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Prostate Cancer - Special Issue

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"CAN AGGRESSIVE PROSTATIC CARCINOMAS BE IDENTIFIED AND CAN THEIR NATURAL HISTORY BE ALTERED BY TREATMENT?"

This question is the title of the article by Quinlan, Partin and Walsh, UROLOGY 46 (Suppl 3A), 1995, for which a partial answer is gradually emerging. The extent of relevance of this issue today is documented by the prevalence of high-grade prostate cancer at diagnosis reported in "Prevalence of Prostate Cancer Among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter" (Ian Thompson et al, NEJM May 27, 2004). Fifteen percent of the total of 2950 biopsied men [the control arm of the finasteride study] showed cancer, and 15% *of these* had high-grade cancer (Gleason 4+3, 8, and 9). Based on an estimated 232,000 new cases for 2005, and considering that many men will be diagnosed with a PSA value of greater than 4 ng/mL, in 2005 high-grade disease will be found in more than 35,000 men!

Organ Confinement of Prostate Cancer at Diagnosis: A Critical Factor for Optimal Treatment Outcome for High-Grade Disease

It is well recognized that the magnitude of "aggressiveness" of high-grade disease and the outcome of its treatment are significantly influenced by the interplay of the PSA level at diagnosis, Gleason score, and the clinical and pathologic tumor stage. The Partin tables and the nomogram built on CaPSURE data, which substitutes percentage of biopsy cores positive for clinical tumor stage, are relied upon to predict the underlying prostate pathology that is likely associated with the various permutations of these three predictive factors. The Kattan, Wheeler, and Scardino article, "Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer" - the title of their JCO May 1999 analysis, extends predictions based on these variables to an estimation of a man's freedom from PSA recurrence at 2, 5, and 7 years. (This is available on the Web at www.mskcc.org/mskcc/html/5794.cmf). Underlying all these calculations is the primacy of organ confinement of prostate cancer as the major predictor of favorable treatment outcome, and the most heavily weighted factor that determines organ confinement is the absence of extra-capsular extension of cancer. The pathologic description of capsular invasion may be further refined by measurement of the *extent* of capsular penetration and a determination of

"specimen confinement" in the surgical specimen. The critical importance of capsular invasion was highlighted by Wheeler, Scardino et al in their August 1998 Human Pathology article: "Prostate cancer does not appear to metastasize in the absence of invasion into the capsule regardless of the volume or grade of the intracapsular tumor".

Outcomes of Surgical Treatment of High-Grade Prostate Cancer

Is there a documented benefit to treatment of high-grade cancer when it is organ confined? Two representative surgical series document improved outcome when high-grade disease is treated at this stage. Mian et al (M.D.Anderson) analyzed this issue in "Outcome of Patients with Gleason Score 8 or Higher Prostate Cancer Following Radical Prostatectomy" (J UROL, April, 2002) and concluded: "Patients with *specimen confined* disease had a significantly higher 5-year disease free survival than those with non specimen confined disease (84% and 50%, p <0.0001)" and "the pathological status of the surgical specimen was the most significant independent predictor of disease recurrence".

Hull, Wheeler, Scardino et al (J UROL February 2002) - "Cancer Control with Radical Prostatectomy Alone in 1,000 Consecutive Patients" - found that "poorly differentiated cancer that is confined to the prostate pathologically is highly likely to be controlled with radical prostatectomy." Additionally, "Further evidence of the efficacy of surgery in poorly differentiated [organ confined] cancer was the 57.6% $\pm$ 21% 10 year metastases free survival rate for high-grade cancer in this series..."

The outcome of diagnosis and surgery of organ confined high-grade (in this case Gleason 8-10) was reported by Epstein, Watch, Kattan et al in "Probability of Biochemical Recurrence by Analysis of Pathologic Stage, Gleason Score, and Margin Status for Localized Prostate Cancer, UROLOGY 62(5),2003. Men with Gleason scores 8-10 organ confined cancer showed a bRFS at five years of 62% (range 51-70) and 41% (range 29-55) at 10 years. The Kattan post-operative nomogram individualizes estimates by entering the parameters as continuous variables. For example, a man with a pretreatment PSA of 4, a specimen Gleason score of 9, with organ confined cancer is predicted to have a 91% probability of bRFS at 7 years.

"**Early Diagnosis" Doesn't Diminish the Likelihood of Finding High-Grade Disease**

Unfortunately, "early" diagnosis of prostate cancer at a low PSA level and in low volume doesn't have a commensurate "pay off" in finding less aggressive histology. Kupelian and Klein in their Cleveland Clinic series (CANCER. Dec. 2002) observed "that tumors of Gleason score 8 and above are not associated with the dominant pathologic stage migration observed with lower grade tumors during the PSA era...". In the data from the Prostate Cancer Prevention Trial referred to earlier, the prevalence of cancer was 15.2% in men with normal DRE exams and PSA levels of less than PSA 4 ng/mL. *Within this group* high-grade disease was found in 16% of men in the PSA range $\leq$.5 to 3.0 ng/mL and in 25% in the PSA range between 3.1 and 4.0 ng/mL. Although in the past it was believed that a more aggressive histology gradually evolved over time as a result of increasing mutations, currently there is an emerging body of evidence that in most instances high-grade disease is "born that way". PSA screening and increased prostate cancer awareness has resulted in the diagnosis of cancer at the cT1c stage in 60% to 70% of new cases suggesting that the major gains of finding low volume prostate cancer have been made and that clinicians will continue to confront a significant percentage of high-grade disease at diagnosis.

The Dilemma Posed By The Decreasing Specificity of PSA At Low Levels For Identifying Low Volume, Organ Confined High-Grade Prostate Cancer

The question that arises from these considerations is what methods are available to clinicians to optimize the usefulness of the PSA test so as to increase the likelihood of finding organ confined disease in this relatively small, but important cohort of men with high-grade cancer? The amount of prostate-specific antigen that can be attributed to *prostate cancer* is considered to be proportional to the volume of that cancer, although when in association with significant amounts of BPH, initially the contribution of the prostate cancer to the total PSA can be hidden. Nonetheless it will always be advantageous to find prostate cancer - all grades of cancer - at the lowest possible PSA, but the diagnosis of high-grade disease at a point of low volume and organ confinement is especially crucial for optimal treatment.
Drs. Stamey and McNeal in their article in the Journal of Urology, October 2004, highlighted the increasing difficulty of identifying high-grade cancer in current PSA screening programs. Their analysis spanning 20 years of PSA screening found a decreasing utility of the *PSA level itself* in identifying low volume, high-grade cancer. Clinicians may have to transition from focusing on a "normal" PSA level of 4 ng/mL to other types of diagnostic information that can be gained from PSA interpretation particularly in the range of *less than 4 ng/mL*. The principle candidates for facilitating a more sophisticated interpretation of PSA values are: age-specific PSA ranges, percentage free PSA in PSA levels below 4 ng/mL, and the rate of PSA increase over time (PSA velocity).

Age-Specific PSA Ranges

The average PSA in men between 41-50 years is 1.2 ng/ml; for 51-60, 1.7; 61-70, 2.2; and for 71-80, 3.8. These values are soberingly lower than the upper range of "normal" set generously by Oesterling to include 99% of normal men (containing, of course, many men with cancer): age 40-49, <2.5 ng/mL; 50-59, <3.5; 60-70, <4.5; and 70-80, <6.5. By reducing the sensitivity level to only include 97.5% of normals the values would change, for example, to <1.81 for age 40-49 and <3.36, 50-59. It is interesting that the ranges chosen in the European literature are considerably lower. In the background for these ranges is the estimate that "For a healthy 60-year old man with no evidence of prostate cancer, the PSA concentration increases by approximately 3.2% per year, i.e. about 0.04 ng/mL yearly (Oesterling JE. JAMA. 1993 Aug).

In Judd Moul's excellent article "Population Screening for Prostate Cancer and Emerging Concepts for Young Men" (Clinical Prostate Cancer, Sept. 2003) he reports that the median PSA for army officers age 40 - 49 is between 0.7 and 0.8 ng/mL with only 8.2% over 1.5 ng/mL. Because of his heightened alertness to cancer Dr. Moul may be a more aggressive diagnostician than average, but it is instructive to note that and he would consider biopsying a man in this age group if his PSA were consistently >1.7 ng/mL.

In men younger than 60 years the use of age-specific PSA range to trigger a biopsy increases cancer detection by 8 - 18% and " 81% had favorable pathological results [i.e., organ confinement or capsular penetration with a Gleason score of < 7] (Partin & Oesterling, J Urol. 1996 Apr.).

Percentage Free PSA In The PSA Range of 2 - 4 ng./mL.

The application of the percent free PSA in this PSA range is controversial. However there is agreement that within this PSA window 20% to 30% of men with negative DREs harbor prostate cancer, and "up to 80% of those prostate cancers are clinically significant". Catalona found that in the PSA range 2.51 to 4 ng/mL 91% were pathologically organ confined (Urology, 54:220,1999).

The crux of the issue is the sensitivity/specificity trade off; but also relevant to the total issue is the intensity of a clinician's inclination to biopsy into this pool in search of high-grade cancers, for which there is the greatest gain from finding organ confined disease. If a clinician's

tendency is to biopsy early and often, then restricting biopsies to those men with normal DRE exams and free PSA values below 18% to 20% will avoid 73% of unnecessary biopsies (Haese and Partin. J Urol. 2002). But if a clinician has a conservative inclination, then he may be motivated by the information that a prostate biopsy of a man with ≤ 20% free PSA will yield a positive result in 50% of cases (Haese). Haese supports his suggestion by the comment "*Assuming regular monitoring of individual patients* with PSA of 2 to 4 ng./mL., sensitivity may not need to be as high as in the total PSA 4 to 10 ng./mL. range"; i.e. missed cancers will be found in subsequent testing.

Roehl and Catalona (J Urol 2002) were less sanguine about the application of % free PSA to guide biopsy decisions in the PSA range 2.6 - 4.0 in men with normal DRE exams. In their study of the outcome of biopsies in 965 men they found: "A 25% free PSA cutoff detected 85% of cancers and avoided 19% negative (cancer-free) biopsies..." and "Of those men who underwent radical prostatectomy 132 (80%) had pathologically organ confined disease." However, it is not standard clinical practice to perform biopsies in most men who have normal DRE exam and a PSA between 2.6 and 4.0 ng/mL. It could be concluded that by using Haese's cutoff of 18% to 20%, biopsies will be done, and cancers will be discovered - ones that would otherwise not have been found - and there will be a high probability of organ confinement

PSA Velocity

Probably the most informative dynamic of PSA is its rate of change over time - the PSA velocity. It is generally recognized that an increment of > .75 ng/mL per year signals a 72% likelihood of underlying cancer, but what is less recognized is that this figure is best applied in the PSA of 4 to 10 ng/mL. Because of the lower volume of cancers in the PSA range of < 4 ng/Ml a considerably smaller velocity can be informative.

This issue was addressed nicely by Fang, Ballentine Carter, et al in "PSA Velocity for Assessing Prostate Cancer Risk in Men with PSA Levels Between 2.0 and 4.0 ng/mL" (UROLOGY, June 2002). Access to sequential PSA levels in 21 men over a period of 18 or more months preceding the diagnosis of cancer allowed them to make a comparison with 68 controls and conclude that "The sensitivity and specificity [for predicting cancer] of a PSAV of 0.1 ng/mL/year was 81% and 50%, respectively". Also, they found that "The relative risk of prostate cancer was *6.53* (range 1.90 to 22.51) when the PSAV was 0.1 ng/mL per year or more compared with a PSAV of less than 0.1 ng/mL per year (P = 0.0029)". "The median PSA velocity across three measurements was 0.02 ng/mL for those with cancer and 0.01 ng/mL for those without cancer...". Their study suggests that in this low range of PSA a yearly increase of ≥ 20% may indicate cancer.

Riffenburgh's analysis, "Use of early PSA velocity to predict eventual abnormal PSA values in men at risk for prostate cancer" (Prostate Cancer and Prostate Diseases. 2003. June) comes to a similar conclusion: a yearly rise of 0.13 ng/mL was enough to "trigger the assignment of the patient to a high risk group".

D'Amico has emphasized the perspective that can be provided by awareness of the PSA velocity over several observations. The PSA velocity places *any subsequent PSA test into its dynamic context.* This has led him to suggest that several years of PSA testing should precede the now conventional starting point of age 50 for the average man, so that the most informed interpretation can be made.

Bottom Line: In the effort to find organ confined high-grade cancer - the stage associated with optimal treatment outcome - an informed use of age-specific PSA ranges, percent free PSA, and PSA velocity - singly or in combination - offers the strongest leverage.