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DIAGNOSIS — A Nomogram Integrating Variables Affecting Outcome Of Salvage Radiation Therapy Post-Rp:

The decision of whether to offer "salvage" XRT to men showing only biochemical evidence of recurrence post-RP is currently and will remain an inexact science. The distinction of whether there is a systemic component in addition to local recurrence is just too subtle for clear analysis with our current diagnostic modalities. Even though the great majority of men, possibly as many as 85%, undergoing salvage XRT will show a marked PSA decline, thus indicating some component of local recurrence, subsequently PSA failure reoccurs in well over 50%. The prudent desire to avoid the morbidity of local XRT has spawned a great plethora of studies each with its unique set of chosen variables and resulting guideline. A promise of assistance in this this decision appears in abstract #1577 in the 2003 ASCO Proceedings wherein a consortium of prominent specialists collaborated to create a nomogram (to be published soon) integrating multiple variables to predict the outcome of salvage XRT. The pre-treatment variables selected

are: pre-RP PSA, pre-XRT PSA, pre-XRT PSA doubling time, Gleason sum, pathologic stage, surgical margin status, time to biochemical recurrence, neoadjuvant hormone therapy, and XRT dose. Their model is based on 375 men, 108 exhibiting a persistently post-RP elevated PSA (above 0.1 ng/ml) and a second group of 267 who developed biochemical recurrence defined as a PSA rising above 0.1 ng/ml. The median follow-up post XRT was 35.8 months, the median time to recurrence was 11.6 months, and the median freedom from progression was 32.2 months. In keeping with many other studies, the highly significant variables were Gleason sum, P=0.0002; pre-XRT PSA, P=0.001; PSA doubling time, P=0.002; positive surgical margins, P=0.003; and neoadjuvant hormone therapy, P=0.003. Overall the 2-year and 5-year actuarial biochemical progression free probability was 57% and 31% respectively.

Many good studies have addressed this issue and the familiar gestalt for successful application of salvage XRT is in situations of low grade cancer and a slow and low rise in PSA. Shild from the Mayo Clinic selected a rise of PSA above 1.1 ng/ml as the critical point. He is somewhat unique in reporting usefulness for the Prostascint scan: a negative scan was associated with a 70% "biochemical control rate" which fell to 22% for a positive scan. However, in his opinion its value was unclear when the PSA was <1 ng/ml. A second study by Do, UCI Medical Center, reported on 73 men with adverse pathological features on the RP specimen who underwent salvage XRT for rising PSA. This group showed a 45% bRFS at 10 years. These two studies and many more are difficult to compare. The difficulty of arriving at a unified generalization results from small sample sizes, selection of different variables, and different definitions of end points, and different means to exclude systemic disease.

And therein lies the value of the forthcoming "Kattan" nomogram, which has ample sample size and incorporates the most important predictive factors. Most importantly the nomogram permits data point entry along a spectrum of continuous variables instead of entry into a grouping of values, such as "PSA 4 - 10". In this way each element is allowed to influence the final outcome prediction according to its own degree of adversity for affecting outcome. The clinician is still left with the decision of how to employ this risk data in his management choice, but with the nomogram he can feel that the factors of known significance have been given due weight.

Bottom Line: The Kattan nomogram will be published soon to help in the decision about offering salvage XRT post-RP in situations of rising PSA.

BIOLOGY Genetic Variations Causing PSA Variations

An Additional Snippet of Difficulty in PSA Interpretation: As if management decisions based on PSA values were not already difficult enough, an additional confounding factor has been reported. An article in JNCI, July 16, 2003 ("Association Between Genetic Polymorphisms in the Prostate-Specific Antigen Gene Promoter and Serum Prostate-Specific Antigen Levels") reports that as many as 20% of men may have PSA values raised by the presence of single nucleotide polymorphisms (SNPs - commonly called "snips") that render the promoter of the PSA gene more responsive to androgen receptor activation, thereby increasing the cellular PSA production. A "SNP" refers to the mistaken substitution of a single nucleotide in a gene, such as a substitution of Cytosine for Adenine, thereby subtly changing the genetic code sequence, and as a result, altering the resulting translated protein (in this case the rate of protein production) to a slight, but consequential extent. This was a meticulous genetic study of 409 healthy men. The study found that in the age group 51 - 60 years men with "normal" genetics had a mean PSA of 1.0 ng/mL, whereas in the 20% of men carrying the SNPs the mean PSA was 1.5 ng/mL. In age range

61 - 70 the increase was from a mean of 1.6 ng/mL to 2.4 ng/mL. In their overall study cohort (≤ 50 - >70) the increase was from 1.4 ng/mL to 2 ng/mL. They proposed "the initiation of studies that comprehensively assess the utility of these SNPs in models that attempt to define the appropriate PSA cutoff value for determining whether a man should undergo further screening by prostate needle biopsy."

Bottom Line: Give us a break! But we will have to accept further challenges in PSA interpretation.

HORMONE INTERVENTION Hormone News - (Actually, Anti-Hormone News)

SOMETHING GOOD IS HAPPENING. "Since the introduction of testing for PSA, the incidence of prostate cancer has increased, whereas the mortality from this disease has decreased" from a death rate of 26.4/100,000 to 21.5/100,000, a decline of 2.6% per year (Albertson, "The Prostate Cancer Conundrum", JNCI, July 2, 2003). Why? Whether this is due to PSA screening, better local control, or the more widespread use of hormone intervention is unclear. Cooperberg (ibid) cites the marked increase in androgen deprivation therapies at all risk levels of prostate cancer and highlights the survival advantage of its early use in the Bolla trial involving XRT in high risk PC patients, and Messing trial in N1 patients post RP. An even more forceful endorsement of the early use of androgen deprivation intervention came from the prominent biostatistician, Sir Richard Peto, PhD, at the European Cancer Conference (abst. 328), September 2003, reporting on the worldwide collaborative meta-anaylses of the randomized trials of hormonal treatments for early breast cancer and non-metastatic prostate cancer. In both diseases there was a highly significant decrease (P=<0.00001) in cancer specific mortality over the past 10 years and this was seen with little effect on mortality from other causes. The prostate trials were composed of a total of 3000 men with non-metastatic PC and compared immediate versus deferred hormonal treatment. Their analysis contends that the earlier application of hormone intervention (as opposed to "delayed") was associated with a 12% lower mortality. Overall, in the last ten years, Dr. Peto reported there was a 33% decline in risk of prostate cancer deaths in the USA resulting from earlier detection, local control, and hormone therapy.

ALTERNATIVES TO LUPRON AND ZOLADEX: AN UPATE

CASODEX 150 mg: Some men decline the appropriate recommendation for androgen deprivation because of the concern about the "side effects" that accompany the testosterone lowering resulting from from LHRH agonists. In Europe a common form of hormone intervention is 150 mg/day of Casodex, a drug that actually raises testosterone while lowering the intracellular dihydrotestosterone by 90%. The regimen combats the progressive loss of bone density associated with LHRH agonists. Abstract #83 in the Proceedings of the 45th Annual ASTRO Meeting ("Bicalutamide 150 mg as Adjuvant to Radiotherapy Significantly Increases Progression-Free Survival [PFS] in Early Prostate Cancer") presents an interim report at 3 years of the Early Prostate Cancer (placebo controlled) Trial in which the drug was associated with a 42% comparative prolongation of PSA-PFS. The benefit was clearest for patients at greatest risk for disease progression. Gynecomastia was the major side effect, and nipple irradiation should precede therapy. Astra-Zeneca, the drug manufacturer, has recently cautioned about a slight increase in cardiac events from this dose, a dose not currently approved for use in the USA.

PROSCAR (finasteride)/ EULEXIN or CASODEX: Proscar 5 mg/day combined with either Eulexin 250 mg/tid or Casodex 50 mg/day represents another alternative to LHRH agonists. The question of whether an LHRH agonist or castration could "salvage" men upon failure from one of these combinations was addressed in the article, "Finasteride and Flutamide Therapy in Patients with Advanced Prostate Cancer: Response to Subsequent Castration and Long-Term Follow-up" (UROL, July 2003, p.99). The initial fall

in PSA from the F/F combination was 94%, gynecomastia was mild to moderate, erectile function remained intact in 55% of men whose function was normal at baseline, and in 25% (5 of 20) the disease remained under control at 7 years. Twelve men who subsequently failed initial F/F treatment were then treated with Lupron (11) or castration. All experienced a >50% decline in PSA (mean 89%, range 62% - 100%). "Castration [with Lupron] appears to have a shorter duration of response than if started initially, but the overall period of hormonally sensitive prostate cancer is more than 4 years."

Bottom Line: There are several ways to intervene in androgen sensitive prostate cancer, but intervention - possibly especially early intervention - is increasing survival.

DIAGNOSIS Post Therapy PSA Doubling Time Of <3 Months Is A Surrogate For Prostate Cancer Specific Mortality

It is intuitively known that a rapid post primary treatment rise in PSA is an adverse predictor for survival. However, quantification and refinement of this relationship was the subject of a study by D'Amico et. al. in the September 17, 2003 issue of the JNCI: "Surrogate End Point for Prostate Cancer-Specific Mortality After Radical Prostatectomy or Radiation Therapy." The analysis was performed on the combined CAPSURE and CPDR data bases involving 8669 men with localizedor locally advanced, non-metastatic disease. 5918 were treated with RP and 2751 with radiation. PSA was evaluated q 3 months for 2 years, q 6 months for 3 more years, and then annually. The median follow-up for the 1451 treatment failures was 4 years. The minimum PSA level for calculating the PSA-DT (doubling time) was >.2 ng/mL (the biochemical failure point) and doubling time was based on at least 3 PSA measurements with a requirement that each increase was > .2 ng/mL. In order to establish a common PSA starting point for DT estimation between the two types of treatments, in calculating the PSA-DT for radiation patients the post treatment nadir PSA value ("typically less than 1.0 ng/mL within 2 years after radiation therapy") was subtracted from any subsequent measured PSA. For example if the nadir had been 6 ng/mL and a subsequent measured PSA was .9 ng/mL, .3 (a "failure" since it exceeds .2) would be entered in the DT calculation for that data point. Their conclusion: the cohort with a < 3 month PSA-DT after PSA failure had a nearly 20-fold increased risk of prostate cancer-specific mortality compared to the > 3 month cohort, and "the median survival after PSA-defined recurrence in such patients is only 6 years." By validating our intuitive concern in this matter, the authors provide a strong rationale for the early institution of additional therapy in this high risk group.

Bottom Line: A post treatment PSA doubling time of <3 months argues for preventive intervention

SCREENING Screening Interval And PSA < 2 ng/ml: Second Study Suggests Screening Interval Of 2 Years.

Dr. David Crawford has already reported that a man with a PSA of 1.0 - 1.9 ng/mL has a 98% likelihood of having a PSA of <4 after two more years (PCa Commentary, December 2002). Now a second report gives support to a screening interval of 2 years for men with a PSA of < 2 ng/mL ("Prostate specific antigen based biennial screening is sufficient to detect almost all prostate cancers while still curable," J Urol 2003, May). The study reported on a screening program in men (ages: 50 to 65 years) first screened in 1995-96 (5854 men), and again in 1997-98 (5267 men). If a screening PSA was >3 ng/mL a DRE, TRUS, and sextant biopsy were done. At the first screening 145 cancers (2.5%) were diagnosed, and 111 (2%) at the second screening 2 years later. Only 9 cancers ("interval cancers") were diagnosed outside of the screening program during the 2 year interval. "None of the 2950 men with an initial PSA of < 1 ng/mL had [developed] a PSA of > 3 ng/mL or interval cancer." After analysis of all data they

concluded: "In men with a PSA of less then 2 ng/mL it seems safe to offer repeat screening after two years with PSA only."

This less aggressive screening schedule is given indirect support by Dr. Stamey et. al. who concluded "Serum PSA levels between 2 and 9 ng/ml have a weak and unreliable relationship with prostate cancer but a strong relationship with prostate weight and hence BPH." Their analysis addressed in detail the confounding effect of the contribution to total PSA of an enlarging mass of BPH in the lower PSA range. The article: "Preoperative Serum Prostate Specific Antigen Levels between 2 and 22 ng/ml Correlate Poorly with Post-Radical Prostatectomy Cancer Morphology: Prostate Specific Antigen Cure Rates Appear Constant Between 2 and 9 ng/ml", J Urol, January 2002.

Bottom Line: A two year screening interval for men with PSA <2 ng/mL is acceptable

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