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DIAGNOSTICS: A Revisit: Strategy For Re-Biopsy After An Initial Diagnosis Of Isolated HGPIN

The best strategy as to when to repeat a biopsy and the identification of predictors that might offer guidance in selecting those men at greatest risk for subsequent cancer remains a "work in progress". The discussion in the March 2003 PCa Commentary (indexed under "Pathology") concluded by approvingly citing the work of Lefkowitz who reported that if *only* HGPIN were diagnosed on a initial *12 core biopsy,* cancer was found in 2.3% of men on repeat biopsy at one year, and in 25.8% at three years. Several recent articles, however, have provided some useful additional clarification.

As background it should be pointed out that the prevalence of HGPIN is a moving target and increases with age. This necessarily influences the interpretation of all the studies, requiring information about the demographics of the population under study. Two autopsy studies have documented finding HGPIN in men in their third to eighth decades in 3.6% and 8%, 8.8% and 23%, 14.3% and 29%, 23.8% and 50%, 31.7% and 60%, and 33% and 70%, respectively. (Interestingly, the same studies showed that latent prostate cancer was found in similar numbers decade for decade.) One study further documented that in autopsy studies *multifocal* HGPIN was found in decade three through six in 0%, 2%, 5%, and 12% of men. The prevalence in African Americans is slightly higher than in Caucasians in comparable decades. Isolated HGPIN (ie not accompanied by cancer) is found on average in 5% to 9% of the more than 2 million prostate biopsies done yearly in the USA, yielding more - possibly many more -

than 115,000 new cases in which the issue of management has to be addressed. Bostwick combined the figures for prevalence and US male population between ages 40 and 90 and estimated that 16,842,640 men harbor HGPIN!

Clinicians who try to digest the many articles addressing this subject will likely find, as did I, that their cerebral hard drive begins to freeze up under the burden of the plethora of varying results. A summary of 10 published studies recording the finding of cancer on re-biopsy after an initial diagnosis of isolated HGPIN ranged from 15% to 79%! Further complicating management decisions is the fact that in about 20% of repeat biopsies no HGPIN will be found, possibly due to sampling error. Or could the disease regress? Dr. Tickman, prostate pathologist, Swedish Hospital, Seattle, points up the practical reality that even in some "definitive" analyses of the subject the definition of HGPIN lacks clarity, and "there is quite a bit of interobserver variability in diagnosis".

Two 2004 articles are particularly useful in their observations and present an overall perspective. In "Predictors of Prostate Cancer on Extended Biopsy in Patients with High-Grade Prostatic Intraepithelial Neoplasia: a Multivariate Analysis Model", Abdel-Khalek, BJU INT, 94, 528-533, evaluated the importance of an extended biopsy in 83 men who had been diagnosed with HGPIN on an initial six core biopsy (in one core, 30%, in two cores 22%, and in $\geq$ 2 cores, 48%). Re-biopsy was premised on a PSA rise of $\geq$ 1 ng/mL per year or an abnormal DRE. Cancer was found in 36% on the extended 11 core biopsy, which added 23% more cancers to what was discovered by only recording the yield of the 6 core portion of the extended procedure. The significant predictors for cancer in this study (each at $P < 0.001$) were age $\geq$ 65 vs. less (56% vs. 18%); PSAD $\geq$ 1.5 ng/cc vs less (53% vs 16%); and > 2 cores with HGPIN on the initial biopsy vs $\leq$ 2 (56% vs 16%). The PSA value was not significantly different between the two groups. Similar to the findings in other studies, subsequent prostatectomy predominantly showed organ confined disease with Gleason $\leq$ 7 (28 of 30 men).

"Monofocal and Plurifocal High-Grade Prostatic Intraepithelial Neoplasia: Factors Predicting Cancer Detection on Extended Repeat Biopsy", Roscigno, UROLOGY June 2004, focuses on the importance of the predictive value of the volume of HGPIN and reports that a repeat biopsy (10 to 12 cores) at a median of 11.4 months following the initial HGPIN diagnosis found cancer in 70% (19 of 27) of men who initially had *plurifocal* HGPIN as compared to 10% (2 of 20) with *monofocal* disease. PSAD was significant only on univariate analysis. However, the PSAD value for men showing no cancer was 0.11 +/- 0.05 versus 0.25 +/- 0.04 ng/cc for those in whom cancer was found. The median PSA for the entire study group was 8.25 ng/mL with no significant difference between the cancer and no-cancer groups. They reconfirmed the results of other studies and found that re-biopsy should not be focused only on the site of the original HGPIN, since in their study 24% of cancers were found at a different site. Of the 14 men who underwent radical prostatectomy organ confined disease was found in 13 (93%).

Perhaps, future studies addressing this issue will include the newly available uPM3 test from the Bostwick Laboratory which is based on a "molecular cytology" in cells in masssage-induced prostatic secretions. (Discussed in Pca Commentary, October 2003, and indexed under "Diagnostics".) In tests of 91 men at high-risk for cancer with PSA values < 4ng/mL a positive uPM3 test showed a 74% sensitivity and a 87% specificity for identifying those with cancer on re-biopsy.

Bottom Line: The management of men with HGPIN remains clinically challenging requiring considerable clinical judgment, but emerging data is contributing useful guidance.

DIET & PREVENTION: "High Grade Prostatic Intraepithelial Neoplasia Is A Disease" ...And When Appropriate Therapies Become Available, It Merits Treatment.

The quoted declarative, somewhat arresting, statement above is the title of Mitchell Steiner's discussion in Current Urology Reports, Feb. 2001, and sets the stage for his subsequent work and that of others implicating the role of estrogen in the genesis of HGPIN - and hence prostate cancer - and the potential role of the estrogen blocker, Toremifene to arrest this process. The hypothesis that PIN is both a marker and a precursor to cancer is being increasingly strengthened by many lines of evidence, admittedly falling short of an ultimate observation capturing in time-lapse photography this transition correlated with sequential gene expression profiles. In his article, "High-grade prostatic intraepithelial neoplasia", Modern Pathology, 2004;17, Bostwick sets out the varied evidence that convinces him of this progression, concluding with "Most patients with PIN [HGPIN] will develop carcinoma with 10 years". Histologically, he defines, "PIN is the abnormal proliferation withinA the prostatic ducts, ductules, and large acini of premalignant foci of cellular dysplasia and carcinoma *in situ* without stromal invasion". Whereas normal prostate cellular proliferation occurs in the basal cell layers, in "PIN the greatest proliferation occurs on the luminal surface, similar to preinvasion lesions in colon (tubular adenoma) and other sites [ie uterine cervix, bladder *in situ* carcinoma]." Isolated HGPIN does not elevate PSA. As PIN spreads it replaces the luminal epithelium, initially preserving the basal cell layer, subsequently progressively fragmenting it; and then, in full transition to cancer, invading through the basement membrane into the stroma, and promoting angiogenesis. The guilt of PIN as a transitional precursor to cancer is suggested epidemiologically by the recognition of its well established association with cancer, by its progressive morphologic similarity to cancer, and by its sequential acquisition of prostate cancer's signature genetic alterations, the increasing expression of the enzyme AMACR (upregulated 9 to 55 fold in PC), and the progressive silencing of the gene glutathione S transferase P1, a protector from cellular oxidative damage.

A proposed biologic mechanism to explain this putative example of the classic transition - hyperplasia, dysplasia, carcinoma *in situ* and invasion - has been suggested by Steiner and others and surprisingly the finger points toward estrogen as an instigating factor. Steiner's article, "Selective estrogen receptor modulators for chemoprevention of prostate cancer", UROLOGY 57, Suppl.1 April 2001, records that "Both animal models and human epidemiologic studies have implicated estrogen as an initiator of prostate cancer", and reminds us that "In the aging male, prostate cancer occurs in an environment of rising estrogen and decreasing testosterone." In the male, and in the female, estradiol interfaces with the two estrogen receptors, ER *alpha* and ER *beta*, in each case with slightly different results based on unique tissue specificities and coactivator enlistment. Activation of "ER *alpha* stimulates transcription and cellular proliferation, while ER *beta* quenches ER *alpha* activation. In an environment of rising estrogen, androgen receptors in the prostate cell are upregulated thereby increasing sensitivity to androgens. Whereas ER *beta* resides in the luminal epithelial cell, ER alpha is found in the stroma and its activation elicits the proliferative peptide cytokines insulin like growth factor and epidermal growth factor, and the inhibitory transforming growth factor *beta.* These molecules affect the luminal cells in a paracrine fashion. As the title of the article suggests evidence is accumulating that this adverse process can be counteracted by inhibitory antagonists of the prostate's estrogen receptors.

"Selective Estrogen Receptor Modulator" (SERM) is the term for the evolving repertoire of drugs, such as well known Tamoxifen; and the most studied SERM in chemoprevention of

prostate cancer is Toremifene (“Acapodene”, GTx Inc.). SERMs have weak affinity for estrogen receptors - functioning as partial antagonists much like genistein (soy) - and preempt the ligand pocket thereby preventing attachment and signaling by the more avid estradiol. Toremifene primarily antagonizes ER *alpha*. Kawashima, Urol Res.2004, Aug, reports that the anti-androgenic aspect of anti-estrogens may function by inhibiting AR-mediated transcription.

“Phase IIA Clinical Trial to Test the Efficacy and Safety of Toremifene in Men with High-Grade Prostatic Intraepithelial Neoplasia” by Drs. Steiner and Pound, Department of Urology, University of Tennessee, reported findings in 18 men with HGPIN [based on $\geq$ 6 core biopsies] using 60 mg/day of Toremifene (“Acapodene”,GTx,Inc.) for 120 days. “After Toremifene treatment, 72% of these 18 men (vs. 17.9% of historical controls) had no HGPIN on subsequent [8 core] biopsies.” Four (22%) showed a limited response (defined as a $\geq$ 25% reduction in HGPIN), and one had stable disease. In this small study “No changes were noted for libido, erectile function, and hot flashes. ... Mean total testosterone was significantly increased [5.5 ng/mL]...at day 120.” Slight, but significant, reductions in hemoglobin and platelets were seen.

This early “proof-of-concept” trial was followed by the IIb double-blind, placebo-controlled, one-year trial using 20 mg Toremifene in 514 men with HGPIN. The trial end point was the diagnosis of prostate cancer. At the 2004 Fourth International Prostate Cancer Congress Dr.Steiner, CEO GTx, reported “a statistically and clinically significant reduction of prostate cancer cumulative risk at one year in the “Acapodene” 20mg arm compared to placebo, 24.4% vs 31.2%, respectively ($p<0.05$)”. An additional observation was that longer usage increased the likelihood of risk reduction. The side effects - fatigue, hot flashes, nausea - were mild, < 5%, and very similar in both arms. A definitive large-scale Phase III trial is planned and Dr. Bob Boger (GTx, Inc.) has indicated that this will include sites in the Northwest.

Bottom Line: It is possible that an estrogen receptor modulator, such as Toremifene, may become an effective chemopreventive agent for prostate cancer - with an acceptable “side effect” profile.