SEATTLE PROSTATE INSTITUTE

PCa Commentary

Vol. 36: Oct.-Nov. 2005

Contents

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

This month's issue plus a compilation of past articles is available online at www.seattleprostateinst.com/pcacommentary.htm

QUALITY OF LIFE: What Are The Side-Effects Of Your Treatment, Doctor? – A Discussion Of Urinary, Bowel And Sexual Complications Of Primary Treatments Of Prostate Cancer.

When the question is asked, "What are the unwanted complications that result from prostate surgery, irradiation and brachytherapy?", you might expect there are straightforward answers. There are, of course, some overriding generalities: surgery is associated with the most urinary incontinence and sexual dysfunction; external beam radiotherapy with most bowel symptoms; and brachytherapy with urinary irritation; and both radiation modalities cause the least deterioration of sexual function, which, however, further deteriorates as follow-up lengthens. But the "devil is in the details". More detailed analyses reveal complicating issues that blur simple generalizations: e.g., what were the baseline functional capacities; how does age affect the comparison of treatment complications; are tumor stage and treatment techniques and comorbidities comparable in the groups being compared; what evolution occurs in symptom severity over time, e.g. at 3 months, and at one, two and five years after treatment?

The most reliable assessments emerge from the use of one or several validated questionnaires, self administrated by each man and reported prospectively prior to and sequentially during treatment. Many excellent single institution, single modality studies are available that are very appropriate for internal use, but don't have the features that allow informative inter-modality comparisons.

An exemplar study that does incorporate these necessary features was reported by Talcott, D'Amico et al. in JCO Nov. 2003: "Time Course and Predictors of Symptoms After Primary Prostate Cancer". This analysis focuses on urinary, bowel, and sexual function over a two years period of follow-up and compares outcomes from radical prostatectomy (with and without nerve-sparing), external beam radiotherapy, and brachytherapy. The study was conducted by a consortium of Boston teaching hospitals and involved 417 men (EBRT - 182, RP - 129, BT - 80 patients) segregated into standard risk categories. The time course for the extent of symptoms was graphed beginning with a baseline assessment, with follow-up at 3, 12, and 24 months for each modality, and separate outcome graphs displayed the data for sexual dysfunction (under and over age 65), urinary incontinence, bowel problems, and obstructive/irritative symptoms. The ordinate of each graph was a composite "mean score" for the group under study, ranging from 0, best, to 100, worst. Each domain "mean score" represented an summary integration of confounding factors (e.g age stage), as was suggested above, and combined the several sub-functions that are integral to global satisfaction in that domain. For example, in the sexual domain the mean score integrated information relating to e.g. firmness of erections, difficulty getting and keeping erections, and frequency of ejaculation and orgasm. In the urinary domain the sub-issues assessed were "the degree of urinary control and the frequency and magnitude of leakaqe in men who had less than "complete control" and the need for use of absorptive pads. Obstructive/irritative dysfunction addressed "hesitancy, frequency of urination during the day, nocturia, dysuria and urgency". The final product was an integration of the subcategories of a domain into a numerical "mean score".

The graphs provide a very helpful visual/global comparison among the three treatment modalities, and if the extent of dysfunction assigned by these investigators seems higher than often reported it is because their analysis has tried to capture the full range of component elements that, taken as a group, affect a man's sense of satisfaction in a particular domain.

What are the findings? (Numbers are approximate: +/- 1)

Mean Scores:	Baseline	3 mo.	12 mo.	24 mo.
1) Non-nerve-sparing RP:				
Sexual dysfunction, <65	30	79	84	75
>65	43	84	82	80
Bilateral nerve-sparing	18	74	68	62
Unilateral nerve-sparing	20	82	72	70
Urinary incontinence	4	47	32	30
Bowel problems	4	4	4	4
Obstructive/irritative	19	18	10	10
2) External Beam Radiotherapy				
Sexual dysfunction, <65	32	55	55	52
>65	60	72	72	77
Urinary incontinence	7	9	9	9
Bowel problems	5	13	10	9
Obstructive/irritative	14	20	15	14
3) Brachytherapy				
Sexual dysfunction, <65	24	40	40	40
>65	47	50	50	58
Urinary incontinence	4	8	8	9
Bowel problems	6	9	9	10
Obstructive/irritative	8	18	10	12

For this article numerous reports were reviewed. Most reported follow-up on single modality treatments or comparisons of two treatment types. In general, the outcomes of these many studies fall within the range of results reported by Talcott. However some additional informative points are contributed by several of them.

A paper comparable in detail to the Talcott study was presented by Potosky, JNCI Sept 2004: "Five-Year Outcomes After Prostatectomy or Radiotherapy for Prostate Cancer: The Prostate Cancer Outcome Study". This is a comparison between 901 men treated with RP and 286 with EBRT. Their analysis of erectile dysfunction, similar to other reports, finds that whereas at 2 years the dysfunction rate for RP is 82% versus 50% for EBRT, at 5 years, while the impairment remains stable in the RP group, dysfunction increased in the EBRT group to 63%, an insignificant difference.

An important background point to keep in mind when considering treatment outcome studies in general was highlighted by Hoffman (CANCER Nov 2004) where the sexual function of treated men was compared with matched normal controls. He established, not surprisingly, that over five years sexual function declined significantly among *controls* (whereas urinary function remained stable). This information provides perspective for the interpretation of the functional decrement in sexual function resulting from all treatment types.

Potosky confirmed that at five-year follow-up urinary incontinence (defined as no control or frequent leakage) was worse after RP, 14-16%, versus following EBRT. 4%.

Outcome evaluation for laparoscopic prostatectomy (LRP) was compared to open RP (ORP) and BT by Soderdahl et al. (J Endourol. 2005 Apr). Validated, sequentially self-administered tools were returned by 452 men at 0,3,6,9 and 12 months. Results, reported as % return to baseline function": 1) urinary function - ORP, 38%; LRP, 46%, BT, 75%; 2) sexual function - ORP, 19%: LRP, 19%; BT, 63%.

Studies that compare BT and EBRT establish that greater dysfunction results from EBRT. The addition of EBRT to BT leads to more sexual dysfunction than BT alone. Merrick (Oncology, Vol 17, Number 1) found, as have others, that with radiotherapy men's sexual dysfunction increased over 5 years to 50%. Potency was *preserved* at 5 years in 57% of men undergoing BT as monotherapy but with added EBRT *preservation* dropped to 39%. Encouragingly, he found that Viagra helped the majority of affected men whose pretreatment function had been satisfactory.

Bottom Line: All forms of primary therapy for prostate cancer are associated with varying, but important, degrees of deterioration in urinary, bowel and sexual function, and these complications change over time. These issues need to be factually addressed with men prior to treatment. An excellent validated study which could serve as a desk reference for this discussion is the JCO Talcott report.

DIET & PREVENTION: Does Finasteride Alter The Pathology Of The Prostate And Cancer Grading - Yes? No? ... Maybe?

The landmark article "The Influence of Finasteride on the Development of Prostate Cancer", NEJM July 17, 2003, by Ian Thompson et al. reported a 24.8% finasteride related reduction in the seven-year period-prevalence of cancer and was a source of optimism for the prevention of this disease. It was, however, also a source of a vexing controversy that still evades a definitive answer. The heading of this Commentary article is the title of the analysis of this issue by David Bostwick et al. published in Clinical Prostate Cancer, March 2004. But first, a review of the facts.

Of the total of 18,882 men in the Prostate Cancer Prevention Trial, Gleason grade 7, 8, 9, or 10 was found in 37% of the tumors diagnosed in men on the finasteride arm (280/757), which represented 6.4% of the 4368 men taking the drug. In contrast, of the tumors found in the 4692 men in the placebo group, only 22% were high-grade (237/1068), or 5.1%; P=0.005 for the comparison between the two groups. In

a commentary on the trial, Talcott (JCO, Oct 10, 2005) pointed out that the nearly 25% reduction in cancers (24.4% reduced to 18.4%, an absolute reduction of 6%) was comprised of tumors of Gleason score ≤ 6. Gleason 7 tumors were equally represented in both arms, while there was a 27% increase in cancers with Gleason score 8 - 10, and with the inclusion of Gleason 7 tumors this was an absolute overall increase of 1.3%.

If this higher proportion of Gleason 8, 9, and 10 cancers was an actual biologic consequence of the relatively weak (compared to an LHRH agonist) intraprostatic androgen deprivation resulting from finasteride, a type II 5-alpha-reductase inhibitor, what mechanisms might be operative? By competitive enzyme blockade, finasteride decreases intraprostatic DHT by > 90%, and presumably this reduction swamps the effect of a seven-fold increase in intraprostatic testosterone. It isn't unreasonable to speculate that the DHT reduction inhibits the proliferation of premalignant and androgen dependent prostate cancer, and commensurately favors the growth of cells with more aggressive histology, which are thought to be both less growth dependent on DHT and less "hormone sensitive". Additionally, it is well known that one of the consequences of androgen deprivation is an associated alteration in the pattern of gene expression leading to increased transcription of the anti-apoptotic enzymes Bcl2 and survivin and other unwelcome gene products that may transform cells toward a higher grade.

One important result of finasteride's 5-alpha-reductase inhibition is a 25% reduction in gland size over about two years, an effect which would compress the gland density and actually should relatively increase the positive biopsy yields in finasteride treated prostates.

Does androgen deprivation lead to histologic alterations that artifactually confound pathologic grading? Epstein et al. addressed this issue in UROLOGY 53(4)1999: "Does long-term finasteride therapy affect the histologic features of benign prostatic tissue and prostate cancer on biopsy?" He commented "Leuprolide induces marked atrophy of prostate carcinoma cells, which sometimes makes pathologic diagnosis of cancer difficult, although evaluation at radical prostatectomy is easier than at biopsy". The more marked histologic alterations that result from Lupron treatment and castration has led to a consensus that Gleason grading should not be used after these treatments. The Epstein study addressed grading after finasteride and compared 53 biopsies showing cancer from 35 men treated with finasteride, and 18 on placebo, and concluded there were "no significant histologic differences" between the groups and that cancer could reliably be identified after finasteride treatment.

Kattan, Scardino et al. extended observations on this issue in BJU Int 95, 2005: "Gleason grade remains an important prognostic predictor in men diagnosed with prostate cancer while on finasteride therapy". They studied 45 men who had been on finasteride for > 6 months before the diagnosis of prostate cancer and reported the outcome after a median of 23.6 months of follow-up. The Kattan post-prostatectomy nomogram predicted a 5-year PFS of 85%. The real-life actuarial PFS was 86%. Conclusion: "Finasteride does not appear to compromise the assignment of Gleason grade for use in prediction tools before or after RP... ".

In the Epstein study the numbers were too small to allow detection of a difference in Gleason scores that might have developed in their two groups as a result of finasteride therapy. And, likewise, the Kattan study of 45 men did not address that point, and was underpowered to do so.

Drs. Eric Klein, Ian Thompson et al.(JCO, Oct. 2005) presented an innovative analysis, "Assessing Benefit and Risk in the Prevention of Prostate Cancer: The Prostate Cancer Prevention Trial Revisited", in which several absolute benefit/absolute risk ratios were calculated based on assumptions that the higher Gleason scores were produced to various extents (e.g., 0%, 10%, 25%, or 50% of cases) by a hormone induced artifact from finasteride and were, therefore, not biologically consequential. The benefit/risk ratio assuming no artifact (e.g. entirely due to a biologic effect) was 4.6:1 and increased to 9.2:1 if artifact accounted for 50% of the higher Gleason scores. The Klein article led to a rather

insightful rejoinder commentary by James Talcott in the same JCO issue wherein the reader was reminded of "type I and type II errors of inference" and, simply put, argued that in the case of the PCPT it was much more important to avoid interpretations that, if in reality were incorrect, would lead to harm (e.g discounting the possible consequence of the more aggressive Gleason scores). He cautioned that greater potential harm resulted from focusing on reductions in the more "benign" cancers, which characteristically are slower to develop and are better treated, and thereby miss the chance to intervene in what might be more aggressive cases.

We now return to a brief summary of the Bostwick, Civantos review, the title of which is the lead for this Commentary article. Their conclusion: "The Gleason grading system should not be used after finasteride treatment as it is not validated in this setting and is likely to overestimate the biologic potential of high-grade cancer observed after therapy". They clearly imply that the histologic changes that have raised such concern are hormone induced artifacts, and that chemoprevention trials using agents that alter morphology should not rely on Gleason grading as a endpoint, but instead focus on survival outcome (an endpoint that will eventually emerge from the PCPT data). They noted that the histopathologic alterations were less prominent than following LHRH agents, but "Finasteride treatment created small clusters of shrunken acini morphologically similar to post atrophic hyperplasia and atypical adenomatous hyperplasia" with "variable distribution throughout the prostate ... strikingly reminiscent of lobular carcinoma of the breast". Their conclusion regarding artifactual alteration was supported by their observation that "the relative over-interpretation of Gleason score $\geq$ 7 in the finasteride arm was more pronounced in years 1 and 2 of the PCPT and thus more likely caused by treatment-induced architectural changes rather than to the de novo development of more aggressive cancer."

Dutasteride, a dual inhibitor of the 5-alpha-reductases, is replacing finasteride in many urologic practices and is the agent under study in the placebo-controlled chemoprevention trial, "REDUCE". Bostwick, Andriole et al. addressed the histologic effects of this newer drug in "The dual 5-alpha-reductase inhibitor dutasteride induces atrophic changes and decreases relative cancer volume in human prostate", UROLOGY 65(1)2005. In a treatment period of 5 - 10 weeks 17 men took dutasteride and 18 placebo. Results: tumor volume was significantly reduced in the dutasteride group, the percentage of atrophic epithelium increased, and the stromal/gland ratio was doubled. If these post-dutasteride architectural changes, similar to those following finasteride therapy, are associated with Gleason upgrading in the REDUCE trial, Bostwick and others will likely offer the same caveats to the interpretation of the REDUCE trial as they posited for the PCPT.

Bottom Line: Although the evidence is still being weighed, currently the preponderance of evidence suggests that finasteride treatment does not lead to the development of more aggressive prostate cancer.