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PRIMARY TX UPDATES: PCa Management: Three Expert "Consultations" Discussing Primary Treatment Options For A Newly Diagnosed PCa Patient - Presented On-line in the New England Journal of Medicine.

In the December 11, 2008, issue the NEJM began a new interactive feature, the first of which focuses on decisions regarding the primary treatment of prostate cancer. The link is: http://content.nejm.org/cgi/content/full/359/24/2605?query=TOC. The clinical details are briefly set forth of a 63 year old man with a very common presentation of early prostate cancer. Thereafter, the primary therapy options of radical prostatectomy, brachytherapy, or active surveillance are discussed by a recognized expert in each modality - and the reader is invited to vote his choice, defend his choice, and comment about the expert's discussion.

Expectant management [active surveillance] is discussed by Fritz Schroder, M.D. of Erasmus University, Rotterdam, the Netherlands. The option is clearly presented - pros and cons, including comment regarding the usefulness of re-biopsy to guard against misclassification.

Mack Roach, M.D., UCSF, very nicely describes brachytherapy - the technique, treatment outcomes (when performed by experienced hands), and side-effects in comparison to other modalities.

The case for radical prostatectomy is made by Peter Scardino, M.D., MSKCC, He offers his opinion about the expected outcome for this man and the side effects of surgery in comparison with expectant management and brachytherapy.

Each expert provides a comprehensive selection of relevant references. The "consultations" are informative, succinct, and straightforward, and likely would be quite useful for clinicians, and also for patients facing this decision

DIAGNOSTICS: POSITRON EMISSION TOMOGRAPHY: It's Role in Clinical Staging Upon PSA Relapse

"Is there a role for positron emission tomography [PET] imaging in the early evaluation of prostate cancer relapse?" This is the title of a review by Greco et al., in Prostate Cancer and Prostatic Diseases, Nov. 2008. Clinicians are keenly aware of the great need for accurate localization of disease at PSA relapse in order to properly select appropriate therapy. The article sets the stage for their analysis by noting: "The patient population with a rising prostate specific antigen (PSA) post-therapy with no evidence of disease on standard imaging studies currently represents the second largest group of prostate cancer patients." Greco's conclusion, however, states: "So far no tracer has been shown to be able to detect local recurrence within the clinically useful 1 ng/mL PSA threshold ... ," the range considered optimal for the application of "salvage" therapy.

An article published subsequent to and therefore not included in the Greco review, reported the most successful PET imaging results to date at low PSA levels: "Role of whole-body 18F-choline PET/CT [FCH] in disease detection in patients with biochemical relapse after radical treatment for prostate cancer," (Pelosi et al., Radiol Med, (2008:113.) This Italian study scanned 56 patients relapsing with only rising PSA values and subdivided the group into those with PSA of $\leq$1, 1 - $\leq$5, and > 5 ng/mL. True-positive studies were found in 20, 44, and 81.8%, respectively. Of the 42.9% (24/56) positive scans (mean PSA, 7.15 $\pm$ 9.77 ng/mL) 4 were local recurrences and 20 were systemic, including 10 with lymph node metastases.

The local recurrences were confirmed by prostate-bed biopsies; and systemic pathological FCH uptake in the 20 with distant spread was confirmed by biopsy or MRI. In the negative scan group "further studies and prostate-bed biopsies identified local disease recurrence in five of them," i.e. false negative FCH studies.

The authors suggested that these false negative scans in five patients could likely be explained by the spatial limitation of current PET technology to lesions larger than 5 to 10 mm. Their conclusion: Despite positive findings in only 20% of men with PSA values < 1ng/ml, "PET was positive and provided correct localization of disease in 44% of patients in the subgroup with PSA between 1 and 5 ng/ml."

[FDA approval for clinical use of 18F-choline in currently pending.]

The Greco review, however, tempers enthusiasm for the radioisotope tracers currently under study when the imaging goal is "to discriminate between local relapse and distant disease to optimally tailor treatment strategy." Cited in the review was the study by Cimitan et al. (Eur J Nucl Med Mol Imaging, 2006, Feb) which reported positive FCH PET/CT scans in 54 of 100 men in PSA relapse "mostly in patients with PSA values > 4ng/ml. Of the negative scans, 89% were observed in patients with PSA <4 ng/ml." Also cited was Seltzer's search (J.Urol, 1999) for recurrent disease using the clinically available 18F FDG (fluorodeoxyglucose) tracer, in which the FDG PET was "positive for distant disease in 50% patients with PSA >4, and only in 4% with PSA <4ng/ml." In the setting of PSA relapse the best results were obtained with the 11C labeled tracers (11C-choline and 11C-acetate), but the "relatively short half-life of 20 minutes limits their use to centers with on-site cyclotrons." (The half-life of the 18F-choline and 18FDG radioisotopes is 110 minutes, which enables their speedy delivery from a supplier to the PET site.)

Greco stated, "Currently, no imaging modality is able to accurately detect lymph-node metastases in patients with early biochemical recurrence following primary local therapy." CT and 18F-FDG-PET performed poorly at this task, and "Prostascint has an ever lower detection rate."

David Djang, M.D., nuclear medicine specialist at Swedish Hospital, Seattle, commented: "I think the general conclusion that the lower the PSA, the lower the yield of PET/CT (no matter the tracer) will hold true for a long time. The small physical volume/mass of cells required to produce a PSA of 1 ng/ml will be an ongoing challenge for any imaging modality, - CT, PET/CT, or MRI." The Greco review concludes that "The role of PET imaging in prostate cancer is evolving but still remains within the experimental stage", especially if the goal is localizing cancer in the PSA range of 1 ng/ml.

DIAGNOSTICS: The Role of Repeat Prostate Biopsies in Men Choosing Active Surveillance

The Achilles heel of the biopsy Gleason score is misclassification resulting from sampling error; but accuracy in Gleason grading is crucial to optimal selection of patients for the management strategy of active surveillance. Berglund et al., MSKCC, address the misclassification issue in their study, "Pathological Upgrading and Upstaging With Immediate Repeat Biopsy in Patients Eligible for Active Surveillance, J.Urol, Nov 2008. One hundred four men met the study eligibility requirement: PSA < 10 ng/ml, clinical stage T2a or less, Gleason pattern 3 or less, 3 or fewer positive cores and no single core with 50% or greater cancer involvement. At repeat biopsy within 3 months, 27 (26%) were *negative (italics mine)*, 59 (57%) had a Gleason score of 6 or less, and 17 (16%) had a Gleason score of 7, and one man had a Gleason score of 9. On rebiopsy ten were found to have >3 cores involved and 12 had "50% or greater involvement of at least one core." In total, "Of 104 cases (27%) 28 were upgraded and/or upstaged." All initial biopsies were performed at referring institutions where the median number of cores was 10 (range 2 - 27); median PSA 4.7 ng/ml. The repeat biopsies were done at MSKCC with 14 cores and additional cores taken from areas suspicious on DRE. Of the 27 men with a negative repeat biopsy, "96% had only 1 positive core on initial biopsy, while 32% with up staging/or upgrading on repeat biopsy had 2 or 3 positive cores on initial biopsy."

The Jan/Feb, 2008, issue of the PCa Commentary included a nomogram published in the article (CANCER June 15, 2007) by Kulkami, "Clinical

Predictors of Gleason Score Upgrading: Implications for Patients Considering Watchful Waiting, Active Surveillance, or Brachytherapy." It is possible that by utilizing this nomogram men with a higher risk of reclassification could be selected and the number of repeat biopsies reduced.

What does the future hold for a man whose repeat biopsy is *negative* following an initial positive biopsy? This is the subject of an article from a Montreal group, "Role of Repeated Biopsy of the Prostate in Predicting Disease Progression in Patients With Prostate Cancer on Active Surveillance," by Otaibi et al, CANCER July 15,2008.

Ninety two men on the active surveillance [AS] protocol underwent the offered repeat biopsy one year after initial diagnosis. The continuing follow-up offered annual rebiopsy, or a biopsy "if there was a change on DRE or in the PSA value." Eligibility for the AS program required a prostate cancer clinical stage ≤T2a with ≤2 cores positive, no core with >50% cancer, and no major Gleason pattern 4. The median follow-up for the study was 76 months.

The first rebiopsy was negative in 44 patients (47.8%) and for this group "the 5-year actuarial progression-free probability was 82%." The definition of clinical disease progression while on AS was exceeding the criteria for eligibility for the program. Of those who progressed only 5 (15%) developed a primary Gleason pattern of 4. Many, or most, of the men who showed progression by the study's definition remained candidates for definitive primary therapy aimed at cure, or at least long-term disease control.

Ten men with progression went on to radical prostatectomy and only one had extracapsular disease. Of the 44 patients with a negative first rebiopsy, 11 (25%) developed disease progression at a mean of 40 months. Thirteen men had a negative second rebiopsy, and "5 patients had ≥3 consecutive repeat prostate biopsies."

A "negative" result on repeat biopsy is itself a "misclassification" of a sort, and is with associated with low-volume disease. The authors concluded:

"The result of the first repeated biopsy appears to have a strong impact on disease progression."

DIAGNOSTICS: Does the Addition of PSA Velocity to PSA Increase the Likelihood of Diagnosing Prostate Cancer on Biopsy in Men Whose PSA is <4 ng/ml?

It is intuitively appealing that the combination of PSA and PSA velocity (PSAV) would give better guidance in the clinical decision of whom to biopsy. This sense was nicely expressed in Vickers' recent review: "Cancer is a growth process, and it seems reasonable to suppose that the rate of change of a tumor marker would be a more sensitive marker of disease aggressiveness than an absolute level" (JCO, Dec. 2008, "Systematic Review of Pretreatment Prostate-Specific Antigen Velocity and Doubling Time as Predictors for Prostate Cancer"). There has been intense research activity to determine if PSA velocity (PSAV) or PSA doubling-time improves the predictive accuracy of PSA alone. Vickers el al.(MSKCC) analyzed the association between these two metrics and identified 87 relevant reports, but concluded that only one report documented a slight diagnostic benefit for the combination over PSA alone.

However, the conclusion that PSAV is *not* helpful in making an initial diagnosis of prostate cancer is controversial. As noted in the Vickers's review: "The National Cancer Center Network

2007 guidelines for prostate cancer detection include a recommendation that men with a PSA velocity greater than 0.35ng/mL/yr should consider biopsy, even if their PSA is low." The Baltimore Longitudinal Study on Aging (Carter, JNCI, 2006) suggested that a PSAV of greater than the 0.35ng/mL/yr. would aid in identifying life-threatening prostate cancer in the PSA range of <4ng/mL, when cure is sometimes possible. D'Amico (Editorial, JCO, Feb. 2008) was uncomfortable in accepting the conclusion that PSAV wasn't clinically useful until the issue was evaluated in a clinical trial. Loeb et al.(J.Urol, Dec, 2007) was persuaded of the usefulness of a threshold velocity of 0.4 ng/mL/yr in guiding the decision to biopsy men with PSA levels <4 ng/mL. Loeb's conclusion was based on a screening study of 22,019 men in which he found that "Overall, prostate cancer was diagnosed in 223 (2%)men with a prostate specific antigen velocity of less than 0.4 ng/mL per year compared to 278 (13%) men with a PSAV greater than 0.4 ng/mL/yr (p<0.001)".

Vicker's analysis, as it turned out, was unique. It focused on PSA and PSAV in the pretreatment setting and asked the question as to whether PSAV *improved* on PSA *alone* for predicting the risk of prostate cancer. "Although PSA dynamics were generally found to be associated with outcome," of the 42 reviewed studies that dealt with predicting the risk of cancer on initial biopsy "only one article [Loeb's] compared predictive accuracy of models with and without a PSA dynamic." The study end point for Loeb's analysis was the biopsy diagnosis of cancer in 6844 men undergoing PSA screening. Vickers noted that in the Loeb study "that the PSA velocity improved prediction slightly (from [AUC of] 0.81 to 0.83), but was subject to verification bias", i.e. "men not undergoing biopsy assumed to be cancer free." In general Vickers noted that the studies they reviewed addressed the question of whether PSA *or* PSAV had greater predictive accuracy. The conclusion in Vickers was that the *combination* of the two metrics did not function better than PSA alone.

Thompson et al. (JNCI, 2006) in their report of results from the Prostate Cancer Prevention Trial found that PSA dynamics (i.e. such as PSAV) did not improve prediction of finding cancer on biopsy. Therefore, PSAV is not included in their on-line calculator for predicting risk of biopsy-detectable prostate cancer: http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp.

Vickers stated: "In Summary, we have found little evidence that pretreatment PSA velocity or PSA doubling time are of value for early-stage prostate cancer. There is therefore no justification for the use of PSA dynamics in the clinical setting or as an inclusion criterion for clinical trials in this population."