopsied low-grade prostate cancer. He had heard that proton beam radiation therapy (positively charged subatomic particles) caused fewer side effects than conventional radiation (electromagnetic energy lacking mass and charge), such as intensity modulated radiation therapy (IMRT) or permanent seed brachytherapy. The source of his belief was unclear, but could have arisen from the Loma Linda Proton Beam Website (http://www.protons.com/), which states as a matter of fact:

> "Proton Therapy is a precise form of radiation treatment for cancer and other conditions. Minimizing damage to healthy tissue and surrounding organs, proton treatment is highly successful and results in fewer side effects."

The site's essentially unreferenced chart comparing toxicities of proton beam therapy versus external beam radiotherapy (EBRT) lists the occurrence in proton therapy as "low" versus "moderate" for EBRT in the domains of "impotency, incontinence, risk of secondary cancer, and healthy tissue damage." (http://www.protons.com/proton-therapy/conditions-treated/prostate-cancer/treatment-options.html)

Do we know anything "for sure" about the comparative incidence of toxicities between proton versus photon therapy? The short answer is "No," since there have been no reported carefully controlled

clinical trials. However, the Massachusetts General Hospital and the University of Pennsylvania are trying to organize sorely needed randomized trials (personal communication, A. Zietman, MD).

The question of comparative toxicity, however, will be asked with increasing frequency for two reasons.

First, data to date show that the outcomes of treatment with these two modalities are similar for many low-risk patients, in which case men tend to make treatment decisions based on therapy side effects. An extensive review of the literature regarding proton beam therapy and conventional radiation (Terasawa, Annals of Internal Medicine, Sept 2009) surveyed 10 prostate cancer trials and included those findings in their general conclusion: "No comparative study reported statistically significant or important differences in overall cancer-specific survival or in total serious adverse events."

Second, and equally important, proton beam facilities are proliferating nationally. Two facilities are planned in the Seattle region in the near future.

The claimed superiority of proton beam therapy over external beam radiation − and its cited minimization of toxicity - is largely based on the physical characteristic of proton delivery termed the "Bragg" peak, as a result of which the majority of the energy is deposited at the target with a sharp fall-off beyond. Efstathiou, Trofimov, and Zietman, The Cancer Journal, 2009, Jul/Aug, present a detailed discussion of proton beam therapy in "Life, Liberty, and the Pursuit of Protons: An Evidence Based Review of the Role of Particle Therapy in the Treatment of Prostate Cancer." They explain that the *theoretical advantage* of the Bragg peak as regards treatment toxicity is actually eroded in the *practical application* of therapy.

Studies in patients and "phantoms" have shown that small three-dimensional changes in the position of a patient's prostate due to patient movement or gas in the rectum can significantly reduce the planned proton dose to the target (more so than with IMRT). Adjustment of proton targeting to accommodate movement is not practical at this time.

Efstathiou concludes: "Only a randomized comparison between protons and IMRT with careful acute and late toxicity profiling and patient-reported quality of life analysis can appropriately address these important questions."

One major study evaluating treatment toxicity for high-dose therapy combining protons and EBRT has been published: "Patient-Reported Long-term Outcomes After Conventional and High-Dose Combined Proton and Photon Radiation for Early Prostate Cancer, PROG 9509," JAMA 2010 March. Talcott, Zietman et al. reported the toxicities seen in this Proton Radiation Oncology Group trial. Men in each study arm received similar doses of conformal radiation (IMRT), to the prostate combined with two differing proton doses. The purpose was to examine the toxicity profile of high-dose therapy, 79.2 Gy, with a lower dose of 70.2 Gy. Because both protons and photons were used in each arm, the individual contribution of each to toxicity could not be assigned, but the study is relevant since it established that the higher dose, which is the current goal for either modality given alone, was more effective in cancer control at no increase in toxicity. The study offers an indication of the extent of toxicities to be expected from current high-dose regimens.

In the PROG 9509 high-dose arm both early and late urinary toxicity was a major problem for only 2% of men; rectal toxicity occurred in 1% for both time periods. At a median follow-up of 9.4 years the reported occurrence of toxicities in the high-dose arm were (using a scale of 1 - 100 where 100 is the most undesirable): urinary obstruction/irritation 24.6; urinary incontinence 9.7; bowel problems 7.9; and sexual dysfunction 65.9. These numbers are likely to define the toxicity profile of the currently employed high-dose therapy.

A Japanese study of late rectal and bladder toxicity in 151 patients receiving proton therapy, Int J Radiat Oncol Bio Phys. 2010 Sept, reported that at >2 years following treatment the incidence of Grade 2 or greater rectal and bladder toxicity was 2.0% and 4.1%, respectively.

Second malignancies brought about by radiation therapy are an important long-term concern. In the case of prostate treatment the lower portion of the bladder is the site at greatest risk for "in-field" cancer

induction, but radiation "scatter" around the targeted region is also a potential problem. There are theoretical considerations that suggest the protons - because of the Bragg peak - would present the least liability for secondary cancers. But as it's said "The proof of the pudding is ...," and it takes possibly ten years for these induced tumors to become manifest. So, again, we must await real data for protons. For conventional radiation the reported incidence is less than 1% for secondary bladder malignancies.

So... would high-dose proton therapy as a single modality be better or worse than the benchmark toxicities reported in PROG 9509? Talcott and Zietman did attempt to indirectly address this question by comparing the patient-reported function in the Boston cohort of men receiving protons in the PROG 9509 trial with group of men of the same age (~75) - matched as carefully as possible - who received high-dose photons (EBRT) in another study. Using the same 1 - 100 scale (protons v. photons) the results were: urinary obstruction/irritation 24.0 v. 21.8; urinary incontinence 10.2 v. 11.2; bowel problem 7.8 v.10.6; and sexual dysfunction 67.1 v.76.3. Late GU toxicity of lesser severity (Grades 1 & 2) was the same for high-dose rate external beam treatment and protons; the more severe complications (Grade 3) were seen in 2% EBRT and 1% for protons.

BOTTOM LINE: Due to the absence of data from controlled clinical trials, the jury is still out on this important issue of comparative treatment toxicity of proton therapy versus IMRT for prostate cancer. Fortunately, for both modalities the incidence of serious toxicities is small; however, any claims of superiority for protons - or in fact for either modality - in the toxicity domain must be held suspect for lack of substantiation.

CASTRATE RESISTANT PCA: ABIRATERONE: Encouraging Phase III Trial Results Move Drug Toward FDA Approval.

A presentation at the European Society of Medical Oncology, October 11, highlighted the final results from a multinational, 1195 man trial, comparing abiraterone (1000 mg po qd) plus 5 mg bid of prednisone (A/P) with a placebo plus prednisone. (Protocol details at http://clinicaltrials.gov/ct2/show/NCT00638690)

The patients had metastatic castration-resistant prostate cancer (CRPC) refractory to one or two chemotherapy therapies, one to have included a taxane. A serum testosterone level of <50 ng/dl was required, which in most cases required the continuation of a LHRH agonist. A/P was received by 787 men, and 398 had the placebo.

SALIENT RESULT: A/P yielded a 35% reduction of risk of cancer deaths yielding a 36% increase in median survival, 14.8 months v. 10.9 months. Abiraterone delayed the time to tumor progression to 10.2 months v. 6.6 months for the placebo (P>0.0001). In the A/P group 38% showed a PSA decline of >50%. These extremely favorable outcomes for A/P led the data monitoring committee to close the trial. Men in the placebo arm were then given the opportunity to receive abiraterone.

Abiraterone's mechanism of action and earlier trial results have been reviewed several times in this Commentary (Indexed under CRPC). Briefly, the drug inhibits a critical steroidogenic enzyme (CYP17A1) essential for two steps in the anabolic pathway building androgens from cholesterol. Abiraterone inhibits this pathway in the testes, adrenal glands, and in the cancer itself.

The enzymatic inhibition of abiraterone leads to a compensatory increase in serum cortisol and this elevation is responsible for fluid retention (30.5%), hypokalemia (17.1%), and mild controllable hypertension. Significant hypertension occurred in only 1.3% of men.

Marketing application to the FDA requesting approval for abiraterone will likely be presented before the end of the year, and marketing could begin possibly next year.

A program for "compassionate use" that will give access to abiraterone to patients who meet specified criteria (as yet undetermined) is planned. There would be a very substantial number of men who progressed after chemotherapy for whom the drug would be appropriate if the criteria for access

resembled those used in the study. An even greater number would be potential recipients if drug access were expanded to include men with CRPC who had as yet not received chemotherapy.

The medical centers which will participate in offering the drug will be listed on www.clinicaltrials.gov when the program is ready.

PRIMARY TX OPTIONS: ACTIVE SURVEILLANCE: A Suggested Patient Selection Guideline

Active surveillance would be a flawed strategy if delay in treatment would lead to a poorer outcome. Successful application of this strategy demands careful patient selection.

No one in the urologic oncology community has been more dedicated to researching this crucial issue of patient selection for active surveillance (AS) than Peter Carroll, MD, MPH, Professor and Chair, Department of Urology, UCSF. He and colleagues from UC Davis, and the Universities of Pittsburgh and Minnesota, have collaborated to produce a seminal study: "Surgical management after active surveillance for low-risk prostate cancer: pathologic outcome compared with men undergoing immediate treatment," BJU Int. 2010 Aug.

From the UCSF data base of 1902 men managed between 1996 and 2008 with either surgery or AS, 570 men (30% of the total) met stringent low-risk criteria for AS eligibility: "PSA <10 ng/ml, Gleason sum ≤6, absence of Gleason grade 4 or 5 cancer, involvement of ≤33% of core biopsies and ≤50% of any single core, clinical stage T1/T2." At diagnosis 6 to 11 biopsy cores were taken in 44% of men and 12-17 in 48%. Of these 570 men, 337 had immediate surgery (RP), i.e. within 6 months of diagnosis, and 233 underwent AS. Of these 233 men, 33 later had surgery (RP+AS) at a median (range) of 18 months (range 7-72) from diagnosis. The median age was 59; the median PSA 5.8 ng/ml. Carroll's analysis compared the two groups (RP v. RP+AS) with regard to Gleason upgrade to ≥7 after surgery, with secondary endpoints being pathologic stage and positive surgical margins.

EXECUTIVE SUMMARY: "... appropriately selected men with prostate cancer can undergo AS with delayed prostatectomy without the added risk of missing an opportunity for cure because the majority of tumors [79% at 18 months] remain organ confined."

Those men who chose AS were followed with serial PSA testing at 3-month intervals, received a TRUS at 6-12 months, and underwent a 12 core biopsy at 12- 24 months (now recommended at 3 months). Surgical intervention was recommended in 23 of the men because of Gleason upgrading on surveillance biopsies based on the fact that "Natural history data show that tumor grade is the most important predictor of disease-specific mortality in men being followed for prostate cancer." Ten men chose surgery as a preference.

FINDINGS: "... the rates of upgrading to ≥7, staging of pT3 and positive surgical margins did not differ significantly between the AS+RP and immediate RP groups." In the AS+RP cohort, 30%, and in the group RP, 35%, were upgraded to Gleason 3 + 4, with one man in the AS-RP group upgraded to Gleason 4 + 3. Among low-risk AS+RP men 77% had organ confined disease (T2)compared to 90% in the RP group, a non-significant difference. All of the men with non-organ-confined cancer in the the AS+RP group had stage pT3a. In the RP arm 6% had pT3a and 4% pT3b disease. Positive surgical margins were seen in 18% of RP and 12% of AS+RP patients. At four years follow-up for both groups the biochemical disease-free survival was 98-100%.

The authors acknowledged that the study's small size limited detecting minor differences in outcome between the two groups. Additionally, "It is acknowledged that the main pathologic outcomes of the present study are simply surrogates for the more clinically relevant outcomes of disease-specific survival and overall survival." One can hope that a future review of this data will address these issues.

For clinicians offering active surveillance to carefully selected patients, this article deserves a careful read.

BOTTOM LINE: Guidelines are emerging from studies such as this to assist clinicians in selecting men who are optimally appropriate for active surveillance.

PSA SCREENING: STATINS, THIAZIDE DIURETICS, and NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) LOWER PSA

A report by Change et al.: "Impact of Common Medications on Serum Total Prostate-Specific Antigen Levels: Analysis of the National Health and Nutritional Examination Survey,"(Journal of Clinical Oncology, Aug 2010) analyzed the effect of these common medications over five years on PSA levels in 1864 healthy men ≥40 years old, an age when PSA screening might be initiated. The median age was 53 years, and the median total PSA was 0.8 ng/ml.

Principle Findings: "Five years of NSAID, statin, and thiazide diuretic use was associated with PSA levels lower by 6%, 13%, and 26%, respectively."

The one-year reductions were 1%, 3%, and 6%. It is not unusual for men to be taking an NSAID intermittently and both a statin and a thiazide diuretic continuously for many years. The results for combined statin/thiazide usage over one year led to an 8% reduction in PSA, and over five years, a 36% lowering.

The mechanism of action of statins in lowering PSA is unclear, but in part relates to the prime drug effect of lowering cholesterol parameters. However a variety of non-cholesterol mediated mechanisms are also postulated.

Two mechanisms for PSA reduction are considered in relation to thiazides: 1), serum vitamin D3 levels are reduced by the drug leading to decreased PSA production; and 2), bioavailable testosterone is reduced by 30% possibly lowering PSA.

Of note is the finding that for these healthy men the median serum Vitamin D3 level was 23 ng/ml underscoring the common finding that many men are deficient in this vitamin, considering that the optimal range for serum D3 is 40-80 ng/ml. It is suggested that achieving levels in the recommended range requires titrating vitamin D supplements with the measured serum level.

BOTTOM LINE: A clinician's awareness of a patient's usage of statin and thiazide medications adds a relevant nuance in PSA interpretation.

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