SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 27: December 2004

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

DIAGNOSTICS: The Prostate Specific Antigen Has Become Less Informative Over The Past 20 Years.

Drs. Stamey, McNeal et al have offered a significant and consequential observation that the serum PSA level, especially in the range of < 10 ng/mL, no longer is reflective of prostate cancer, but only of benign prostate hypertrophy. Their important report, "The Prostate Specific Antigen Era in the United States is Over for Prostate Cancer: What Happened in the Last 20 Years?" (J Urol, Oct. 2004) documents their observations based on 1317 radical prostatectomy specimens. The issue under evaluation was "how well preoperative serum prostate specific antigen (PSA) reflects the *largest cancer* in consecutive untreated radical prostatectomies during the last 20 years at Stanford University." At its essence this article presents a challenge to the validity of the premise underlying PSA screening. Stamey maintains that "current evidence from the last 10 years is convincing that the relationship between prostate cancer and serum PSA is tenuous at best, especially with serum PSA less than 10 ng/mL...". They interpret their data as showing that there are "serious limitations in the relationship of serum PSA to prostate cancer volume and Gleason grade 4/5 cancer", rendering PSA currently "misleading in the diagnosis of prostate cancer".

As is well recognized, the characteristics of diagnosed prostate cancer have markedly changed over 20 years. The researchers categorized their findings into four 5-year periods. In the earliest 5-year period, beginning in 8/1983, the PSA level at diagnosis was highly significantly related to the *largest cancer*, and to the presence of capsular penetration, positive lymph nodes, seminal vesicle invasion, and to the percent of Gleason grade 4/5 in the largest cancer.

In the most recent period, 1/1999-7/2003, the statistically significant relationship in these associations has been lost. The differences in prostate cancer characteristics between the first and last period, no

doubt due to extensive screening, are not surprising and reveal the changing face of prostate cancer. The percent of palpable cancers on DRE decreased from 90.8% to 16.7%; the mean serum PSA at diagnosis dropped from 24.7 to 8.14 ng/mL; and the mean volume of the *largest cancer* shrank from 5.33 to 2.44 cc. Positive lymph node discovery decreased from 12.5% to 0.0%, and seminal vesicle invasion decreased from 23% to 5.4%. Notably, however, there was no significant change in prostate weight, 46.5 gm at first and 43.5 gm in the last period, which continued to be reflected by the PSA level.

The "nuts and bolts" of Stamey's argument lie in the calculations reflected in Table 4: "Comparison of Pearson correlations of preoperative serum PSA with radical prostatectomy morphology in the first and last periods". [Courtesy of Google: the Pearson coefficient measures the strength of a linear relationship between two variables, with a value of 0 (range -0.3 to +0.30) showing little or no association; +0.3 to +0.7 a weak association; and +0.7 to 1.0 a strong positive association.] The table shows that for the largest cancer the coefficient decreased from 0.659 to 0.148; for capsular penetration it declined from 0.539 to 0.033; for % seminal vesicle invasion - 0.437 to 0.069; and finally, for % Gleason grade 4/5 in the largest cancer the decrease was 0.274 to 0.031. By the last 5-year period there was "***no*** correlation of [the preoperative] serum PSA with any morphological variable except prostate weight.

An observation relevant to the increasing awareness that adverse histology may be present very early in the life history of some cancers was the finding that *despite* the observed transition over time to smaller, lower PSA cancers, 83% of which were eventually T1c compared to 7% at first, the percent with Gleason grade 4/5 showed a 13% increase from 31% to 35%!

In the background of Stamey's argument - and referred to in the article - is the data obtained by Sakr (Eur Urol,30:138,1996) who examined the prostates of accidental death victims of a wide range of ages. He found that the prevalence of *invasive* prostate cancer increased from 8% in 20 year old men to 80% in men in their 70's. Interestingly, the presence of HGPIN showed narly identical increasing figures for prevalence with aging.

Conclusions from the Stanford data suggest that in the current setting the PSA value no longer gives useful guidance for the detection of "significant" cancers. "This means that any excuse to biopsy the prostate has an excellent, age dependent chance of being positive." The authors' overall conclusion was that "What is urgently needed is a serum marker [in the PSA range of 2 to 10 ng/mL] for prostate cancer that is truly proportional to the volume and grade of this ubiquitous cancer, and solid observations on who should and who should not be treated...".

Bottom Line:: If we are persuaded by Stamey's argument that the "PSA today as a basis for diagnosing and treating prostate cancer is related only to the amount of benign prostatic hypertrophy in the prostate", where do we go from here?

DIAGNOSTICS: Candidates For The Next Generation Of Prostate Cancer Detection Tools

A resourceful effort has been made to tweak increasingly useful guidance from the PSA molecule and its several permutations, but a barrier preventing further progress seems to have been encountered. By optimally using tPSA information in the range of 2.5 to 10 ng/mL the positive biopsy rate remains around 20% - 30%. The use of complexed PSA may provide a modest, but significant, improvement over tPSA, increasing specificity from 20% to 34%. Combining the three forms of Pro-PSA may boost detection to > 40%. By using a cutoff value of <15% for the fPSA/tPRA ratio in the tPSA range of 2.5 - 4.0 ng/mL to indicate the need for biopsy 10% to 36% will be biopsied and 30% to 54% will have detectable cancers. Even more sophisticated combinations have been studied, such as fPSA/complexed PSA ratio, which achieved a 45% specificity.

Probably the most useful guide to detectable cancer is PSA velocity. Cancer will be found in 72% of men whose PSA velocity is >.75 ng/year, a value that maximizes the sensitivity/specificity balance at .20/.91. In fact, Riffenburgh (Prostate Cancer and Prostate Diseases, 2003) reported that in the PSA range of < 4 ng/mL the PSA velocity begins to be informative even at as low a rate of increase as 0.13 ng/year.

So what emerging measures might improve upon the current state of cancer detection? The prostate cancer research literature is awash with early reports of new candidates. An overview of forthcoming techniques was presented in the November issue of the Journal of Urology with discussions of gene expression profiles, predictive molecular markers, and predictions of prostate cancer behavior using transcript profiles (Authors: Rubin, Gelmann, and Nelson, respectively). None, however, are ready for prime time. Some of the best studied options are discussed below.

AMACR (alpha-methylacyl-CoA-racemse) is a much studied enzyme that is a promising candidate for identifying prostate cancer in tissue sections, prostate secretions and urine. Its cellular expression seems to gradually increase in the postulated transition from HGPIN to cancer. As a good example of translational research, AMACR was identified in gene expression array analyses in which it was found strongly related to cancer as opposed to benign prostate tissue. Although its known function is related to the oxidation of branched-chain fatty acids, it appears also to play a role in prostate cancer growth and proliferation. Quantitative reverse transcriptase PCR studies have found that the ratio of AMACR-to-PSA transcripts in post prostate massage secretions may be able to identify "men at increased risk for harboring prostate cancer despite negative biopsy". AMACR "has a potential application for stratifying patients into low and high risk groups for surveillance vs. repeat biopsies". The authors regard this test as promising for noninvasive screening for prostate cancer. (Rogers, J Urol Oct 2004).

"Upm3" URINE TEST: Upm3 is already commercially available (discussed in October PCa Commentary) and identifies the gene products of the PCA3 gene, which is heavily overexpresssed in prostate cancer. Early evaluation indicated a 74% sensitivity and a 91% specificity for detection in screening trials.

Another urine test based on the identification of telomerase activity in epithelial cells shed after prostate massage showed a diagnostic efficiency of 88% in distinguishing cancerous cells from epithelial cells.

PROTEOMICS: The proteome refers to the totality of the complex mixture of proteins in serum. These proteins originate with the transcription of mRNAs from expressed genes. Ultimately, however, the proteome is composed of the ribosomal translated products of spliced and unspliced mRNA, which may be further modified by post translational protein alterations, and then further incorporated into complex associations with carrier proteins. Proteomics is the study of this composite of all these protein products. One sophisticated analytic technique identifies the ion signatures of these proteins utilizing a mass spectroscopic method with the acronym "SELDI-TOF", surface enhanced laser desorption ionization time-of-flight. This procedure generates and displays thousands of disparate ion peaks which, when interpreted comparatively (in this context - cancer vs. no cancer), can be assigned to represent a distinct complex aggregate protein signature associated with a cancer along with the proteins evoked by the host's response. A limitation of the usefulness of the technique is that the proteins of interest are difficult to individually characterize, but an advantage is that once the reference of the pattern of interest is clinically verified, the technique supports the high throughput analysis that is needed for screening large numbers of specimens quickly.

A recent report of this type of analysis is "Serum proteomic profiling can discriminate prostate cancer from benign prostates in men with total prostate specific antigen levels between 2.5 and 15.0 ng/mL" (Ornstein,D. J Urol Oct 2004). Using the SELDI method the authors evaluated whether the identification of "key discriminating ion signatures" in prebiopsy serum from 154 men could guide the selection of

whom to biopsy. In retrospective analysis "if the proteomic pattern had been used to determine the need for prostate biopsy in this cohort of men with PSA between 2.5 and 15 ng/mL, 67% (42 of 63) with negative biopsies would have avoided unnecessary biopsy, while no cancer would have been missed.

GENE EXPRESSION PROFILING: Clinician have been aware of the emergence of the technique of identifying gene expression in tissue analysis with cDNA microarrays. Assisted by powerful bioinformatics, gene expression profiling has an almost unlimited potential to tease out patterns of inherent molecular signatures that show promise in predicting tumor behavior and clinical outcome, and in establishing risk stratification. Predictions based on this technique may soon complement or surpass those from the venerable triumvirate of PSA, tumor stage, and Gleason score. Currently, the application of this technique to prostate core biopsy specimens is in its infancy and encounters the limitation of sampling error. Several studies based on gene expression analysis of prostatectomy specimens are illustrative of this technique's potential:

"Gene expression correlates of clinical prostate cancer behavior", (Singh, Cancer Cell Mar. 2002), reports a retrospective study showing that a "molecular classifier" comprised of five genes could accurately distinguish those cancers that relapsed within four years after prostatectomy from those that did not.

"Gene Expression Alterations in Prostate Cancer Predicting Tumor Aggressiveness and Preceeding Development of Malignancy" (Yu, JCO July 15,2004) described a 70 gene expression profile that showed a 78% accuracy of predicting tumor aggressiveness compared to 52% accuracy for Gleason score classification comparing <7 versus ≥ 7. Aggressiveness was defined in terms of pT3 stage, clinical relapse or distant metastases. "The '70 gene' model correctly predicted 27 of 29 aggressive tumors, and 32 of 37 nonaggressive tumors...".

"A molecular signature of metastasis in primary solid tumors" (Ramaswany, Nat Genet 2003 Jan) "compared the gene-expression profile of adenocarcinoma metastases to unmatched primary adenocarcinomas" and "found that a subset of primary tumors resembled metastatic tumors with respect to this gene-expression signature." The subset in which the primary tumor displayed the metastatic phenotype had a comparatively poor outcome ($P < 0.03$).

A caveat: In his J Urol article, Nelson points out that "A major confounding factor when assessing tumor outcome based on expression profiles concerns variables in the host, such as "immune response, dietary factors, and hormone milieu." The importance of the host response in determining outcome was made clear in the November 18, 2004 NEJM article, "Prediction of Survival in Follicular Lymphoma Based on Molecular Features of Tumor-Infiltrating Immune Cells. In their gene expression studies a clear difference in survival "correlated with the molecular features of *nonmalignant* immune cells present in the tumor at diagnosis."

Bottom Line: These techniques have great potential in assisting the diagnosis and management of prostate cancer, but currently need extensive clinical validation.