rent gold standard radionuclide technique of ^{99m}Tc-hexamethylpropyleneamine 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.

Ka Kit Wong
Morand Piert*
**University of Michigan Health System*
University Hospital B1G505C
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0028
E-mail: mpiert@med.umich.edu

Published online Nov. 6, 2013.
DOI: 10.2967/jnumed.113.132902

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

avoidance of radiomicrosphere hepatotoxicity (*3*). The converse is true: only a minority, that is, 16%, of patients may be at risk of significant tumor under-dosing or inadvertent radiomicrosphere hepatotoxicity. Considering the general complexity of ^{90}Y radioembolization, most physicians will find these treatment odds favorable and consistent with best practice in the modern era of personalized medicine.

A conservative mean T/N ratio of 2 was used in this example of colorectal liver metastasis. Most patients have higher, more favorable mean T/N ratios (*4*), which enable deliberate escalation of the intended tumor mean absorbed dose beyond 120 Gy when within safety limitations to the nontumorous liver and lung. Hence, many patients can achieve better dosimetric results than presented in this example. Equation 1 has an infinite number of possible dosimetric scenarios, which the reader is encouraged to explore. A thorough understanding of the interplay between mean T/N ratios, intended mean absorbed doses, tissue masses, and hepatopulmonary shunting is paramount for safe and effective predictive dosimetry by partition modeling (*2,4*).

It has been common knowledge for years that ^{99m}Tc-MAA is an imperfect surrogate for ^{90}Y-resin microspheres (*5*), and no study has claimed otherwise. ^{99m}Tc-MAA should be regarded as a tool, and the usefulness of any tool is only as good as its user and the complexity of the task at hand. For basic predictive dosimetry, partition modeling can be performed using a pocket calculator (*2*), and SPECT/CT (*4*) is now widely available to replace planar ^{99m}Tc-MAA scintigraphy. For advanced predictive dosimetry, affordable and increasingly powerful computers and software can rapidly generate dose–volume histograms from ^{99m}Tc-MAA SPECT/CT data (*6*). Correlation of ^{90}Y SPECT or ^{90}Y PET dose distributions with ^{99m}Tc-MAA and newer microspheres as they appear will add further confidence in the utility of the treatment planning procedure, but for the moment, it is reasonable to proceed with ^{99m}Tc-MAA. Today, the major barrier to the routine application of predictive dosimetry for ^{90}Y radioembolization is no longer the state of the art but rather the state of our hearts.

REFERENCES

1. Wondergem M, Smits ML, Elschot M, et al. ^{99m}Tc-macroaggregated albumin poorly predicts the intrahepatic distribution of ^{90}Y resin microspheres in hepatic radioembolization. *J Nucl Med.* 2013;54:1294–1301.
2. Ho S, Lau WY, Leung TW, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. *Eur J Nucl Med.* 1996;23:947–952.
3. Lau WY, Kennedy AS, Kim YH, et al. Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres. *Int J Radiat Oncol Biol Phys.* 2012;82:401–407.
4. Kao YH, Hock Tan AE, Burgmans MC, et al. Image-guided personalized predictive dosimetry by artery-specific SPECT/CT partition modeling for safe and effective ^{90}Y radioembolization. *J Nucl Med.* 2012;53:559–566.
5. Van de Wiele C, Maes A, Brugman E, et al. SIRT of liver metastases: physiological and pathophysiological considerations. *Eur J Nucl Med Mol Imaging.* 2012;39:1646–1655.
6. Dieudonné A, Garin E, Laffont S, et al. Clinical feasibility of fast 3-dimensional dosimetry of the liver for treatment planning of hepatocellular carcinoma with ^{90}Y-microspheres. *J Nucl Med.* 2011;52:1930–1937.

Yung Hsiang Kao
Austin Hospital
Level 1, Harold Stokes Building
145 Studley Rd.
Melbourne, Victoria 3084, Australia
E-mail: yung.h.kao@gmail.com

Published online Nov. 6, 2013.
DOI: 10.2967/jnumed.113.128553

REPLY: With great interest we read Dr. Kao's comments on our work. Advanced dosimetry and individualized treatment planning play a crucial role in further development and optimization of hepatic ^{90}Y radioembolization. Pretreatment scout dose imaging is an important tool for this purpose. In our publication, we showed the limitations of ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) as a scout dose to predict subsequent intrahepatic ^{90}Y distribution (*1*). In 68% of all 225 evaluated liver segments (according to Couinaud's liver segmentation), a difference of more than 10% between ^{99m}Tc-MAA and ^{90}Y activity distribution was found. A difference of more than 20% and more than 30% of the mean activity per milliliter was found in, respectively, 97 (43%) and 72 (32%) of 225 segments. The overall mean difference between pretreatment and posttreatment distribution of activity concentration for all segments was −0.022 MBq/mL, with 95% limits of agreement of −0.581 to 0.537 MBq/mL (−28.9 to 26.7 Gy absorbed dose). Dr. Kao translated these findings to clinical practice and ultimately emphasized the utility of ^{99m}Tc-MAA scout dose imaging for individualized treatment planning, using the so-called partition model (*2*), regardless of the reported limitations. We fully agree with Dr. Kao's suggestion that the drawbacks of scout dose imaging should not withhold us from using advanced treatment planning techniques, especially because the alternative methods, the often-used body surface area–based method for resin microspheres and the whole liver volume–based method for glass microspheres, leave much room for improvement and are highly inaccurate from a dosimetry perspective.

It is generally true that the partition method leads to higher administered activities, because it takes the differential dose between tumorous and nontumorous tissue (T/N ratio) into account, which is usually greater than 1 (*3*). In the example given by Dr. Kao, the aimed tumor-absorbed dose is 120 Gy. Because of expected differences between ^{99m}Tc-MAA and ^{90}Y distribution, the final expected tumor dose will not be 120 Gy in every patient, but a tumor dose greater than 90 Gy may still be reached in as many as 84% of the patients. This seems acceptable indeed. Moreover, this percentage will further increase with improvements in radioembolization techniques focused on diminishing the discrepancies between ^{99m}Tc-MAA and ^{90}Y distribution, such as selective administrations distal to major bifurcations and major side branches. In our study, these factors significantly influenced the distribution differences between ^{99m}Tc-MAA and ^{90}Y (*1*).

On the other hand, one has to keep in mind that it is not the absorbed dose to the tumors but rather the absorbed dose to the nontumorous liver tissue that is the dose-limiting factor, especially for whole-liver treatments. In Dr. Kao's example, the target nontumorous liver dose of 60 Gy will not be met in a significant number of patients. According to Dr. Kao's analysis, the upper acceptable limit of 70 Gy is expected to be crossed in as many as 16% of the patients. In the light of radioembolization-induced liver disease as a potential complication after high-dose radioembolization, this number seems to be unacceptably high. One should therefore choose a conservative approach when using the partition method for whole-liver treatments. In addition, Dr. Kao's scenario was sketched for a T/N ratio of 2; higher T/N ratios will lead to lower nontumorous liver doses. The uncertainty in estimating the nontumorous liver dose will then be less relevant. For lobar treatments, in which the partition method is mostly used today, the nontumorous dose is of course not that important because the contralateral lobe will be spared.