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DIAGNOSTICS: Percentage of Positive Biopsy Cores: Riddle - "When is the risk of a Gleason 4 + 3, not that of a "4 + 3"? Answer: When less the 50% of the cores show cancer.

The riddle's answer is discussed in "Impact of the percentage of positive biopsy cores on the further stratification of primary grade 3 and grade 4 Gleason score 7 tumors in radical prostatectomy specimens" by Vira et al., UROLOGY 66(5),2005.

This study examined the median biochemical progression-free survival (bPFS), set at less than 0.2 ng/mL, at 5 years for 290 men with primary biopsy grade 3 tumors and 89 men with primary grade 4. Consistent with the bulk of prior analyses, the 60-month probability of bPFS for men with primary grade 3 tumors was 71% versus 55% for grade 4. However, the new finding from this study was that "When segregated for percentage of core biopsies positive ... the 60-month actuarial PSA progression-free survival for patients with [primary] grade 3 and 4 *and less than 50% core biopsies positive* as compared with grade 3 and 4 and *50% or more positive biopsies* [was] 85%, 85%, 61% and 33%, respectively. In multivariate analysis of this

intermediate-risk population (after taking into account the predictive factors of PSA level, surgical margin status, and pathologic stage) the primary Gleason grade lost independent significance. However, on subgroup analysis of those men with > 50% positive cores, the dominant Gleason grade remained a significant independent predictor of biochemical progression. The take-home message of this study: “Patients with primary grade 4 disease who have 50% or fewer biopsies positive have an excellent prognosis after radical prostatectomy”.

But in any sampling system such as core biopsies there is always a whiff of ambiguity. Partin, Walsh, Epstein et al. analyzed the “Relationship between primary Gleason pattern on needle biopsy and clinicopathologic outcomes among men with Gleason 7 adenocarcinoma of the prostate”, UROL. 67, Jan 2006. Relevant to the Vira article (above) they determined by examining surgical the specimens of 320 men with Gleason 7 tumors on core biopsy that approximately 47% of men with a Gleason pattern of 4 + 3 on needle biopsy were downgraded on final pathologic analysis to primary pattern 3 or less, and those with biopsy Gleason score of 3 + 4 were upgraded in 24% to primary pattern 4 or more. The PSA recurrence-free outcomes were consistent with what was expected from the scores on the surgical specimens.

The literature is replete with many studies documenting that the percentage of positive biopsy cores (PPBC) is an independent predictor of pathological stage and clinical outcome, taking its place along with the basic standards of PSA, Gleason score and clinical stage. And a predominant finding in these studies has been that within each of the standard risk categories, prediction can be further refined by considering this PPBC variable, reinforcing the intuitive generalization that “fewer is better”.

The increment of improved prediction added by PPBC is not uniform among the three standard risk categories. One clinically useful observation is discussed in the classic paper by D’Amico et al., “Clinical Utility of the Percentage of Positive Prostate Biopsies in Defining Biochemical Outcome After Radical Prostatectomy for Patients with Clinically Localized Prostate Cancer”, JCO, Mar 2000. This study of 960 men matched the well known bPFS outcome graphs based on Partin’s three standard risk categories with graphs displaying outcome data *within each risk* group further segregated by PPBC data. Their PPBC groupings were <34%, 34% - 50%, and > 50%. Result: It was in the *intermediate-risk group*, PSA >10 but ≤ 20 ng/mL, or Gleason score 7, or clinical stage T2b (‘92), where the PPBC was most revealing. The < 34% PPBC cohort showed a ~90% 5 year bPFS, whereas the standard Partin data assigns the intermediate-risk group, unstratified by PPBC, a bPFS figure of ~ 50%. In the high-risk group an important further stratification was also seen: 4 year bPFS for the <34% group, 70%, versus the Partin estimate, unstratified for PPBC, of 30%. In the low-risk group further stratification by PPBC was not further informative. A potential weakness of the study was that a sextant biopsy strategy was most commonly used. D’Amico concluded, “the stratification of PSA outcome after RP provided by percentage of positive biopsies was also clinically significant in that the vast majority (78% to 80%) of the intermediate-risk patients in the study and in the validation cohorts could be categorized into a high- or low-risk category for PSA outcome after RP”. In D’Amico’s opinion this study finding was clinically useful, since it is “the intermediate-risk group, for whom improvements in the prediction of PSA outcome are most needed.” Again, fewer is better, and the D’Amico study is complimentary to the Vira study already discussed.

The risk of seminal vesicle involvement (SVI) is also independently predicted by considering PPBC. SVI increases with increases of positive biopsy cores. Antunes et al. (BJU Int. 96, 2005) in their analysis of 534 patients with clinically localized prostate cancer confirmed that the standard three predictors were significantly associated with PPBC, but PPBC was the only

independent predictor of seminal vesicle cancer. In a study of the surgical specimens of 1056 men, of whom 7.4% had SVI, only 0.5% of men with < 17% of core biopsies positive had involvement (Guzzo TJ, J. Urol. Feb 2006). In their article, "A nomogram to predict seminal vesicle invasion by the extent and location of cancer in systematic biopsy results" (J.Urol. 2003 Oct), Scardino, Wheeler, Kattan et al. pointed up the increased risk of SVI arising from positive cores at the *base of the prostate*. Their finding: "Cancer was present in a biopsy core from the base in 437 patients, of whom 12.8% had SVI compared with only 1.2% of the 326 without cancer at the base". Their conclusion: "The predictive accuracy of a standard model that included only stage, grade and PSA was maximally enhanced by including the percent cancer at the base (p=0,0013)".

Bottom Line: The percentage of biopsy cores positive is a powerful independent predictor of pathologic stage and outcome.

DIET & PREVENTION: LYCOPENE - Small study finds lycopene suppresses HG-PIN's transition into prostate cancer.

There is strong support for a benefit of lycopene in retarding prostate cancer at all clinical stages (see Feb/Mar PCa Commentary - "Diet and Prostate Cancer"). Now evidence from a small study indicates that lycopene can interrupt the progression of HG-PIN into occult prostate cancer: "Lycopene as a chemopreventative agent in the treatment of high-grade prostate intraepithelial neoplasm, Mohanty NK, Urologic Oncology 23 (2005) 383-385.

The study design: Prostate cancer was excluded by careful work-up and prostate biopsy in 230 men who then underwent a TURP for their BPH. Of this group 40 were found to have HG-PIN. Twenty were treated with 4 mg lycopene (Lyc-O-Mato) twice daily for one year and instructed to follow their regular diet. The untreated control group was advised to reduce the intake of tomato products and melon.

At one year follow-up the median PSA in the treatment group had fallen from 6.07 to 3.5 ng/mL, but PSA in the control group increased from 6.55 to 8.06 ng/mL. Unique to this study, baseline and 1 year serum lycopene levels were measured (normal - 300 ng/mL): mean values for the treated group - 360 ng/mL increasing to 680 ng/mL at one year; and in the control group, 378 ng/mL at baseline dropping to 180 ng/mL.

PSA and lycopene levels, and DREs were checked at 3 month intervals during the 2 year study. Over the second year of the study, any man who developed an abnormal DRE or an increased PSA underwent prostate biopsy. Result: adenocarcinoma was diagnosed in 2 men in the treated group versus 6 in the control group.

The authors find the data very suggestive, but acknowledge that such a small study needs confirmation. However, the study was well done, and was especially notable for the inclusion of serum lycopene measurements.

The lycopene "dose" most cited in the literature is 30 mg/day, which can easily be obtained from 8 oz. tomato juice daily and one or two servings of tomato based products weekly.

In clinical practice when HG-PIN has been diagnosed and follow-up advised, there is no downside to recommending a high lycopene diet, which has no toxicity and is well tolerated.

Bottom Line: Evidence suggests lycopene as a beneficial chemopreventive agent for men with HG-PIN

DIAGNOSTICS: **UPM3 - A diagnostic urine test with greater accuracy for cancer detection than PSA**

The “Achilles’ heel” of the venerable PSA test is its low specificity for prostate cancer detection, ~25% to 35%, when used for screening and in the work-up of suspicious palpable abnormalities, allowing critics to charge an unacceptably high rate of “unnecessary biopsies”. An excellent, and concise, discussion of the detection efficiency of PSA for initial and repeat biopsies is: “Prostate biopsy: who, how and when. An Update” by Bob Djavan et al., Canadian Journal of Urology; 12(Supplement 1);February 2005. They report data from the European Prostate Cancer Detection “study of 1051 men with a total PSA of between 4 ng/mL and 10 ng/mL who underwent a 12 core biopsy (two in the transitional zone). Those with negative biopsies were rebiopsed at 6 weeks, and, if negative, then biopsied again a third and fourth time at 8 week intervals. Results: “Cancer detection rate on first, second, third and fourth biopsy was 22% (231/1051), 10%(83/820), 5% (36/737) and 4% (4/94).” Clearly there is room for improvement!

The uPM3 offers such improvement, and is discussed by Fred Saad, Canadian Journal of Urology (see above): “UPM3: review of a new molecular diagnostic urine test for prostate cancer”. “In a large multi-center study of 517 cases the overall sensitivity was 66% with a specificity of 89%. The positive (PPV) predictive values for the uPM3 test was 75% compared to 38% for a serum PSA cutoff of 4 ng/mL” - yielding a two-fold better accuracy. For PSA cutoff of 2.5 to 4 ng/mL the comparative accuracy was 81% versus 43% for PSA. In the PSA range of < 4 ng/mL: sensitivity, 74%, specificity, 95%.

The test focuses on exfolliated cells loosened by a “vigorous” prostatic massage, 30 seconds for each lobe, and swept from the urethra into the urinary stream. The key test target is PCA3 mRNA identifying the presence of cells carrying the PCA3 gene, “one of the most prostate cancer specific genes described to date, with overexpression in 95% of cancers tested and a median 66-fold up-regulation compared to adjacent non-neoplastic prostate tissue”. The simultaneous presence of PSA **and** target PCA3 mRNA assures that the cells in question are of prostate origin.

The test kit is available from the Bostwick Laboratories (webkeeper@bostwicklboratories.com) and costs about $450. The marketing specialist in Seattle is Bonnie Scott (206-853-2573). Scientific questions can be addressed to Junqi Qian, MD, Director of Molecular Diagnostics, (jquin@bostswicklaborotories; 804-288-6564), who informed me that in June, 2006, the next generation of the test (“PCA3”) will be available.

The Djavan article discusses currently available methods to improve the detection rate for PSA prompted biopsies. The Vienna nomogram (J Urol. 2005 Oct;174(4 Pt 1):1256-60) offers a strategy for “defining the optimal number of cores based on patient age and prostate volume” which raised the detection rate to 36.7% on the initial biopsy “compared with 22% on the first and 10% on the repeat biopsy in the control group” of their 1051 man study. Also discussed was a PowerDoppler-TRUS imaging technique which “excluded prostate cancer in 89.7% (52/58) and 94.4% (17/18) of patients on the first and repeat biopsies.

How might the uPM3 test be best integrated into clinical practice? “Very discretely” might be the answer by many physicians. At $450 a pop there may be a substantial number of instances where uMP3 test would be an expensive “add on” considering that an experienced clinician could likely make a sound decision based upon a sufficiently adverse constellation of findings combining a worrisome palpable abnormality, a low percent free PSA, a PSA level

concerningly above the appropriate level for a man's age group, or a PSA rise of more than .75 ng/mL per year. Yet, there may well be many clinically marginal situations in which an initial biopsy might be conservatively "on hold" where the uMP3 test would be clearly helpful.

It is possible that at first this test may be most useful to help decide whom to rebiopsy after an initial negative biopsy, but in which the presentation remains suspicious for cancer. In this setting of one or more negative biopsies the "uPM3 had a 74% sensitivity and a 87% specificity corresponding to a negative predictive value of 87% and a positive predictive value of 74% (from Saad). Similarly the uPM3 may be helpful in cases where HGPIN was found in several foci and rebiopsy is under consideration.

Bottom Line: The uPM3 test is available for thoughtful integration into clinical practice and has excellent sensitivity and specificity for cancer detection.

HORMONE INTERVENTION: Androgen Deprivation and Memory Loss.

Research conducted by Dr. Tomasz Beer and colleagues have documented a consequence of androgen deprivation that may often be too subtle to be detected in clinical practice in individual patients - that testosterone deficiency is associated with memory impairment. Their study, "Testosterone Loss and Estradiol Administration Modify Memory in Men", J Urol. Jan 2006, used a battery of tests to evaluate memory in 18 men on androgen deprivation therapy (ADT), 17 men on ADT combined with transdermal estradiol, and 17 healthy control subjects. All men on ADT had serum testosterone levels of < 50 ng/dl.

There is a sound biologic basis for this finding. The cortical centers that process memory - the prefrontal cortex and the amygdala and hyppocampus - are rich in sex steroid receptors, and alterations in steroid levels might be expected to affect neurophysiological function. Studies have shown that "gonadectomy results in a 40% or greater reduction of synaptic spine density in the CA1 region of the hyppocampus in male monkeys and rats, and androgen replacement restores synapse number to pre-gonadectory levels in male rats". Adverse consequences of ADT have previously been reported in prostate cancer patients which "decrease memory, attention or executive function".

Beer's research assessed immediate and delayed verbal memory by testing the subjects' recall immediately after two paragraphs were read to them, and then testing again 30 minutes later. Cognitive tests and Profile of Mood State assessment established that ADT was associated with greater confusion, fatigue, depression, and decreased vigor compared to the healthy controls. Another assessment indicated that the men on ADT exhibited a "slower processing speed", although tests of working memory found no significant difference among the three groups. The concomitant exposure to estrogen did not ameliorate the adverse effects of ADT. Since the study was small, the authors acknowledge that confirmation would strengthen and clarify their findings.

Their conclusion: "Thus, long-term androgen deprivation therapy has the potential to significantly affect cognition with particular effects on memory". Their recommendation: When ADT is an option the "potential for cognitive toxicity of treatment should be considered in the risk-benefit calculation".