Letters to the Editor

Regarding Dynamic Bone Imaging with ^{99m}Tc-Labeled Diphosphonates and ^{18}F-NaF: Mechanisms and Applications

TO THE EDITOR: In the April 2013 issue of *The Journal of Nuclear Medicine,* Wong and Piert (*1*) provided an excellent review on skeletal imaging with ^{99m}Tc-labeled diphosphonates and ^{18}F-NaF. An important aspect of their paper was the use and the role of dynamic (3-phase) bone scanning. The authors stated that, for semiquantitative routine clinical applications, ^{18}F-NaF PET (or PET/CT) could be performed similarly to a 3-phase bone scan by obtaining a short (0–10 min) dynamic acquisition of an area of interest. This acquisition would then represent both the angiographic flow and the soft-tissue phases in the region, enabling replacement of a 3-phase bone scan at a fraction of time. In agreement with this concept, we have recently published data on early dynamic ^{18}F-FDG protocols in patients with chronic osteomyelitis (*2*).

For the purpose of a routine clinical approach, however, the review and current guidelines did not mention a possible use of 2-phase whole-body PET with ^{18}F-NaF (*1,3,4*). This is an emerging modality with the potential to become a substitute for 2-phase bone scans for the identification of bone inflammation sites. The advantages of 2-phase whole-body ^{18}F-NaF PET would be manifold: faster acquisition times, superior spatial resolution, exact quantification, and direct morphologic correlation with CT (if SPECT/CT is not available, as in our center).

As stated by Wong and Piert, ^{18}F-NaF has much faster kinetics than ^{99m}Tc-labeled diphosphonates; therefore, soft-tissue scans must be obtained much more rapidly than in 2-phase bone scintigraphy. Indeed, fast early whole-body ^{18}F-NaF PET scans have become feasible through the recent availability of scanners with enhanced detector sensitivity and expanded per-bed coverage due to a larger axial field of view. According to our experience (unpublished data, 2012 and 2013), these characteristics enable the acquisition of rapid whole-body scans immediately after administration of ^{18}F-NaF, representing the soft-tissue phase in analogy to that provided by 2-phase bone scans.

In some clinical applications at our center—for example, with the aim of identifying distant or secondary bone inflammatory foci in addition to known local pathology—we used a Biograph mCT 40 4-ring scanner (Siemens; TrueV option with 21.6-cm axial field of view; 14 bed positions; 6 s/bed position, including bed-changing time) and obtained 2-phase ^{18}NaF-PET scans within approximately 80 s after injection of 200–300 MBq of ^{18}F-NaF. In the early phase, a typical soft-tissue distribution became apparent. The only partial limitation was a slight skeletal uptake in some cases (e.g., when scanning began with the feet, depiction of the upper ribs and acromioclavicular joints was marginal).

According to our experience, therefore, early and fast whole-body ^{18}F-NaF PET scans are—in analogy to 2-phase bone scans—a valuable addition to the standard late technique. This option should be considered at least in cases of suspected disseminated inflammatory pathology.

REFERENCES

1. Wong KK, Piert M. Dynamic bone imaging with ^{99}Tc-labeled diphosphonates and ^{18}F-NaF: mechanisms and applications. *J Nucl Med.* 2013;54:590–599.
2. Stecker FF, Schierz JH, Opfermann T, et al. Early dynamic ^{18}F-FDG PET/CT to diagnose chronic osteomyelitis following lower extremity fractures: a pilot study. *Nuklearmedizin.* June 19, 2013 [Epub ahead of print].
3. Segall G, Delbeke D, Stabin MG, et al. SNM Guideline for Sodium ^{18}F-Fluoride PET/CT Bone Scans. *J Nucl Med.* 2010;51:1813–1820.
4. Hellwig D, Krause BJ, Schirrmeister H, Freesmeyer M. Bone scanning with sodium ^{18}F-fluoride PET and PET/CT: German guideline version 1.0 [in German]. *Nuklearmedizin.* 2010;49:195–201.

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REPLY: We thank Dr. Freesmeyer for his interest in our review article on dynamic bone imaging using ^{99m}Tc-labeled diphosphonates and ^{18}F-NaF in which we postulated that it would technically be possible to perform early soft-tissue phase imaging with ^{18}F-NaF PET (*1*), although this technique has not been described in the literature or in recent guidelines (*2*). Compared with ^{99m}Tc-labeled diphosphonates, ^{18}F-NaF provides more rapid blood clearance and higher bone-to-background uptake ratios. In combination with dynamic PET acquisition, ^{18}F-NaF allows for quantitative kinetic modeling of bone blood flow and metabolism for various applications, including investigation of bone viability (*3*) or diffuse metabolic bone disease (*4*), although limited to the available field of view. The fast kinetic properties of ^{18}F-NaF have led to concerns that obtaining a soft-tissue phase would not be feasible with ^{18}F-NaF PET; instead, ^{18}F-FDG PET or 3-phase ^{99m}Tc-methyl diphosphonate bone scanning would be required under the assumption that the acquisition of tomographic PET data, even in 3-dimensional mode, may have insufficient temporal resolution to capture the rapid soft-tissue phase of ^{18}F-NaF (*5*).

Therefore, we read with great interest the description of a novel technique of 2-phase whole-body ^{18}F-NaF PET scanning. This technique is similar to performing early whole-body soft-tissue imaging with ^{99m}Tc-labeled diphosphonate bone scanning using a sweep protocol as a screening tool for sites of joint inflammation. The proposed technique is analogous to prior published work on 2-phase or 3-phase ^{18}F-FDG PET for chronic osteomyelitis (*6*). ^{18}F-FDG PET for imaging of osteomyelitis has been found to have excellent sensitivity and specificity for bone infection, with possibly even higher accuracy than the cur-

rent gold standard radionuclide technique of ^{99m}Tc-hexamethyl-propyleneamine oxime– or ^{111}In-labeled white blood cell scintigraphy (7,8). Whether the addition of an early phase could augment the ^{18}F-FDG PET scan and further improve its diagnostic capability is an intriguing question. However, the kinetic behavior of ^{18}F-FDG and ^{18}F-NaF clearly differs, with the high net transport of ^{18}F-NaF into bone expected to provide technical challenges.

Dr. Freesmeyer describes his preliminary experience with early combined angiographic/soft-tissue–phase ^{18}F-NaF PET within 80 s of injection to acquire a whole-body scan. Using a modern scanner with an extended field of view, he reports that a typical soft-tissue distribution is clearly visually discernible with only slight skeletal uptake noted toward the end of the short acquisition. Similarly, ^{99m}Tc-labeled diphosphonate bone scans often show skeletal uptake on the soft-tissue phase when imaging is delayed to obtain multiple projections. Under the condition that the PET scanner design allows for ultra-short whole-body acquisitions with acceptable image quality, we agree that such a protocol would provide evidence of active inflammation and help distinguish the etiology of observed increased ^{18}F-NaF osseous uptake. We caution, however, that with the described image protocol, factors such as the injected radiotracer volume and concentration, the duration of radiotracer injection, cardiac output, and renal function are expected to have a significant influence on soft-tissue uptake and, therefore, may interfere with image interpretation.

REFERENCES

1. Wong KK, Piert M. Dynamic bone imaging with ^{99}Tc-labeled diphosphonates and ^{18}F-NaF: mechanisms and applications. *J Nucl Med.* 2013;54:590–599.
2. Segall G, Delbeke D, Stabin MG, et al. SNM Guideline for Sodium ^{18}F-Fluoride PET/CT Bone Scans. *J Nucl Med.* 2010;51:1813–1820.
3. Piert M, Winter E, Becker GA, et al. Allogenic bone graft viability after hip revision arthroplasty assessed by dynamic [^{18}F]fluoride ion positron emission tomography. *Eur J Nucl Med.* 1999;26:615–624.
4. Schiepers C, Nuyts J, Bormans G, et al. Fluoride kinetics of the axial skeleton measured in vivo with fluorine-18-fluoride PET. *J Nucl Med.* 1997;38:1970–1976.
5. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with ^{18}F-fluoride: applying new technology to an old tracer. *J Nucl Med.* 2008;49:68–78.
6. Stecker FF, Schierz JH, Opfermann T, et al. Early dynamic ^{18}F-FDG PET/CT to diagnose chronic osteomyelitis following lower extremity fractures: a pilot study. *Nuklearmedizin.* June 19, 2013 [Epub ahead of print].
7. Wang GL, Zhao K, Liu ZF, Dong MJ, Yang SY. A meta-analysis of fluorodeoxyglucose-positron emission tomography versus scintigraphy in the evaluation of suspected osteomyelitis. *Nucl Med Commun.* 2011;32:1134–1142.
8. Djekidel M, Brown RK, Piert M. Benefits of hybrid SPECT/CT for ^{111}In-oxine- and Tc-99m-hexamethylpropylene amine oxime-labeled leukocyte imaging. *Clin Nucl Med.* 2011;36:e50–e56.

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A Clinical Dosimetric Perspective Uncovers New Evidence and Offers New Insight in Favor of ^{99m}Tc-Macroaggregated Albumin for Predictive Dosimetry in ^{90}Y Resin Microsphere Radioembolization

TO THE EDITOR: At first glance, the results of a recent study by Wondergem et al. (*1*) may appear discouraging for the evolving science of personalized predictive dosimetry for ^{90}Y radioembolization, especially to less experienced readers. However, the dosimetric implications of their data may be interpreted more favorably in support of the use of ^{99m}Tc-macroaggregated albumin (MAA) predictive dosimetry in clinical practice.

Based on 28 procedures among 22 patients deemed to have optimal agreement on catheter tip positions between ^{99m}Tc-MAA and ^{90}Y-resin microsphere injections, Wondergem et al. found the mean difference in liver segment volume-of-interest radioconcentration to be -0.026 MBq/cm^3, with an SD of the differences of 0.2837 MBq/cm^3 (*1*). Their data showed wide 95% limits of agreement that, at the outset, seemed to suggest ^{99m}Tc-MAA to be a poor surrogate to simulate the postradioembolization biodistribution of ^{90}Y-resin microspheres. This may be too stringent a requirement. For a procedure as technically complex as ^{90}Y radioembolization, it may instead be more practical and clinically meaningful to consider the dosimetric implications within ± 1 SD of the differences, that is, 68% limits of agreement.

To illustrate this point, let us take a typical patient from the authors' dataset: a patient with inoperable chemorefractory colorectal liver metastasis without chronic hepatitis, less than 25% liver involvement by tumor, undergoing whole-liver ^{90}Y-resin microsphere radioembolization (*1*). We assign the following typical parameters for this patient: tumor mass of 200 g, nontumorous liver mass of 1,500 g, and a modestly favorable mean tumor-to-normal liver (T/N) ratio of 2. Central to this dosimetric example is the partition model formula for calculating the mean T/N ratio (*2*), which is mathematically independent of the extent of hepatopulmonary shunting. The tumor mean absorbed dose may be expressed as Equation 1, $[D_{mean} \times (m_T + m_L)]/[m_T + (m_L/TNR)]$, where D_{mean} is the whole-liver mean absorbed dose averaged across tumorous and nontumorous liver, m_T is the tumor mass, m_L is the nontumorous liver mass, and TNR is the mean T/N ratio.

By partition modeling, let us aim to deliver intended mean absorbed doses to tumor and nontumorous liver of 120 Gy and 60 Gy, respectively, in keeping with current radiation planning guidelines (*3*). From Equation 1, this translates into an intended D_{mean} of 67 Gy for this patient. Assuming a normal distribution of data and using a ^{90}Y mean absorbed dose conversion factor of 49.7 Gy per MBq/cm^3 (*1*), we now apply the results provided by Wondergem et al.: mean difference in segmental volume-of-interest radioconcentration, -0.026 MBq/cm^3; SD of the differences, 0.2837 MBq/cm^3 (*1*). The actual D_{mean} is now corrected to 65.7 Gy, with its lower and upper 68% limits of agreement at 51.6 and 79.8 Gy, respectively. Applying the latter 2 figures back into Equation 1, we can expect 84% of patients to receive an actual tumor mean absorbed dose of more than 92 Gy, sufficient to achieve at least stable disease for several months or possibly a slight response (*4*). Similarly, we can expect 84% of patients to not exceed an actual nontumorous liver mean absorbed dose of 71 Gy, within recommended limits for the