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DIAGNOSTICS: Detecting prostate cancer: How can we improve?

The current argument that screening for prostate cancer is a fool's mission really misses the point. Admittedly, the experts who opine about the inefficiency of testing to prolong life by using a combination of PSA and DRE routinely end their discussions with a paean about the need for new biomarkers. And they are right. But the understandably unsophisticated lay public gets only half the message: i.e., "don't get a PSA!", screening is useless - or worse.

What are we to do about the 15% of men who have cancer at a PSA less than 4 ng/mL, of which 15% have aggressive disease with Gleason scores $\geq$7; and the +/- 25% men whose disease is already metastatic at diagnosis? Those are the proper targets for renewed efforts to improve early detection. By employing a strategy of active surveillance for appropriately selected men with suspected "insignificant" cancer, combined with an informative discussion with their urologist, can help blunt the criticism of current "overdiagnosis."

Ancillary biomarkers are already in hand which, singly or in combination, can tweak the PSA toward greater specificity: i.e., age related "normal" PSA ranges; percent free PSA; PSA velocity prior to diagnosis; and starting PSA testing at age 40 so as to afford a background trend. D'Amico has shown that a PSA velocity of >2ng/yr points to aggressive disease. All of these refinements have been addressed in prior Commentaries, indexed under "Diagnostics."

Despite criticism of methodology, the recently published European study has claimed that lowering the biopsy threshold to ≥3 conferred a 20% survival benefit. (The US study used a threshold of 4 ng/mL, and failed to show a survival advantage to their screening regimen.) Perhaps combining the additional biomarkers mentioned above with the lower threshold would increase the specificity of the larger group of men who would be caught in the wider net of the lower threshold.

A new frontier in diagnostic technique is emerging and based upon divining the molecular clues found in exfoliated cells and other elements swept into the urine after the proverbial "attentive" prostate massage.

The PCA3 urine test is already commercially available, but perhaps may be underused. [See PCa Commentary, Nov.-Dec. 2008 - PCA Urine Test - Increasing Applications.] A comprehensive review by Kirby of the current status of this test appears in BJU Int, Vol.103, 2009: "Prostate cancer diagnosis in the new millennium: strengths and weaknesses of the prostate-specific antigen and the discovery and clinical evaluation of the prostate cancer gene 3 (PCA3)." For those clinicians who might be considering introducing the PCA3 test into their practice, a "must read" discussion is "Rational approach to implementation of prostate cancer antigen 3 into clinical care," by Wang and Chinnaiyan,(Cancer, June 10, 2009).

The authors collectively point out:

1) PCA3 gene expression is highly specific for prostate cancer and as the ratio of urinary overexpression of PCA3 mRNA relative to PSA mRNA increases so does the likelihood of underlying prostate cancer. The suggested threshold PCA3 value for concern is >35 units.
2) "Adding PCA3 to serum PSA improved prostate cancer prediction. (Wang)." Currently it is recommended that the test only be performed in conjunction with PSA and not used as a screening tool in an unselected population. All the published data about PCA3 is based on men selected for possible biopsy due to an elevated PSA, other biomarkers of concern, or premalignant HGPIN. In this selected cohort, "The overall sensitivity and specificity of a PCA3 score of >35 for a positive biopsy ... were 52.9% and 80%, respectively, with a negative predictive value of 66.1%. With the cut-value raised to 50, the sensitivity was 69%, specificity 79%, and the the negative predictive value increased to the 80% to 90% range. These data are significantly superior to the performance of the PSA test when used alone. Kirby suggests that the test can "increase confidence in an initial biopsy decision where the serum tPSA results are uncertain (2.5-10ng/mL)."
3) PCA3 testing could be used to increase confidence in a re-biopsy in men where the DRE and serum PSA remain suspicious, but the initial biopsy was negative. Repeat biopsies are positive in this setting in about 25% of men. "At a PCA3 score threshold of 20, repeat biopsies would have been reduce by 44% while missing only 9% of cancers" (Kirby).
4) The PCA3 can suggest a distinction between aggressive and indolent cancers. "The median PCA3 scores were higher in "insignificant" cancer than in indolent disease (42.1 vs 21.4, P=0.006); higher for Gleason scores of ≥7 vs <7 (P=0.004); and higher for stage T2 vs T1c cancer (P=0.005).

Wang concludes: "... if our objectives are to minimize unnecessary prostate biopsies and to optimize early PCa detection, then the PCA3 appears to be worthy of systematic, large-scale validation to clarify it role as a passing trend or as a valuable next-generation biomarker for the detection of PCa."

QUALITY OF LIFE: Quality of life after initial therapy for prostate cancer - An assessment at 48 months

Dr. Mark Litwin and his colleagues at UCLA have updated their reported 2-year follow-up (*Cancer. 2007)* of 475 men treated for prostate cancer at their institution: "Survivorship Beyond Convalescence: 48-Month Quality-of- Life Outcomes After Treatment for Localized Prostate Cancer," JNCI. June 16, 2009. The motivation for their careful study arose from their opinion that "no treatment has proven

superiority in prostate cancer control [and] treatment side-effect profiles often determine treatment choices."

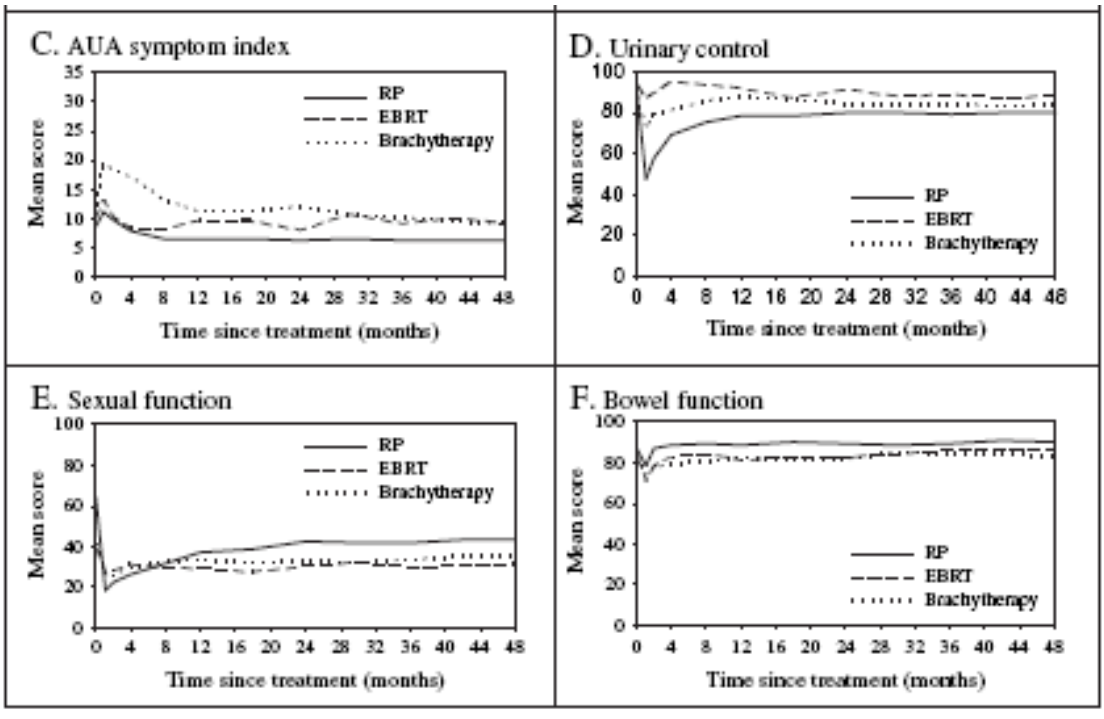
The 2-year study was discussed in the March/April, 2008, PCa Commentary. The new report is based on continued follow-up of these men: 307 treated with prostatectomy (RP); 78 with external beam radiotherapy (ERBT); and 90 who received brachytherapy (BT). Evaluation was made at baseline and at eleven subsequent points up to 48 months. The data illustrates the probability of returning to baseline function following each of these treatments.

Urinary voiding and storage symptoms were evaluated in the AUA Symptom Index, and urinary control, sexual function, and bowel function were registered by the UCLA Prostate Cancer Index. The mean ages of the men in the three cohorts were: RP, 60.1 years; ERBT, 70.8; and 68.4, BT. As would be expected the younger men had better sexual function at baseline; and in this study ERBT patients had "more aggressive tumor characteristics and higher pretreatment PSA levels." The study's findings are summarized below:

"Urinary incontinence was more common after prostatectomy. Voiding and storage urinary symptoms were more common after brachytherapy. Sexual dysfunction profoundly affected all three treatment group, with the lowest likelihood of regaining baseline function after prostatectomy. Bowel dysfunction was more common after either form of radiation therapy."

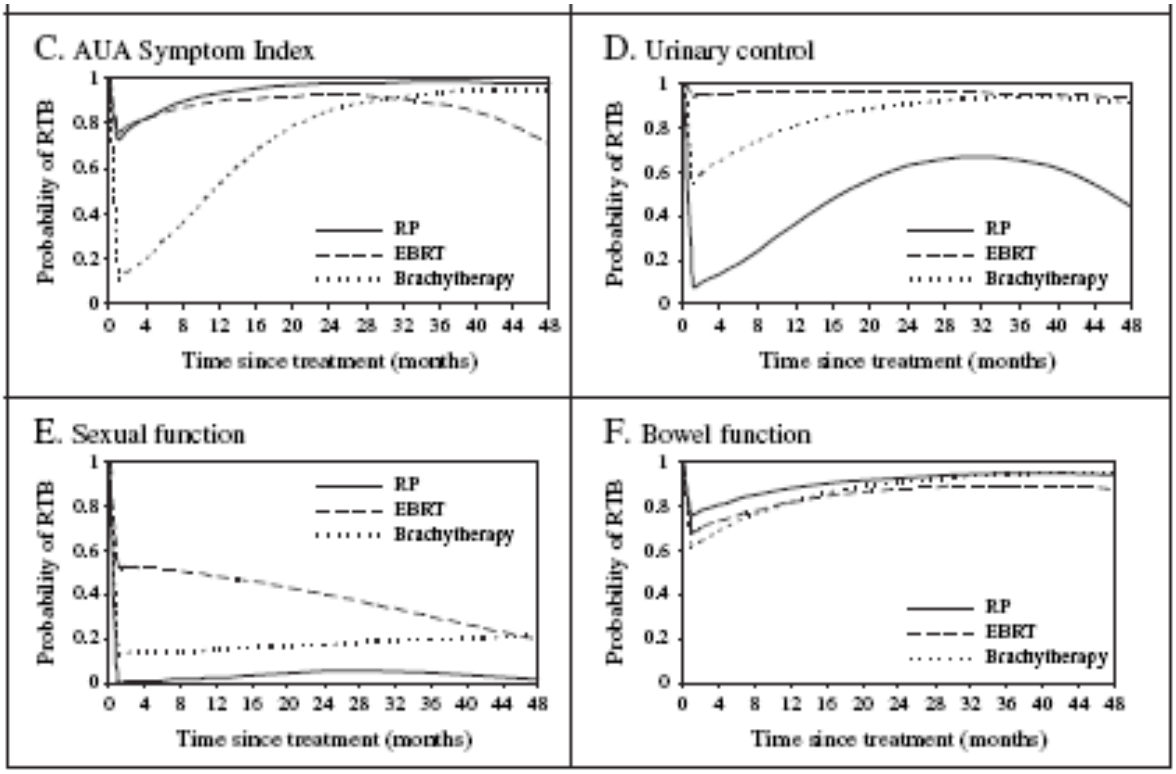
Additionally, ERBT led to a "progressive worsening of urinary function related to storage and voiding symptoms. ... [and] progressive decline in sexual function throughout the 48 months of treatment."

The optimal method of displaying this data is graphical. The first set of four graphs presents the longitudinal mean scores of health related quality-of-life from baseline to 48 months. In the AUA Symptom Index higher scores (graphs "C") indicate worse function, whereas on graphs D, E, and F higher scores indicate better function.



Time (Months):	0	1	2	4	8	12	18	24	30	36	42	48
Sample size (No.)	475	400	420	412	402	392	385	357	341	329	303	290

The second set of graphs depict the mean likelihood of return to baseline function.



Time (Months):	0	1	2	4	8	12	18	24	30	36	42	48
Sample size (No.)	475	400	420	412	402	392	385	357	341	329	303	290

Source: Gore JL et.al, Journal of the National Cancer Institute Advance Access Survivorship Beyond Convalescence:48-Month Quality-of-Life Outcomes After Treatment for Localized Prostate Cancer, Vol. 101, June 9, 2009

The study authors felt that their findings might help patients avoid undergoing] treatment discordant with preexisting detriments," i.e. "brachytherapy in men with severe baseline voiding symptoms", or radiation therapy in "subjects who had worse bowel function scores at baseline."

Clearly, this well supported information regarding quality-of-life sequelae from primary treatment can enhance decision making for patients and clinicians alike.

HORMONE INTERVENTION: Increased androgens following castration: New evidence implicates greater role

Dr. Lebrie, Laval University, Toronto, has been a long-time researcher into the role of adrenal androgens driving prostate cancer progression. His concepts led to the regimen of "combined androgen blockade (CAB)" - conventionally an LHRH agonist combined with a non-steroidal antiandrogen. The antiandrogen was employed to combat the *then* estimated 10% of total circulating androgens arising from adrenal sources. His new work, based on mass spectrometry technology, found that castration "reduces the total androgen pool by only about 60% leaving 25 to 50% of intraprostatic dihydrotestosterone (DHT) in the gland after castration. (Journal of Steroid Biochemistry & Molecular Biology, 113(1-2), 2009 Jan.) Metanalyses have indicated that conventional CAB only confers a 3-5% survival advantage over castration alone (medical or surgical) in men with advanced disease. Labrie's new data may suggest that this rather modest benefit may actually be a result of relative ineffectiveness of first-generation antiandrogens, i.e. Casodex and Eulexin, used in standard CAB, considering that the

affinity of the available antiandrogens are *30 fold less* than that of DHT, the natural ligand for the receptor.

The current understanding of steroidogensis in prostate cancer has advanced considerably since the early days of CAB, with the work of Montgomery and others establishing the capacity of prostate cells to manufacture androgens endogenously from precursors, such as cholesterol, even in the face of castrate levels of circulating androgens.

Two promising drugs relevant to this biology are under development. Possibly the second-generation antiandrogen, MDV3100, with its much greater affinity for the androgen receptor, combined with abiraterone, a pan-inhibitor of androgen steroidogeneis in testis, adrenal gland, and prostate cells, may become a new and more effective "CAB."

Labrie concluded: "The most significant therapeutic implication of these findings is the absolute need to add a pure (non-steroidal) antiandrogen to castration in men with prostate cancer after castration."

NEW AGENTS FOR TREATMENT: Custirsen, an antisense therapy: - Promising results of a Phase II trial of a new inhibitor of the stress-protective molecule, clusterin, in patients with castrate resistant prostate cancer (CRPC).

The News: At the recent ASCO meeting an abstract was presented detailing a study led by Drs. Martin Gleave and Kim Chi, Vancouver, BC, Prostate Center, along with his colleagues in the National Cancer Institute of Canada Clinical Trials Group. The study compared the new anti-clusterin molecule, custirsen (OGX-011), *combined* with standard docetaxel/prednisone versus the standard docetaxel regimen alone in a randomized trial of 82 metastatic chemotherapy-naive men. Three separate analyses indicated a survival benefit in patients treated with OGX-011 in combination with docetaxel compared to docetaxel alone – the current standard care for patients with advanced prostate cancer. The median overall survival in patients with advanced metastatic prostate cancer who were treated with OGX-011 plus docetaxel in a randomized Phase 2 trial was 23.8 months compared to 16.9 months for patients treated with docetaxel alone, suggesting a 6.9 month survival advantage in the OGX-011 arm. The unadjusted hazard ratio (HR), a measure used to determine the difference in survival between treatment groups, was 0.61, representing a 39% reduction in the rate of death for patients treated with OGX-011. A prospectively defined multivariate analysis indicated that the significant predictors of overall survival were treatment arm, performance status, and presence of visceral metastases. Patients treated with OGX-011 had a rate of death 51% lower than patients treated with docetaxel alone (HR=0.49; p=0.012).

Cellular expression of clusterin was decreased by 18% in the custirsen cohort compared to an increase of 8% in the control arm. The OGX-011 plus docetaxel arm met the primary endpoint of the trial given that 58% of patients treated with OGX-011 plus docetaxel achieved confirmed PSA declines of 50% or greater.

These are early results and planned Phase III trials in men with metastatic CRPC combining OGX with chemotherapy as *first-line* treatment have received Fast Track designation by the FDA. The reported initial results compare very favorably with the customary extension of median survival in the same category of patient of 2 months with standard docetaxel/prednisone chemotherapy, and with the early reports of a ~4 month extension for the immunotherapy drug, Provenge.

OGX-011 is a product of OncoGeneX Technologies, Bothell, WA. and Vancouver, BC.

The Background: Clusterin is a protective intracellular molecule whose production is increased in various conditions of cellular stress - importantly, as a result of hormone therapy, radiation, and chemotherapy. Dr. Gleave et al. presented an extensive discussion of the basic molecular biology and early studies of clusterin in their article: "Custirsen (OGX-011): a second generation antisense inhibitor

of clusterin for the treatment of cancer," in Exper.Opin.Investig.Drugs (2008)**17**(12). Some of the major points are summarized below.

Clusterin "contribute[s] to therapeutic resistance and cancer progression, including increased expression of pro-survival or anti-apoptotic genes... ." Upregulation of clusterin is a *basic* protective response to a wide variety of cellular stresses, functioning in the boiler room of cellular architecture, and operative not only in prostate cancer, but also in breast, non-small lung, colorectal, bladder and kidney cancer. In "preclinical efficacy studies in animal tumor models custirsen has been shown to significantly enhance the therapeutic effect of hormone therapy, chemotherapy and radiation therapy" by inhibiting clusterin's action. In patients with CRPC "encouraging responses were seen with *re-treatment* with docetaxel when combined with custirsen ... .," thereby reversing docetaxel resistance.

As stated in the title of Dr. Gleave's article, custirsen employs "second generation antisense" technology which allows a longer drug half-life and facilitates intermittent IV dosing. Antisense molecules - single strands of DNA - incorporate about 20 carefully selected nucleotides crafted to be *precisely* "complimentary" to a very specific sequence of bases on a very specific strand of mRNA. The antisense molecule bonds to its perfectly matched mRNA "mirror-image" mate and marks it for destruction. Once deployed into the relatively vast nuclear volume, traversed by a myriad of diverse mRNA molecules, a well designed antisense molecule destroys only its intended mRNA target. This is molecular biology's version of the proverbial "finding the needle in the haystack." The advantage is exquisitely targeted specificity and limitation of unwanted side effects, which in the case of custirsen are some degree of rigors, fatigue, fever, rash, diarrhea, and minimal hematologic toxicity.

Antisense technology may very likely be at the leading edge of a new era of therapeutics. Another second-generation antisense therapy, ALT1101, in which Dr. Gleave is also a co-developer, is an inhibitor of the insulin-like growth factor-1 receptor, that in early studies potentiated the the action of Paclitaxel, and, additionally, functioned to overcome resistance to the drug.

Dr. Gleave concludes that if further testing of custirsen is positive "this would be the first antisense therapeutic to demonstrate clinical benefit in patients with cancer."