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Perspective:

Exini Quantitative BSI: Expanded Utility for the planar radionuclide bone scan

"John Henry was a steel driving man… (Ballad of John Henry, American Traditional folk tune)"

John Henry pitted his strength against a steam steel driving machine, and for a day and ½, drove steel "like a man" in a contest, as it turned out, to the death. Although the ballad declares that John Henry technically may have won, it was clearly a pyrrhic victory, since the song goes on to report that at the end of the contest, "John Henry took sick and he had to go to bed…" John Henry was soon buried close to the tracks so he could "hear the engine's roar"… This tale goes to show that there are some things that machines just do better than man. Fans of Johnny Cash will recognize this story.

In the current issue of JNM, a novel methodology is described which also beats out manual effort and represents a significant advance in the analysis of the radionuclide bone scan: "Analytical Validation of the Automated Bone Scan Index as an Imaging Biomarker to Standardize the Quantitative Changes in Bone Scans of Patients with Metastatic Prostate Cancer". The current paper describes validation of an improved and more accurate computerized BSI calculation that mimics the results of the manual approach over the entire range of skeletal involvement, but outperforms manual approaches in terms of reproducibility and especially speed, greatly extending potential for rapid quantitative analysis of the planar bone scan.

The old reliable planar bone scan: bed-rock test of nuclear medicine testing for decades. The right radiometal with calcium like properties or appropriate radionuclide chelated with phosphonates can be used to accurately diagnose boney metastases in bone tropic cancers, usually before CT can see them! The pathophysiology of detecting regional metastases: accelerated hydroxy-apatite crystal turnover in the metabolically active bone near the metastatic tumor. It is the "do one, see one, teach one" test of nuclear medicine. By his/her second day in nuclear medicine (the first day would be a lecture on safe-handling of radioactivity and bone scan interpretation and use), even the greenest resident can do a reasonable job of performing and interpreting the bone scan. You carefully inject in a good vein, the bone seeking radiopharmaceutical, such as 25 mCi of 99mTc MDP, wait for 90 minutes to let the radioactivity target metabolically active bone, have the patient urinate, set the patient comfortably supine on the scanning bed of a dual-headed gamma camera, set the machine to image from head to toe at 8-10 cm per minute, activate "go" and in about 20 minutes, the imaging is done, and the patient is ready to go home. In the process, you have used tracer radioactivity to create an electronic record- a functional snap-shot of the living bone, the moment by moment biochemistry that is a signature of the metabolic homeostasis of that cancer patient's skeleton. You bring up the simultaneously acquired anterior and posterior planar image, and view the results on the electronic work-station in the reading room. What you see is an image, usually light grey, of a skeleton viewed with high enough resolution to name even the smallest bone, in front and back projections. You search for "hot-spots", sites in the image were there is high contrast increased uptake, caused by an increased rate of exchange of radionuclide delivered to the bone, and the bone mineral such as occurs near a metastatic site. On the image, a hot spot is super-imposed on the normal boney contour. Depending on the pattern of uptake, you assign a probability that the hot spot on the bone image is actually a site of boney metastatic disease- with important implications for treatment options for the patient's cancer. The planar bone scan continues to be used widely in nuclear medicine despite advances in SPECT and PET imaging, because of its simplicity, and ease of performance.

Modern approaches to the visual interpretation of bone scanning are still an important part of nuclear medicine and are performed for the clinical indication of suspected metastases in bone tropic tumors, like prostate and breast cancer. We know that even a single verified metastatic lesion in bone greatly modifies prognosis adversely. The planar bone scan test has adapted to the age of precision medicine and is used in the management of individual patients, selectively, for example, in prostate cancer when PSA biomarkers are elevated above 10 [1]. Moreover, the value of planar bone scanning has been greatly extended by the prostate cancer working group II methodology for measuring radiographic progression [2]. This approach is also based on visual interpretation, of a series of bone scans that serve as a kind of contemporaneous reference, timed with respect to the beginning of treatment, in order to overcome the effect of "flair" phenomenon. The flair phenomenon in retrospect, creating false positive results, that in the context of clinical trial, have the bad effect of mis-classifying drug effects. In contrast, with the bone scan is used according to PCWG2 "radiographic progression" criteria, as adapted, [3] can be shown to be highly correlated with survival in large trials of enzalutimide and abiraterone in prostate cancer [4]. This approach to radiographic progression assisted in identifying a positive effect of advanced prostate cancer, and has been accepted by the USFDA as a parameter with potential impact on drug approval decisions[5].

I am happy to say that the EXINI approach is a neural network based computerized extension of a manual method developed by our team of collaborators at MSKCC in the late 80's; the bone scan index or BSI method for quantitating metastatic disease on planar bone scans [6, 7]. In the late 80's we became interested in the quantitative potential of the bone scan and developed BSI technique for measuring the fraction of total skeleton based on subjective interpretation of bone by bone involvement based on bone weights from reference man. We introduced this method as a research tool, and principally for prostate cancer staging. In our manual approach, we create a list of all bones, and their % contribution to the total skeleton, and estimated fractional boney involvement by adding each positive bone to obtain a bone scan index (BSI) or % of involved skeleton by tumor. Our work was primarily in metastatic prostate cancer. We showed that the BSI was strongly prognostic, with higher numbers correlated with the worse prognosis, that with simple training, that there was good intra-observer and inter-observer agreement. We applied this tool in numerous clinical trials, with encouraging results [8, 9]. The big trouble was the effort and time it took to do an accurate job of estimating BSI, especially in advanced disease. It literally took a fellow or technician several weeks to analyze a 200+ bone scan trial, and that was really too labor intensive to be practical.

Other applications of visual interpretation of planar bone scanning include going beyond prognosis to evaluate features of the biology, we present data consistent with the correspondence of early metastasis in bone and the distribution of active adult red marrow [6]. Additional evidence indicates that bone marrow involvement as measured by PET-FDG precedes the positive bone scan by about 6-8 weeks [10]. As an example of pathobiology that could be studied with the BSI, we used the manual BSI to evaluate the rate at which a change in boney metastases occurred in individual patients with prostate cancer. We found that in a group of patients with sequential bone scanning, that the rate of progression by metastatic change followed Gompertzian kinetics , If we follow these patients back to the time of very low BSI (<1% BSI;27 patients), and plot the site of appearance of their initial lesions (we find that the occurrence of the lesion matches the distribution of red or active bone marrow, quite precisely.

When Edenbradt and colleagues developed EXINI as a computerized approach, I was hopeful that a rapid computerized method had been found. However, initial variations of the methodology, while precise, and reproducible, broke down at higher BSI >10% and also gave

much lower numbers than the manual BSI method, suggesting the possibility that accuracy of total skeletal estimates, may be a problem.

In the current paper, the EXINI group reports a revised computer model that corrects these deficiencies, and although there is more work to do in documenting effectiveness in large data sets, appears to open the door to very rapid analysis of bone scan BSI. If successful, the new computerized method could be used in principle for very large clinical trials involving thousands of patients, using a common standardized parameter for treatment response that will allow for quantitative objective stratification of patients, analysis of flair and progression. Finally, a computerized method will be highly valuable in standardizing the use of planar bone scanning according to PCWG2 criteria in advanced prostate cancer, and perhaps in “bone-only” breast cancer. The precision of these methods are outstanding, and in principle EXINI BSI can also be extended to 3 D methodologies, which has not been done for our manual BSI method, because of the labor involved with multiple images required.

Also, the improved EXINI BSI comes at a good time, when novel drugs have extended the life of patients with boney metastases and more monitoring of treatment response is required. Moreover, these quantitative computer based algorithms are applicable in principle to any bone scan seeking radiopharmaceutical.

References:


1. Larson, S.M., *Prostate cancer: Better use of bone scans in prostate cancer.* Nat Rev Urol, 2015. **12**(4): p. 190-1.
2. Scher, H.I., et al., *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol, 2008. **26**(7): p. 1148-59.
3. Morris, M.J., et al., *Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results.* J Clin Oncol, 2015. **33**(12): p. 1356-63.
4. Ryan, C.J., et al., *Abiraterone in metastatic prostate cancer without previous chemotherapy.* N Engl J Med, 2013. **368**(2): p. 138-48.
5. Kluetz, P.G., et al., *Abiraterone acetate in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer: U.S. Food and Drug Administration drug approval summary.* Clin Cancer Res, 2013. **19**(24): p. 6650-6.
6. Imbriaco, M., et al., *A new parameter for measuring metastatic bone involvement by prostate cancer: the Bone Scan Index.* Clin Cancer Res, 1998. **4**(7): p. 1765-72.
7. Sabbatini, P., et al., *Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer.* J Clin Oncol, 1999. **17**(3): p. 948-57.
8. Dennis, E.R., et al., *Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer.* J Clin Oncol, 2012. **30**(5): p. 519-24.
9. Scher, H.I., et al., *Validation and clinical utility of prostate cancer biomarkers.* Nat Rev Clin Oncol, 2013. **10**(4): p. 225-34.
10. Meirelles, G.S., et al., *Prognostic value of baseline [18F] fluorodeoxyglucose positron emission tomography and 99mTc-MDP bone scan in progressing metastatic prostate cancer.* Clin Cancer Res, 2010. **16**(24): p. 6093-9.