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DIAGNOSTICS: The Importance ff Percentage of Gleason Grades 4 Plus 5 in Predicting Biochemical Recurrence in Prostate Cancer

In the management of this disease the ongoing challenge is accurately predicting the future behavior of prostate cancer based on a better understanding of its basic biology. In the May 1, 2005, issue of the JCO Liang Cheng and colleagues from Indiana University make a contribution to that effort by analyzing clinical outcome as related to a critical analysis of Gleason grade in whole mount prostate specimens. In their article, "The Combined Percentage of Gleason Pattern 4 and 5 Is the Best Predictor of Cancer Progression After Radical Prostatectomy" they present data supporting the conclusion: "The combined percentage of Gleason patterns 4 and 5 is one of the most powerful predictor of patient outcome, and appears superior to conventional Gleason score in identifying patients at risk of disease progression". This is not a new concept. It has been extensively examined and convincing presented by Drs. Stamey and McNeal in many articles during the 1990's, but the Cheng report adds useful detail by highlighting the importance of the percentage of involvement by high-grade disease thereby focusing attention upon the biologic and clinical significance of the critical histologic transition from the abortive, but recognizable, gland formation seen in the lower Gleason grades to the architectural disruption of grades 4 and 5.

Cheng's evaluation took note of the previously recognized facts that "two or more separate adenocarcinoma foci were present in 87% of radical prostatectomy specimens", that "there often was extensive histologic heterogeneity among tumors within the same specimen" and that "more than half contain three or more Gleason patterns". Using whole mount specimens they calculated the total area of all grades of cancer and estimated volume of cancer in the entire specimen. They then summed the

individual areas of Gleason grades 4 and 5 in all the tumor sites and derived the percentage of total cancer represented by this aggregate amount of high-grade cancer. The results were tabulated as 5% increments from 0% to 100% Gleason grade 4/5.

Their study was based on 364 men, treated only with surgery, and followed closely for a mean of 14 months [a follow-up report with longer follow-up would be helpful]. Biochemical recurrence was set at a post surgical PSA value in excess of 0.1 ng/mL.

The key graph shows that over the follow-up range of 1.5 to 48 months there was a smooth increase in PSA recurrence in seven designated groupings: 5.4% recurrence in those men with 0% or 1%-10% grade 4/5 cancer; 10% recurrence in the group having 11-30% grade 4/5; 21% with 11-30%; 30% with 51-70%; 50% in the 27 men with 71-90%; and 100% in the two men with 100% grade 4/5.

As was earlier determined by Stamey and McNeal, increasing tumor volume was tightly correlated with increasing histologic grade and worsening clinical outcome. As expected, clinical outcome was correlated, but to a lesser extent, with the customary morphological parameters and also with the preoperative PSA. However, the most predictive factors were tumor volume and percentage of Gleason grade 4/5, with greater than 30% of Gleason grade 4/5 cancer representing a useful breakpoint.

Especially informative are two summary articles by Stamey, McNeal et al. presenting their ten or so years of research that established the critical importance of the extent of Gleason 4/5 cancer.

In "Biological Determinants of Cancer Progression in Men with Prostate Cancer", JAMA April 21, 1999, Vol. 281, 1395-1400 they state that their constant goal has been "to find better ways to distinguish patients who have clinically innocuous cancer from those who have significant disease that can be eradicated by radical prostatectomy or other treatment and those for whom therapy is destined to fail". This study, with a median follow-up of 5.73 years, was based on 379 men who underwent surgery and had no additional therapy until PSA recurrence, set at > 0.07 ng/mL. Their method was to determine the percentage of Gleason 4/5 grade cancer <u>in the largest tumor</u> and concluded that "the % Gleason grade 4/5, cancer volume, positive lymph nodes, and intraprostatic vascular invasion were independently associated with cancer progression" and the first two were most significant. The percent of Gleason grade 4/5 proved to be a more powerful predictor than the convention Gleason grading system.

A figure was developed to illustrate the "increase in failure rates as a function of the percentage of Gleason 4/5 cancer". A smooth increase in recurrence was seen with each 10% increase in percentage of Gleason grade 4/5, from less than 5% recurrence at the O% level to nearly 90% at the 91-100% level. Tumor volume also was a "highly significant and independent determinant of biochemical failure". PSA recurrence developed in 14% of men with a tumor volume of 0.5 to 2.0 cc3; 39% for 2.0 to 6.0 cc3; 67% for 6 to 12 cc3; and 97% for men with tumors larger than 12 cc3.

In a additional article, J Urol April 2000, Stamey, McNeal et al. evaluated the relative significance of the conventional morphological variables as predictors of PSA recurrence and again identified the percentage Gleason 4/5 and tumor volume as the primary determinants of treatment failure. The preop PSA was important; vascular invasion less so; and in the context of this study "capsular penetration, positive surgical margins, and seminal vesicle invasion were insignificant", i.e. not independent causes of biochemical failure.

Regarding information available from biopsies: "We have shown that if enough biopsies are taken, there is an excellent representation of the percent of Gleason grade 4/5 in the index (largest) cancer".

It is the restless cells that leave home ... that is, those prostate cancer cells that comprise the histologic grades 4 and 5. The importance of these higher grades is reflected in studies that show in a qualitative sense the worse performance of men with Gleason sums 4 + 3 versus 3 + 4 cancers. The extent of pattern 4, comprised as it is of these aggressive cells, can vary widely as a component of a Gleason sum

3 + 4 = 7 cancer, but when extent of pattern 4 in a specimen exceeds 50% it becomes, by definition, the primary Gleason grade. Stamey has pointed out "For a score of 7, the proportion of Gleason grade 4 cancer may vary between 5% and 95% without altering the score (sum)".

Current reporting has recently transitioned from the practice of entering the second most ***prevalent*** histologic pattern as "secondary" Gleason pattern. Now, if the worst grade is not the most prevalent pattern, the worst grade - independent of its prevalence in the specimen - is listed as the "secondary pattern". This is a qualitative acknowledgement of the importance of those *restless cells* - those cells that have acquired the metastatic phenotype. Stamey, McNeal, and Cheng would argue for taking that acknowledgement one step further and replacing standard Gleason reporting by a quantitative statement of the percentage of Gleason grade 4/5 in a specimen.

These collective determinations emphasize the importance of focusing research on identifying the basis for this critical transition from the more "benign" cancer cells that comprise the abortive glands of the lower Gleason grades to the inherent aggressiveness of the cells of Gleason grade 4/5 cancer. Stamey has urged that "research efforts at the genetic and enzymatic molecular levels clearly should be directed at the Gleason grade 4 cancer".

PATHOLOGY: The Utility of Bone Scans in Recurrent Prostate Cancer

A bone scan showing malignancy is a rarity when performed in association with the initial work-up for prostate cancer if the PSA value is less than 20 ng/mL. And this 1% likelihood is almost always related to high-risk disease with a PSA value approaching 20 ng/mL., as discussed in detail in PCa Commentary and indexed under "Diagnostics". The focus of this article, however, is the utility of bone scanning at the point of disease recurrence after failure of primary therapy, a subject infrequently addressed in the literature, but the topic of "Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated", by Pablo Gomez, Mark Soloway, et al, BJU Int. Vol.94, 2004.

This study analyzed the characteristic of 35 men with biochemical recurrence - PSA $\geq$0.4 ng/mL - who were scanned within 3 months of recurrence and categorized with respect to having a negative (group 1) or positive (group 2) bone scan. The mean follow-up was 70.4 months. "In group 1 the mean PSA at the bone scan was 5.2 ng/mL and 76% of patients had a PSA of <7 ng/mL. In group 2 the mean PSA at the bone scan was 30.7 ng/mL and all patients had a PSA of >7 ng/mL. The only significant difference between the groups was the PSA at the time of the bone scan (P<0.001)." However, the PSA velocity was informative: "Nine of ten patients in group 2 had a PSA velocity of $\geq$0.5 ng/mL/month and 64% in group 1 has a PSA velocity of <0.5 ng.mL/month".

The authors cite Cher et al (J Urol 1998; 160; 1387-91) who noted a less than 1% likelihood of bone scan positivity at the time of recurrence if the PSA were <10 ng/mL and concluded that in patients who progress after RP "bone scanning is of limited use until the PSA increases to >30-40 ng/mL". Also cited was Kane et al (Urology 2003; 61: 607-11). In their study of men with recurrence the mean value for a positive scan was 61.3 ng/mL, PSA velocity 22.1 ng/mL/month. For a negative scan the mean PSA value was 4.9 ng/mL and PSA velocity was 0.5 ng/mL/month. Only three of 67 (4.5%) scans were positive at a PSA level of < 10 ng/mL.

The Gomez report concluded that in men without skeletal symptoms who exhibit PSA recurrence after RP a positive bone scan is unlikely if the PSA is <7 ng/mL "whereas it is likely to be [positive] if the PSA level is >20 ng/mL."

While this Commentary article was in gestation, a "must read" analysis appeared in the March 20 issue of the JCO, "Pattern of Prostate-Specific Antigen (PSA) Failure Dictates the Probability of a Positive Bone Scan in Patients With an Increasing PSA After Radical Prostatectomy", by Dotan, Kattan et al. A

reading of this report is an excellent exercise for setting the mental compass for this subject, summarizing as it does the relevant prior studies and providing informative biologic insights. Once again the cardinal value of the PSA velocity emerges as the best reflection of a prostate cancer's underlying pathobiology as it does at almost any point in the life history of the disease.

The data base for the study consists of 239 men, having had no androgen suppression, whose post RP PSA rose above 0.04 ng/mL. They had been scanned at the discretion of their physicians. The study indicated that most of the scans ordered in this general clinical practice were negative. Only 14.5% were positive. The purpose of this study's analysis was to incorporate predictors into a nomogram (to be available at http://www.nomogram.org) to assist in selecting the most appropriate candidates for bone scanning. Of the eight predictors built into the nomogram the two most influential for predicting a positive scan were the PSA velocity, P = 0.003, and the PSA value (the "trigger PSA"), preceding the scan, P <0.001. The median and mean for the trigger PSA in all patients were 3.1 and 13.4 ng/mL, and in the group of men with PSA values of 0 to 10 and 10.1 to 20 ng/mL the bone scans were positive in 4% (median 8.4 ng/mL) and 36% (median 13.2 ng/mL), respectively.

The PSA velocity, rate of rise expressed as ngs/mL/month, was based on the last three tests prior to the scan, with each separated by more than 30 days. Both the PSA velocity and the PSA slope can be conveniently calculated by using Kattan's Web site nomogram. The median PSA velocity for positive scans was 1.4 ng/mL/month vs 0.12 for negative scans. Interestingly the PSA doubling time was insignificant as a predictor, P = .83. For positive scans the doubling time was 5.2 months vs 6.6 months for negatives. The nomogram was "constructed with an overfit-corrected concordance of .93", confirming its reliability.

Bottom Line: Evidenced based data is available to provide guidance for the optimal use of bone scanning in men with a rising PSA after primary treatment.