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DIAGNOSTICS: Skeletal Scintigraphy With 18F Sodium Fluoride Positron Emission Tomography (18F-fluoride PET) Offers Greater Overall Accuracy Than 99mTechnetium-MDP for Prostate Cancer Patients

For years and years bone imaging with 99m-Technetium-methylene diphosphate (99mTc-MDP), which in clinical practice is conventionally referred to as "the bone scan", has served as the gold standard for evaluation for metastatic lesions to bone. Scanning with 99mTc was widely recognized as an imperfect guide, with about only 1% of patients with a PSA value of <20 ng/mL testing positive despite the potential of their harboring micrometastatic disease. (It can be argued that for patients at high-risk for metastatic spread the threshold for efficient utilization of BS may be a lower PSA value of (say) >10 ng/mL.) The superior specificity and accuracy of the newer technology, i.e. the 18F-fluoride PET, is

gradually changing the venerable paradigm, although orders for the traditional 99mTc-MDP bone scan may continue due to a lack of availability of the PET scanners or unfavorable logistics for obtaining the isotope, lack of awareness of the PET advantage, or just a lingering emotional attachment to what has become so familiar.

An excellent review comparing the 18F-fluoride PET with other imaging modalities is "Skeletal PET with 18F-Fluoride: Applying New Technology to an Old Tracer", Journal of Nuclear Medicine, January 2008, by Grant FD et al. writing for a consortium from Children's Hospital, Boston, and from Harvard and the University of Pennsylvania medical schools. (Per my request, this article was brought to my attention by Dr. David Djang, Seattle Nuclear Medicine, whose comments were very helpful in the construction of the article.)

The biologic mechanism underlying imaging by both tracers is similar: identification of increased osteoblastic bone turnover resulting from bone remodeling stimulated by tumor/microenvironment interactions. The 18F-fluoride is incorporated into bone as fluoroapatite. After the scan - uniquely - the 18F-fluoride decays into normal hydroxyapatite, leaving no trace of radioactivity. The uptake of 18F-fluoride into the bone is high and rapid and then cleared quickly providing the high bone-to-background ratio that underlies the high spacial resolution/localization characteristics of this tracer. As a result the time to imaging for 18F-fluoride PET scan is about 1-1.5 hours compared to a wait of about 3-4 hours for 99mTc-MDP. The tomographic imaging of the PET provides a lesion resolution of between 4-5 mm as opposed to a resolution of 9-12 mm for the 99mTc-MDP planar presentation. The PET technology offers higher sensitivity and specificity compared to the gamma camera imaging with 99mTc.

In addition to the finer spacial resolution, Dr. Djang explained that the superior localization of PET was the key advantage. Examples: localization of uptake in facet joints occasions much less worry than pedicle uptake; increased activity along an end-plate, possibly emanating from an osteophyte, is of much less concern than a round lesion in a mid-vertebral body. This confidence of localization is not possible with planar 99mTc imaging, which is basically a two dimensional photograph, like a chest X-ray. The 18F-fluoride PET is tomographic, a three-dimensional study like a chest CT - a true upgrade in technology. It is possible to perform tomographic imaging with 99mTc ("SPECT") but the spacial resolution is still inferior, and perhaps more importantly, a patient would have to lie on the table for 4-5 hours to complete a single whole body scan - untenable for most patients.

Grant et al. extensively reviewed studies comparing the 18F-fluoride PET to 99mTc-MDP in a variety of tumors and the 18F-fluoride PET study consistently found more lesions. One study compared the total lesions found on 18F-fluoride PET to the those visualized by the 99mTc-MDP, which showed only 40% of spinal lesions and 82% of lesions in the appendicular skeleton that were seen on PET. The authors' conclusion: "These studies have demonstrated that 18F-fluoride PET is more accurate than planar imaging or SPECT with 99mTc-MDP for localizing and characterizing both malignant and benign lesions."

Even-Sapir et al., Tel Aviv, in J Nucl Med, 2006, February, reported a study of 44 patients, "The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT." "In patient-based analysis 23 patients had skeletal metastatic spread (52%)..."

In their hands the PET/CT was "more specific than the 18F-fluoride PET alone and more sensitive and specific than planar and SPECT BS." "Categorizing equivocal and malignant interpretation as suggestive of malignancy the sensitivity and specificity of 18F-fluoride PET alone were 100% and 62% versus 100% and 100% for PET/CT. The negative predictive value for both scans was 100%.

[The half dozen years of physician experience with the 18F-fluoride PET at Seattle Nuclear Medicine has provided sufficient experience in interpretation so that, for them, the added expense of the hybrid PET/CT is usually unnecessary].

BOTTOM LINE: The most accurate and informative assessment of the skeleton for metastases is critical for appropriate clinical management, especially at initial presentation for patients with higher risk

prostate cancer where evidence of disease spread has the potential of changing an original plan of management. Currently the 18F-fluoride PET or the hybrid PET/CT offer the best opportunity for an optimal diagnosis.

ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE: Immediate Versus Delayed Radiation Therapy For Patients At High Risk For Failure After Radical Prostatectomy - A comparison of outcome for two options in this management dilemma (SWOG Trial 8794)

In their review of this issue, Kibel and Nelson in Prostate Cancer and Prostatic Diseases (2007)10, succinctly cited the current state of affairs:

"...recent randomized trials have demonstrated a biochemical advantage to adjuvant radiation therapy, but it remains to be seen if this will translate to an improvement in survival end points or if salvage radiation would be just as effective." A plethora of articles address and confirm this analysis, with nearly all, however, stopping the comparison at the point of PSA relapse. As the results of the SWOG trial (below) document, following PSA relapse after primary therapy much of the long and unpredictable course of prostate cancer still remains to be revealed.

SWOG Trial 8794 studied 425 men with pT3 NO MO disease, reported by Ian Thompson et al. in JAMA November 15, 2006, provides illuminating data by virtue of a uniquely long follow-up of 10.6 years (interquartile range, 9.2-12.7 years). The study found *no significant difference* in overall survival (including death from any cause) between immediate adjuvant radiation with 60-64 Gy (a bit less than current doses of 64-70 Gy; median dose 65 Gy) and delayed therapy in patients with locally advanced prostate cancer. The median overall survival for the immediate therapy group was 14.7 years and for delayed, 13.8 years (P=.16). As expected, the median PSA relapse-free survival (relapse point set at PSA >0.4 ng/mL) was an impressive 10.3 years for immediate vs. 3.1 years for delayed therapy.

The primary study endpoint was "metastases-free survival, defined as time to first occurrence of metastatic disease or death due to any cause." These two end points were chosen because of their special clinical importance. For the immediate therapy group the median metastatic-free estimate was 14.7 years vs. 13.2 years for the delayed XRT group, just short of significance at P=.06. This lengthy interval to metastases for the delayed group surprised the study planners, who at the outset had "the assumption that the primary end point, metastases free survival, would be 6 years if radiation were delayed and that immediate treatment would decrease the metastases-free survival hazard by one third."

Seventy of the 211 men on the observation arm ultimately "crossed over" and received radiation, and for the 65 men whose PSA values were know at the time of initiation of XRT, 55.4% started treatment at the point of PSA relapse (>0.4 ng/mL), and 41.5% at objective recurrence. The protocol schema did not require an undetectable PSA post surgery for men to be study eligible. In the adjuvant group 65% had a post surgery PSA of less than 0.2 ng/mL, hardly different from the 68% in the observation group with the same PSA value. The crossover to XRT from observation status took place at between 3 days and 9.7 years after randomization (median 2 years, interquartile range 11 months - 4.5 years).

The protocol did not specify the PSA value at which hormonal therapy should be initiated, but "among the observation group, 21% had received hormone therapy by 5 years, compared with 10% among those of the radiotherapy group."

One take away point that emerges from this study focuses on the endpoint of PSA relapse ubiquitously used in so many comparison studies. The SWOG study raises questions about the reliability of time-to-PSA failure as a relevant surrogate for treatment effectiveness when the important endpoints of metastases free survival and life duration are more clinically meaningful concerns. A questioning of the significance of time-to-PSA relapse has also arisen in chemotherapy trials where the time-to-objective disease recurrence seems to be a more appropriate comparison point between regimens.

The SWOG 8794 data established that the early radiation therapy clearly delayed the initiation of hormonal intervention therapy, which conventionally utilizes Lupron with its known toxicity and

degradation of quality of life. However, the development of substantially less toxic alternatives to LHRH agonists such as (say) dutasteride/bicalutamide may significantly replace this classic Lupron paradigm and erode the importance of this delay of hormone intervention.

A second observation from SWOG 8794 - which again was unexpected by the authors - led to their conclusion that "The pattern of treatment failure in high-risk patients is *predominantly local* with a surprisingly low incidence of metastatic failure" (Swanson, JCO, June 2007). The data showed that at a median follow-up of 10.2 years for the patients in both arms who had a post-surgical PSA of ≤0.2ng/mL **reductions** in PSA failure, local failure, and distant failure for the adjuvant group vs. observation were 72% v. 42%, 20% v. 7%, and 12% v. 4%, respectively. For the two study groups in which the post-surgical PSA values were between >0.2 and 10 ng/mL the 10-year **risk reduction** figures in the three categories were 80% v. 73%, 25% v. 9%, and 16% v. 12%, again respectively. This led to the authors to conclude that "further improvement in reducing local treatment failure is likely to have the greatest impact on outcome in high-risk patients after prostatectomy."

Several generalizations emerge from the data of SWOG 8794: 1), the interval of time to PSA failure for prostate cancer therapy is an unreliable predictor of metastases-free and overall survival; 2) the predominant treatment failure after radical prostatectomy is local; and 3), if *prolongation of freedom from PSA failure is a goal*, then in surgically treated men with advanced prostate cancer a high priority should be given to treatment of the post surgical prostatic bed with immediate external beam radiotherapy or [I will add] radiation administered at a low PSA level (see below).

[SWOG 8794 was not designed to explore the finer point of defining a potential window of opportunity for the serviceable application of radiotherapy following surgery for men at high risk for recurrence, i.e. XRT given in the very low ranges of PSA after relapse, (say) at less than 1 ng/mL or at least between 1 and 2 ng/mL. For an analysis of this issue see the articles in the PCa Commentary of November 2007, July 2007, and especially September 2004 indexed under "Adjuvant and Salvage Treatment."]

ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE: "Ten-Year Follow-Up of Radiation Therapy Oncology Group Protocol 92-02: A Phase III Trial of the Duration of Elective Androgen Deprivation in Locally Advanced Prostate Cancer", Horowitz, JCO, to be published, May 20, 2008.

This article is the radiation therapy counterpart of the SWOG 8794 study (reviewed above) with a comparable duration of follow-up of a median 11.3 years. RTOG 92-01 had as its purpose "To determine whether adding 2 years of androgen-deprivatioon therapy (ADT) improved outcome for patients electively treated with ADT before and during radiation therapy." Long term ADT (LTAD+RT) with an LHRH agonist was assigned to 758 men and short term ADT (STAD+RT) to 763. Radiation therapy consisted of 44-46 Gy to the pelvis followed by conedown to the prostate for a total dose of 65-70 Gy. The characteristics of eligible men in the two arms were nearly identical: median age, 70; PSA ≤30, 67%; PSA ≥30 33%; clinical stage, T2c, 45%; T3, 50-52%; T4, 3-5%; Nx, 87-86%; N0 9-11%; and Gleason score was ≤6 in 38%; 7, in 36-39%, and 8-10 in 14%.

The 10-year study results comparing STAD+RT versus LTAD+RT are as follows:

- Local progression (LP): 22.2%, STAD; 12.3%, LTAD; P = <.0001.

  LP was defined as clinical evidence of local recurrence (by any method) during the ten-year follow-up or persistent disease.

- Distant failure (DF): 22.8% (STAD); 14.8% (LTAD); P < .0001

  DF was defined as clinical evidence of metastatic disease by any method.

- Biochemical failure (BF): 68.1% (STAD); 51.9% (LTAD). P < .0001.

  BF was defined as the earliest of the following: three consecutive rises after a post treatment PSA nadir; receiving additional ADT; or PSA greater than 4 ng/mL. Similar to what was seen in SWOG

8794 long term ADT prolonged freedom from PSA relapse. The median time to biochemical failure for the STAD group was at ~2 1/2 years versus ~ 7 years for men in the LTAD arm. For a subset of men with Gleason score 8-10 PSA failure occurred at a median of ~ 1 3/4 years (STAD), compared to ~5 years (LTAD).

- Disease free survival (DFS): 13.2% (STAD); 22.5%, LTAD; P < .0001.

  DFS was defined as *avoidance* of LP, DF, BF, or death. The converse of DFS specifies men who **did** have LP, Distant Failure, BF, or who died, and expressed in this manner the percentages were 86.8% for STAD and 77.5%, LTAD.

- Disease specific survival (DSS): 83.9% (STAD); 88.7% (LTAD); P = .0042

  DSS was defined as avoidance of death due to prostate cancer or treatment toxicity, or from unknown causes in association with metastases. P = .0042

- Overall survival for the two arms at ten years was *not significantly different*, 51.6 % for STAD compared to 53.9% for LTAD, P = .36. However, in the small subset of men with Gleason score 8-10 (~24 men in each arm) the 10-year overall survival was 31.9% (STAD) compared to 45.1% (LTAD), P = 0061.

What observations arise from this important long term study? Despite a much shorter biochemical progression-free interval for the STAD arm, and despite the impressive P values for the comparisons, the absolute differences at 10 years between the two study arms were relative minimal and the 10-year outcomes were quite favorable: DSS at 10-years was 88.7% v. 83.9% and freedom from distant metastases 77.2% v. 85.2% favoring those whose ADT totaled 24 months after primary treatment.

BOTTOM LINE: Similar to the results in the SWOG study, the course of prostate cancer can be long for men after treatment of locally advanced disease. And as with many studies of outcome for primary treatment of prostate cancer in older men, the major cause of death is not from cancer, but from "other causes."

ANDROGEN INSENSITIVE DISEASE: Intermittent Chemotherapy - When Is Enough Enough?

Dr. Tomaz Beer and colleagues have generated a useful guideline for the management of the fortunate minority of men with prostate cancer who experience a very favorable response to chemotherapy. Based on data from a subset of *responding* patients they reported on "Intermittent chemotherapy in patients with metastatic androgen-independent prostate cancer: results from ASCENT, a double-blinded randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel, CANCER Jan 15, 2008. After a median initial treatment duration of 22 weeks 53 of the 250 men (21%) in the ASCENT trial achieved a PSA level of ≤4 ng/mL and were offered the option of interrupted therapy. Forty-five men participated. For these men "Treatment was suspended until the PSA level rose by 50% and was ≥2 ng/mL or until there was any other evidence of disease progression." The median duration of the first holiday was 18 weeks (range 4 - 70 weeks), with 20 of the men off therapy for >20 weeks. Of 33 men who resumed treatment 15 (45.5%) responded again achieving a ≥50% PSA reduction, and 15 others exhibited a stable PSA for at least 12 weeks. At the time of this report 10 patients had completed their second holiday with a median time off of 12 weeks (range 7-22 weeks). Thirteen patients have taken ≥2 chemotherapy holidays.

The responding patients who became eligible for intermittent therapy had favorable profiles for performance status (82% ECOG 1), hemoglobin level(median 13.5 g/dl), and alkaline phosphatase value (median 97 units). This group's median baseline PSA was 25.28 ng/mL; median age, 70 years; and 80% had bone metastases.

This is the first report of a prospective testing of this approach to therapy which offers a "practical method with which to balance disease control and quality of life in the subset of AIPC patients whose disease is very sensitive to docetaxel."