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DIAGNOSIS TheTechnetium-99m Radionuclide Bone Scan - Our "old standard workhorse", warts and all. Is an MRI or a Sodium Fluoride PET a better diagnostic tool for detection of skeletal metastases?

In the past, and hopefully less so in the future, 35% or more men fail primary local therapy for prostate cancer. In 80% or more of these instances metastases to bone is the only site of failure, or a component of failure. Biologically, there is a lengthy - possibly 5 years, maybe 10 year, subclinical latency period during which identification of early spread evades any current diagnostic test. There are many clinical situations in which an "earlier" diagnosis of bone metastases offers no clinical advantage. However, for men who present with "high risk" local disease, often defined by Gleason sums 8-10, high stage, or PSA > 15-20 ng/mL, accurate information about skeletal metastases by imaging methods more sensitive than the Technetium planar bone scan might influence the choice of primary therapy. Does imaging with magnetic resonance (MRI), hopefully soon to be "whole body" MRI, or with Sodium Fluoride Positron Emission Tomography (NaF-18 PET) usefully improve detection?

These three techniques exploit significantly different biologic aspects of tumor and host. The image in the bone scan results from the detection of the radiotracer on the mineralizing surface of bone, rather than in the tumor itself, and reports the host's reactivity, i.e, bone remodeling. Utilizing a parallel mechanism but by employing a different tracer, the NaF-18 PET detects the deposition of fluoride at sites of high bone turnover and remodeling where F-

18 exchanges with hydroxyl groups in hydroxyapatite crystal of bone, to form fluoroapatite (Seminars in Nuclear Medicine,Jan 2001). MR imaging detects information about the tumor cells themselves by sensing chemical characteristics of cells, especially differences in water content.

Many studies have demonstrated the greater sensitivity of MRI and NaF-18 PET as compared to planar bone scanning (BS) in detecting skeletal metastases. Three representative studies addressing this comparison are as follows : 1) reporting sensitivity, specificity, positive predictive value, respectively, MRI- 96%, 100%, 100% versus BS- 72%, 98%, 95% (AJR 1997;169:1655); 2) reporting accuracy, MRI 95% versus BS 79% (Radiology 1999;211:199); 3) and reporting accuracy, MRI 82%, BS 71%, and FDG-PET 90% (AJR 2001;177:229). These percentages are relative to a "total" number of lesions detected by a composite of a variety of techniques often including CT and standard X-Ray images.

One study in particular was instructive on a specific issue, "Sensitivity in Detecting Osseous Lesions Depends on Anatomic Localization: Planar Bone Scintigaphy Versue 18F PET", Schirrmeister, J Nuc Med, Oct 1999. This study, as in many others, presents a comparison between techniques by reporting detectability on a lesion-to-lesion basis. Because bone metastases in prostate cancer usually are osteoblastic/sclerotic as opposed to osteolytic, it's advisable to restrict comparisons of techniques to studies imaging prostate cancer (as opposed to thyroid or lung cancer), even though it is recognized that there is a significant osteolytic component to PC bone metastases. In the prostate cancer patients, NaF-18 PET detected 67 lesions and bone scanning 33 lesions. Again, using a composite of MRI, CT, and X-Rays as the reference "gold standard", on a lesion-to lesion basis the detection rates of bone metastases were 100% with NaF-18 in patients with osteoblastic metastases associated with cancer of the prostate. This was in contrast to detection with bone scanning where only 49% of the osteoblastic lesions were detected. When considering specific regions of the skeleton,... "Compared with PET and the reference methods, [bone scans] had a sensitivity of 82.8% in detecting malignant and benign lesions in the skull, thorax, and extremities and a sensitivity of 40% in the spine and pelvis." The costs for a Tc-99m bone scan is about $250 and a NaF-18 PET and Tc-99m SPECT bone scan are roughly the same at about $750. The medicare reimbursement for an MRI "marrow study" covering skull to pelvis plus ribs and femurs is $3600, and for a non-contrast MRI of thoracic and lumbar spine and pelvis, about $1800. The many studies of whole body MRI scanning have shown that the MRI is more sensitive than planar bone scans for detection of metastases. When the comparison between MRI and planar bone scans is restricted to axial spine and pelvis, the MRI is more sensitive, although bone scanning augmented by SPECT of these areas has comparable sensitivity to MRI.

Where does this leave us with respect to the initial evaluation of the "high risk" prostate cancer patient - the focus of this article? The greater sensitivity of MRI and NaF-18 PET for the detection of bone metastases seems well established. How does this sensitivity information apply in relation to the PSA value of a man at initial diagnosis?

Many studies argue against performing bone scans on men with initial PSAs of < 10 ng/mL, where the positive rate may be as low as 1-2%, with the possible exception of cases with extensive high grade tumor. A study, "MRI of the Skeleton in Prostate Cancer Staging", Scandanavian Journal of Urology and Nephrology, 37(3), 2003, presents information about 76 men correlating the initial PSA level with the results of MR imaging of the lower thoracic and lumber spine and pelvis. In the cohort with PSA < 20 ng/mL 4/27 (17%) were positive; and in the group with PSA > 20 ng/mL 22/52 (42%) were positive. The same authors in 1999 had

done a previous study of 446 men in which they related the initial PSA with bone scan positivity. Results: PSA <5, 4.5% positive; PSA 5-9, 5.2%; PSA 10-19, 3.2% and 20-49, 37%, PSA 50-99, 50.9%. When they factored in tumor grade, bone scan positivity was much less in grade 1 and 2 tumors. The authors then compared the data from both studies. They averaged the results from from the bone scan study for PSA <5 to 19: = 4.3%, which was then compared to the 17% pickup in the men in the same PSA range in the MR study. Their conclusion: "...MRI is a more sensitive indicator of bone metastases than bone scintigraphy in the low range of serum PSA, but less sensitive in the high range." [However, the latter portion of the conclusion is weakened because the MR imaging covered only the axial spine and pelvis whereas bone scanning examines the entire skeleton]

Its important to recognize that the pathway of hematogenous (venous) spread from prostate to bone under situations of increased intraabdominal pressure (coughing, straining) can bypass the caval tributaries and flow preferentially into the pelvic bones and the entire spinal axis via Batson's vertebral venous system.Perhaps this explains why isolated asymptomatic metastases in the peripheral skeleton are very rare (Traill, Clin Radiol 1999;54:448-51). In their comparative study of axial MR versus bone scanning in 200 patients with breast and prostate cancer only 4/200 (2%) had isolated lesions in the peripheral skeleton and 3 of these 4 were symptomatic. Seattle Nuclear Medicine is considering offering the NaF-18 PET in Spring of 2004, but insurance coverage is not yet available for this study in prostate cancer. After considering the sensitivity data presented, and until whole body MRI or NaF-18 PET become available, a clinician might well choose a spinal axis and pelvic MRI, as opposed to planar bone scanning in the initial work-up of the high risk patient.

The formulation of this article is solely mine, but I deeply appreciate the constructive comments and suggestions for references by Drs. Justin Smith, Udo Schmiedl, and Dave Haseley - Ed Weber

Bottom Line: Advances in imaging techniques can enhance staging accuracy for prostate cancer.

HORMONE INTERMENTION Food For Thought - Keep An Open Mind

In the face of the rising PSA of androgen insensitivity clinicians customarily continue Lupron - almost indefinitely. Is this done only in keeping with "custom"? Why do we do this? Is there any biologic rationale or established evidence supporting this practice? True, prostate cancer is always heterogeneous with respect to its androgen sensitive and insensitive components, so possibly the Lupron continues to address with diminishing usefulness the diminishing number of androgen sensitive cells. The only study I am aware of that focused on this issue (and I can't find the reference) was a SWOG study years ago that showed a four month survival benefit for continuing androgen suppression in this clinical situation. In the November 5 JNCI an editorial, "Playing the Old Piano: Another Tune for Endocrine Therapy" and a related article probe deeply into this area, with a focus in this case on breast cancer, and emerge with a related provocative biologic insight.

The emerging biologic understanding of prostate cancer's sister endocrine disease, breast cancer, is always relevant to our concepts about prostatic cancer. In each of these diseases the phases of progression and their underlying mechanisms are parallel. So the work of Craig Jordan, PhD, DSc, the guru of Tamoxifen, reported in this journal, is poignant.

The essence of the study is Jordan's observation that in the hormone deprived environment (resulting for example, from oophorectomy or Tamoxifen) after the initial cellular apopotic wave, the remaining once-hormone sensitive cells reset and lower their threshold for hormone

sensitivity. At this point in our discussion, a historical fact about prior breast cancer therapy is relevant. Ever since 1896 an option of treatment of metastatic breast cancer has been oophorectomy (analogous to using Lupron), and when the disease escaped from this state of hormone deprivation, paradoxically, diethylstilbesterol (DES) at the "industrial strength" dose of 15 mg had a good record of reclaiming disease control, again bringing about apoptosis. "Paradoxical" because initially it was the absence of estrogen that led to the first response, and that a second wave of apoptosis should result from reintroduction of estrogen seemed counter intuitive. The new twist in Jordan's work is that he has established that in the "hypersensitive to estrogen" state that developes in the estrogen deprived cells, even a small amounts of estrogen - actually the amount normally present in a woman's circulation - is sufficient to effect the new round of cell death! "We have confirmed and extended our original observation that low concentrations of estrogen shift the survival of SERM-resistent breast cancer cells by initiating apoptosis" ...[SERM = Tamoxifen; i.e."resistant" because cells achieve growth potential despite estrogen deprivation]..."Overall, these data ... suggest that it is possible for a patient's own estrogen to act as an anticancer agent in SERM-resistent breast cancer."

Of what relevance is this data for the management of prostate cancer? It certainly argues for a reexamination of the custom of continuing Lupron in the face of "androgen insensitivity". And a protocol at Memorial Sloan Kettering (MSKCC-99115) has picked up on this idea with a "Phase I Study of Testosterone in Patients with Progressive Androgen-Independednt Prostate Cancer", thus paralleling the early use of DES in breast cancer management. In this study Lupron is continued, but daily testosterone patches of increasing strength are applied to reintroduce testosterone in a controlled fashion. The proof of the pudding will be in the eating.

Bottom Line: Food for thought - but not quite fully cooked at this point.

PREVENTION AND DIET Tomatoes: Their Promise Of Control Of Prostate Cancer Is Ripening - An Update

The article, "Do Tomatoes Prevent Prostate Cancer", in the January issue of PCa Commentary concluded with the thought that "the usefulness of tomato products in combating PC is a very strong hypothesis, but awaits additional confirmation." Strong support was presented in an editorial in JNCI, Nov. 5, 2003 and in an associated article, "Prostate Carcinogenesis in N-methyl-N-nitrosourea (NMU)-Testosterone Treated Rats Fed Tomato Powder, Lycopene, or Energy Restricted Diets." Rats are considered to be to be excellent experimental animals for prostate cancer study because their presentation of prostate cancer closely mimics the characteristics of the human disease. In this study endogenous testosterone secretion was suppressed, the carcinogen NMU was injected, and prostate tissue growth was stimulated with depo-testosterone. Three different diets were tested: one augmented with whole tomato powder, one with solely lycopene and one offering a placebo. Result: "In the tomato powder group, the risk of developing lethal prostate cancer was reduced by a statistically significant 26% compared to that in the control rats; by contrast, the group receiving lycopene only experienced a 9% (and not statistically significant) risk reduction compared with the controls". The authors of the article were motivated by an interest in determining "whether lycopene itself is associated with reduced risk or whether it is simply a biomarker that is indicative of exposure to tomato products that may contain other phytochemicals with anti-prostate cancer properties."

This is an important area that needs clarification, especially since the preponderance of nutritional studies that have suggested a benefit of tomato derived nutrients in surpressing

prostate cancer have been based on the ingestion of tomato products and not lycopene as a isolated supplement. Although lycopene is the most abundant and potent anti-oxidant (carotenoid) contained in tomatoes, there are at least ten other substances that could modulate prostate cancer, the next most abundant being the family of carotenes.

An excellent coverage of the fundamental biology underlying this issue is "Overview of Mechanism of Action of Lycopene" by David Heber, Exp Biol Med (Maywood) 227(10): 886-93, 2002. Tomatoes are red because of their lycopene content. During the green, early period of tomato development the lycopene is converted to beta-carotene by the enzyme lycopene cyclase. But as ripening occurs this enzyme is down-regulated resulting in the accumulation of lycopene and, voila!, the red color. Lycopene, and other carotenoids, inhibit cancer cell growth by interfering with cell cycle progression and interrupting proliferative stimulae from growth factor receptor signaling, and also by strengthening cell-to-cell adhesion.

Ansari reported a small, but intriging study in BJU Int. Sep 2000, "A comparison of lycopene and orchidectomy [O/L] vs orchidectomy alone in the management of advanced prostate cancer." Twenty seven men received 2 mg lycopene twice daily and 27 were controls. Follow-up extended for two years. Results: after 2 years the mean PSA in the orchidectomy/lycopene group was 3.01 ng/ml v. 9.02; complete PSA response for O/L was 78% v. 40%; disease progression, O/L was 7% v. 28%. Of the 19 men who died, 7 had received lycopene v. 12 in the controls (P=<0.001). This study begs confirmation since the doses of lycopene seem nearly trivial, considering that the average daily lycopene dietary intake in the Canadian population is 25.2 mg. The North Central Cancer Therapy Group (protocol NCCTG-NO351) has proposed a study: "Phase II Study of Lycopene in Patients With Asymptomatic Androgen-Independent Metastatic Prostate Cancer Who Have an Elevated Prostate-Specific Antigen Level." The principle investigator of this Mayo Clinic sponsored protocol has told me that in keeping with current trend, "tomato-based products" (and not lycopene capsules) will supply the 15 mg of lycopene in the twice daily administrations.

It may be that there is a per dose absorption limit to lycopene ingestion. Charles Meyers, M.D., Prostate Forum, October 2003, reported data that suggests that 6 mg of lycopene may be the maximal amount that can be absorbed per ingestion. Dr. Meyers suggests "at least 10 mg lycopene per day", but really there is no data specifying the "proper" dose of lycopene or the optimal amount of tomato products. The current trend, however, is toward recommending that these nutrients be consumed in their natural food form.

Some practical information about lycopene content in foods was presented in the article "Lycopene Content of Tomato Products: Its Stability, Bioavailability and *In Vivo* Antioxidant Properties", Journal of Medicinal Food, Vol.4, No.1, 2001. Lycopene is bound in the cellular matrix of tomatoes and processing (heating) breaks down this matrix and makes the lycopene more absorbable. Heating in oil accomplishes this especially well. Their study used 500 ml (50 mg lycopene) of processed tomato juice (not freshly squeezed) or 126 grams (40 mg lycopene) of tomato sauce (about 1/2 cup) and both of these amounts doubled the serum levels of lycopene over control.

Bottom Line: One or two 8 oz glasses tomato juice, or 1/2 cup tomato sauce daily... or, heck, maybe a whole pizza a day, may well keep the doctor away.