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DIAGNOSTICS: Gleason Score Upgrading From Biopsy To Prostatectomy Specimen

The classic conundrum: identify those who will benefit from treatment while sparing those who don't need it ... at least not at the time of initial diagnosis. This goal has given rise to the strategic option of "expectant management" in which treatment is deferred while still retaining the possibility of cure. As a result of increased PSA screening and greater public awareness of prostate cancer, the demographics of prostate cancer has experienced a seismic shift so that possibly well over 70% - 80% of the 130,000 or so new cancers are now Stage T1c. CaPSURE data indicates that now half of patients in their recent database (increased from 11% in 1989) can be classified as "low-risk" based on D'Amico's definition: biopsy Gleason score $\leq$6, PSA $\leq$10 ng/mL, and clinical stage T1 or T2a. Among these low-risk patients are many with low PSA, low grade, and low volume cancers, often termed "insignificant", that might well exhibit indolent behavior. Men with this presentation of cancer are candidates for "expectant management" in which the decision for future treatment depends on subsequent information. But the trick is how best to find, and with the greatest certainty, those men bearing these potentially indolent tumors.

There is general agreement that prostate cancers harboring Gleason pattern grades 4 or 5 should be considered for active treatment. Dr. Jonathan Epstein's canonical definition of

"insignificant" cancer on biopsy excludes Gleason 7 cancers, and allows, taken together, only a pre-biopsy PSA density of ≤ 0.15 ng/ml/cm3; Gleason score of 6 or less with no pattern grade of 4 or 5; no more than 2 cores positive for cancer, and no more than 50% of any core involved with cancer. The predictive expectation for men with this constellation of biopsy characteristics is the strong likelihood that their prostate harbors a tumor of <0.5cm3 confined to the gland with no Gleason 4 or 5 components.

Therefore, the issue of Gleason *upgrading* from the biopsy diagnosis to the final pathology on the surgical specimen is crucial in making the best management decision. Biopsy Gleason score 6 cancers, combined with a very few Gleason fives, are now the most common presentation - the new Partin tables show that 77% of recent biopsy diagnosed cancers are Gleason score 5 or 6. An informed prediction regarding the risk of upgrading to Gleason score 7 is a necessity. Many studies have shown that the final surgical pathology following prostatectomy upgrades Gleason grade 6 in a variable 20% to 40% of instances.

Until an accurate predictive panel of biomarkers is developed, clinicians must work in the realm of probable risk. Currently, there are no reliable criteria to determine which biopsies will be upgraded. Studies have suggested a variety of predictive factors weighted as to their importance.

"Predicting the Risk of Patients With Biopsy Gleason Score 6 to Harbor a Higher Grade Cancer", Gofrit et al., J Urol, Nov 2007, reported 20.3% upgrade among 448 patients. In men with PSA values greater than 12 ng/ml the risk of upgrade was 62%, and was 18% for PSA values less than 12 ng/mL. Among this 18% "The risk [of an upgrade] was 22.6% and 10.5% when the greatest percent of cancer in a core was higher than 5% versus 5% or lower, respectively." Ninety-seven percent of upgrades were to Gleason score 7, with 83% to Gleason grade 3 + 4 and 17% to 4 + 3. This relatively low rate of upgrading probably resulted from the extent of biopsy sampling: all men had more than 8-9 cores, 28.8% had 10 or 11, and 65% had 12 or more cores. No significant influence was found for "patient age, clinical stage, PSA density, disease bilaterality, and the percent of positive cores." The combination of these parameters allowed a prediction rate for upgrading "as high as 62% and as low as 10.5%."

A skeptical opinion challenging the claims of accuracy for predicting true "insignificant" cancers from biopsy parameters was voiced by a group from Emory University in their article, "'Insignificant' prostate cancer on biopsy: pathologic results from subsequent radical prostatectomy," Prostate Cancer And Prostatic Diseases (2007) Oct. They argued that the most accurate prediction for an insignificant tumor required addition information about PSA velocity (PSAV) and clinical tumor stage. They cited Patel's finding (JCO 2005 Sep) that a pre-biopsy PSA velocity of > 2ng/ml/yr was associated with tumors > 1 cm3 in 86% of men and predicted for advanced stage cancer with > 10% grade 4/5 on final pathology, and a median time to relapse of 16 months post prostatectomy. Their review of 800 cases in 11 studies found that all required a clinical stage of T1c as one criterion for "insignificance."

Considering that multiple parameters, each to an varying extent, influence the risk of an upgrade in Gleason score from biopsy to surgical specimen, the estimation of risk is nicely suited to a nomogram. "Clinical Predictors of Gleason Upgrading", Kulkarni, Fleshner et al., CANCER JUNE 15, 2007, presents such a nomogram based on 175 low-risk cancers treated with radical prostatectomy. Eleven elements, each weighted for its significance, were incorporated: age; PSA, DRE, PIN, volume, TRUS findings, number of cores (6 vs >10), percentage of cancer in the total biopsy specimen, and the experience of the pathologist. All elements contributed to an extent in appraising the risk, but interestingly, on univariate analysis

only a PSA value of ≥6.5 ng/mL (P=.02), and the "the level of pathologist expertise" (P=.007) were significant. Cited was a study that found 47% "undergrading to Gleason 7 tumors by general pathologists."

In the Kulkarni study 34% of patients were upgraded to higher grade disease. Although this nomogram has not been externally validated, the authors believe they have "presented a nomogram that can serve as a useful adjunct when counseling patients with low-risk disease" as to their management options.

"Expectant management" will increasingly be a reasonable strategy for the many men who are being diagnosed with cancers with low PSA values, low volume, and low Gleason grade, but the choice of this course must be made with proper consideration of the issue of biopsy Gleason score upgrading.

DIAGNOSTICS: "Magnetic Resonance Imaging of the Axial Skeleton for Detecting Bone Metastases in Patients with High-Risk Prostate Cancer: Diagnostic and Cost-Effectiveness and Comparison With Current Detection Strategies" (JCO August 1, 2007)

The early identification of skeletal metastases in high-risk or recurrent prostate cancer is essential for proper clinical management. The title article by a consortium of authors from Europe and Harvard evaluated 66 patients at high-risk for bone metastases: 22 men with newly diagnosed cancer with biopsy Gleason scores ≥8 and PSA levels ≥ 20 ng/mL; 12 with PSA recurrence 3 years after surgery and PSA doubling times of < 12 months; and 28 men with a rising PSA during androgen deprivation with PSA doubling times of < 12 months. The comparison was between an MRI of the axial spine (MRIas) versus an initial technetium-99M bone scan (BS) followed by targeted x-rays (TXR) of equivocal sites; and, if needed, an MRI on request (BS/TXR/MRIor) for further definition of inconclusive BS/TXR findings. The "gold standard" for diagnosing bone metastases was a judgment based on a review of initial and 6-month follow-up MRI findings, BS/TXR, and all available baseline biologic data supplemented as needed by CT correlation of equivocal MRI findings plus prospective follow-up BS and MRI studies at six months. By using this combination of data 62% of patients were judged to have had bone metastases.

The findings: "Sensitivities were 46% for BS alone, 63% for BS/TXR, 83% for BS/TXR/MRIor, and 100% for MRIas; and the corresponding specificities were 32%, 64%, 100%, and 88%, respectively."

The biologic basis for the superiority of MRI evaluation is its "ability to detect cells seeded into the normal hematopoietic marrow and its fat cells at an early stage, compared to bone scans, which require an osteoblastic response in the bone evoked by a larger tumor burden, and X-rays, known to be insensitive to minor structural damage from metastatic tumor.

The authors effectively addressed the common concern that by limiting the field of search to only the axial spine, metastatic sites elsewhere in the skeleton would be missed. Metastatic lesions were diagnosed in 41 of 66 (62%) patients based on MRIas findings. Of these 41 men 16 had non-axial lesions on the bases of BS/TXR, e.g. in ribs, humerus, distal femur, skull, clavicle and tibia. However, final analysis showed that "each of these patients [also] had spinal, pelvic, and/or femoral metastases detected at MRIas." Four BS hot spots were benign on the basis of TXR and further follow-up. In the opinion of the authors "The probability of finding metastases in these [non-axial] locations with no metastases in the axial skeleton is indeed negligible."

Whereas positive emission tomography (PET) "fused" with whole body CT has become a very effective diagnostic tool in oncology, the authors cite data showing that "[18F]fluorodeoxyglucose-PET and [18F]fluoride-PET, used alone or with PET-CT image fusion, are less sensitive than MRI in the detection of bone metastases [in prostate cancer patients]."

Their conclusion: "MRIas identified metastases in seven of 23 (30%) of patients considered negative and eight of 17 (47%) patients considered equivocal by other strategies." "Overall initial treatment plans were modified in 15 patients (22%) as a consequence of MRIas results."

DIAGNOSTICS: Partin Tables Updated

Updated Nomogram to Predict Pathologic Stage of Prostate Cancer Given Prostate-Specific Antigen Level, Clinical Stage, and Biopsy Gleason Score (Partin Tables) Based on Cases from 2000 to 2005" UROLOGY 69 (6), June, 2007

This updated nomogram, based on 5730 men treated at Johns Hopkins, reflects the dramatic and significant shift in clinical features of recently diagnosed prostate cancer. "Seventy-seven percent of patients had T1c, 76% had Gleason score 5 to 6, 80% had a PSA level between 2.5 and 10 ng/mL, and 73% had organ confined disease." Clinical stage T2c decreased significantly so that the categories cT2b and cT2c were combined.

DIAGNOSTICS: PSA "Bounce" Following Permanent Seed Brachytherapy - A Challenge To Identify And A Cause Of Anxiety For Patients.

The optimal outcome after radical prostatectomy is an undetectable PSA several weeks following surgery. However, brachytherapy leads to a prolonged process of cell kill with a potential nadir often taking 2 - 5 years. During this period 30% - 40% of patients experience a temporary rise in PSA termed a "bounce", or "spike". This worrisome event was analyzed by, Juanita Crook et al., Princess Margaret Hospital, Toronto, in 292 men in their report "PSA Kinetics and PSA Bounce Following [125I] Permanent Seed Prostate Brachytherapy," Int.J.Rad.Oncol.Biol.Phys., Vol 69 (2), 2007.

These authors define "bounce" as a "benign temporary increase in PSA level of varying magnitude that spontaneously decreases without therapeutic intervention to a level at or less than the pre-bounce PSA reading." They were careful to define their terms: specifying "bounce" as a temporary rise in PSA level of $\geq$ 0.2 ng/mL; PSA nadir as a post treatment PSA value of $\leq$ 0.1 ng/mL or three consecutive stable readings separated by at least 3 months; and PSA failure as a PSA value > 2 ng/mL above the nadir. The median follow-up in the study was 44 months (range 8 - 81 months); median patient age, 64 years; and median baseline PSA, 5.6 ng/mL. All but 4 patients had Gleason score 6 or less, and 65% of men were tumor clinical stage T1c and 35% T2a. Initial follow-up was every 3-6 months for the first two years and then less frequently. "The median nadir was 0.05 ng/mL (range 0.01 - 0.2 ng/mL) and was reached at a median of 40.8 months."

Many studies have found, as did Crook et al., that younger men are more likely to experience a bounce. Crook cited a study by Critz (J Urol 2000, 163) that reported a bounce in 57% of men aged $\leq$ 65; in 41% between age 61-70; and in 26% of men $\geq$ 71 years.

The median *onset* of a bounce was at 15.2 months; the median magnitude, 0.76 ng/mL; and the median duration was 6.8 months. In the Crook study a graph shows a bell shaped curve depicting the distribution for time of *onset* for the bounce with the median onset at 15.2 months. The trailing edge of the curve shows that the onset of all bounces had essentially

returned to baseline at 36 months. PSA failure, of course, occurred much less frequently and the same graph shows the failure events curve as a low, slow rise and fall with the the median onset of PSA failure at 30 months (based on ASTRO definition). By using the "nadir + 2 ng/mL" definition the median onset of PSA failure is 22.3 months. While median time to bounce occurs earlier than the median time to PSA failure (by both definitions for failure), there is considerable overlap for these two curves so that an early PSA rise can be suggestive of, but not conclusive for, designating a bounce.

The magnitude of the bounce varies greatly, but in general the higher the PSA rises the less likelihood that a bounce is the explanation.

"The magnitudes of the bounce were <1 ng/mL in 64%, 1-2 ng/mL in 21%, and >2 ng/mL in 15%." Thus in Crook's series "15% of subsequently resolved benign bounces would have been mistakenly called failures using a "PSA nadir +2" definition for biochemical failure." Critz's article reported one bounce of 15.8 ng/mL!

Unfortunately, despite close scrutiny by many researchers, the only prospective *hint* that a PSA rise will ultimately be a "bounce" is the time of onset for the PSA rise. The PSA doubling time prior to a PSA rise has not proved to be a reliable indicator of bounce. Prostate biopsies in the 2 or so years following brachytherapy may still show cancer cells even in cases where in the ultimate outcome is favorable, so the authors discourage biopsies in an effort to resolve the issue during this time period.

What management suggestions do the authors present? When a PSA rise occurs the patient's PSA should be monitored every 3 months, and if the level doesn't correct by 30 months a biopsy should be considered. If the PSA level rises to >10 ng/mL they suggest systemic investigations.

During the period of inconclusiveness as to bounce or failure, a patient needs the perspective and supportive counseling of an experienced clinician to help weather this anxiety laden event.