Number of Iterations When Comparing MLEM/OSEM with FBP

TO THE EDITOR: The work that van der Weerdt et al. (*1*) reported in the article "Postinjection transmission scanning in myocardial ^{18}F-FDG PET studies using both filtered backprojection and iterative reconstruction" has afforded useful and needed results on this topic. It is indeed surprising that so important a study had not been conducted before.

The study had an additional aim: "to compare images reconstructed with both standard filtered backprojection (FBP) and an iterative reconstruction algorithm based on ordered-subset expectation maximization (OSEM)" (*1*). FBP reconstructions have been performed with the classic Hanning filter at 0.5 of the Nyquist frequency and OSEM reconstructions with 2 iterations and 12 subsets. This configuration of OSEM is equivalent to 24 iterations with the maximum-likelihood expectation maximization (MLEM) algorithm (*2*). It has clearly been demonstrated that such a low number of iterations generates reconstructed images with a low noise level but at the expense of a biased contrast (*3*). The convergence speed of MLEM and OSEM depends on the number of counts and is slower for the low-count regions than for the high-count regions (*3,4*).

In view of the number of iterations used by van der Weerdt et al. (*1*), it could be anticipated that no region had reached the convergence. This could explain the systematically lower value for the ^{18}F-FDG uptake recorded on OSEM reconstructed slices (Tables 1 and 2). The encountered differences are limited and not always statistically significant, but they are pointed out 3 times by van der Weerdt et al. (*1*) in the "Results" section. In Figure 2D, the largest differences in ^{18}F-FDG uptake between FBP and OSEM slices appear to be recorded for the segments with the lowest uptake. This observation could clearly result from the slower convergence of these low-count regions.

In conclusion, one might suggest that the number of subsets and iterations chosen should be close to the convergence for all studied regions before quantitative comparisons are made between FBP and OSEM. The number of requested iterations will probably result in images that are too noisy, and a postprocessing filter should be applied (*3*).

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REPLY: Our paper addresses the effect of emission spillover into transmission scans (*1*). In addition, a comparison between data reconstructed using FBP and OSEM was made. For OSEM reconstructions, the small number of 24 expectation-maximization-equivalent iterations (2 iterations and 12 subsets) was applied. Prof. Seret is correct in stating that by using such a small number of iterations, full convergence has not been reached and biased contrast will result. However, several considerations may justify the use of a small number of iterations.

First, the (pixel) variance properties of OSEM, as compared with FBP, were considered. It has been demonstrated that for large background regions with low uptake (e.g., soft tissue), pixel variance of OSEM-reconstructed data is lower than that of FBP. That explains the successful use of OSEM for reconstruction of oncology whole-body studies; that is, the low variance in the background improves the detection of small tumors. However, Boellaard et al. (*2*) and Riddell et al. (*3*) have shown that for small objects (<5-cm diameter) such as tumors or myocardium, pixel variance obtained with OSEM, already at a low number of iterations, is worse than that obtained with FBP. Increasing the number of iterations to ensure convergence will further increase variance, which may be reduced by additional postprocessing smoothing of the images. To obtain approximately equal variance at pixels located in the myocardium between fully converged OSEM and FBP data, more filtering of OSEM than of FBP reconstructed images would be required. The resulting lower resolution of OSEM images than of FBP images would result in biased contrast (worse cold-spot recovery) as well.

Second, van der Weerdt et al. (*1*) showed that using OSEM with only 24-emission-equivalent iterations resulted in only minor underestimations of ^{18}F-FDG uptake (~2%), compared with FBP, for most regions (Table 1). Larger underestimations (~10% on average, with a maximum of ~20%) were observed in regions with low uptake (Fig. 2D). The impact of these underestimations on the quality of clinical evaluation of myocardial ^{18}F-FDG studies was assessed and was found to be not significant (Table 3).

Although Prof. Seret is right is stating that OSEM with 24 iterations does not provide fully converged data, it is our opinion that the choice of applied OSEM parameters is a good compromise between reaching sufficient (but not full) convergence and restricting noise within acceptable levels for the purpose of clinical evaluation of myocardial ^{18}F-FDG PET studies. We thank Prof. Seret for the fruitful discussion and would also like to state that the use of OSEM reconstruction for quantitative (dynamic) PET studies without ensuring full convergence and fully validating the effects of OSEM reconstruction parameters on the accuracy and precision of these types of scans is strongly discouraged. Such validations have been addressed (*2,4,5*) and will be further studied (*6*).

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Re: Tetraphenylphosphonium as a Novel Molecular Probe for Imaging Tumors

TO THE EDITOR: The recent paper by Min et al. (*1*), extending earlier work by Delmon-Moingeon et al. (*2*) and Madar et al. (*3,4*), is an elegant presentation of the potential use of tetraphenylphosphonium (TPP) as a tumor probe for PET (*1*). Min et al. contend that the specificity of TPP for tumor imaging would not be compromised by accumulation in inflammatory lesions, which is a problem with ^{18}F-FDG imaging (*1*). As noted by the authors, TPP is a delocalized lipophilic cation, much like the ^{99m}Tc-labeled myocardial imaging agents sestamibi and tetrofosmin, which are also used for tumor imaging. The selective accumulation of this class of compounds in tumors (and the heart) is related to the highly negative inner mitochondrial membrane potential in these cells (*2*).

However, Min et al. (*1*) fail to mention that lipophilic cations, such as TPP, sestamibi, and tetrofosmin, are transport substrates for the multidrug resistance transporter P-glycoprotein (*5–7*). Multidrug resistance refers to a phenotype in which a tumor is inherently resistant or develops resistance to a variety of structurally unrelated chemotherapeutic agents, including such common drugs as anthracyclines, taxanes, and vinca alkaloids. The prevalence of P-glycoprotein overexpression varies greatly among tumor types. Tumors that overexpress P-glycoprotein will show lower accumulation of these tracers than will P-glycoprotein–negative tumors, because of active efflux of the tracer. Indeed, the ~10% false-negative rate observed in scintimammography with sestamibi and tetrofosmin could actually be a true-negative rate because of multidrug resistance. This reduces the sensitivity of such a tracer for tumor detection, though the tracer may still be useful for tumor characterization.

Thus, in proposing an agent that may be more specific for tumors, they have sacrificed sensitivity. Although there is often a trade-off between sensitivity and specificity in nuclear medicine, in this instance the trade-off could have been predicted from the literature.

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REPLY: We agree with the comments that TPP is a substrate for P-glycoprotein, as has been published previously. We did not claim that TPP is not such a substrate in the original paper (*1*) but, instead, that it requires further evaluation as an imaging agent based on the results of our study in comparing it with ^{18}F-FDG. It should also be kept in mind that as modifications to TPP are made to incorporate a positron emitter (e.g., ^{18}F), each derivative will have to be tested as a potential substrate for P-glycoprotein. It may eventually be possible to develop a molecule that is a derivative of TPP and is a poor substrate for P-glycoprotein. This may lead to an imaging probe that is both sensitive and specific. Even if any modified TPP is still a substrate for P-glycoprotein, it may prove to be a useful imaging tracer in many different applications, including characterizing the P-glycoprotein status of a given tumor.

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Dosimetry and Radioimmunotherapy of Non-Hodgkin's Lymphoma

TO THE EDITOR: With interest I read the letter of Britton concerning radioimmunotherapy (RIT) of non-Hodgkin's lymphoma (NHL) (*1*). In brief, he compares RIT of NHL with other therapies using radionuclides, in which a tracer dose of a radiopharmaceutical is given and imaging is performed before the actual treatment. This procedure allows selection of patients based on assessment of uptake of the radiopharmaceutical, and it allows (tumor) dosimetry. Britton notices that neither procedure is advocated when planning RIT using ^{90}Y-ibritumomab. He therefore raises the question of whether we should uphold our own nuclear medicine approach to selecting patients and dosing the radiopharmaceutical.

In NHL patients, the maximum tolerated dose of radiolabeled monoclonal antibodies (mAbs) is limited by the absorbed dose that

the bone marrow can tolerate or by second-organ toxicity in myeloablative RIT (*2*). Every radiopharmaceutical for RIT of NHL patients has its own dosing scheme, based on body weight, bone marrow dosimetry, or body surface area (*2*). So far, no nonmyeloablative dosing method has been proven to be superior or to lead to higher response rates than others. None of the dosing methods use tumor dosimetry to determine the dose to be administered to the patient. One reason is that the myelotoxicity of the radiopharmaceutical will limit further increments of radioactivity doses, and not the absorbed dose to the tumor, but there are 2 more reasons.

First, in not all patients can lymphoma sites clearly be seen on scintigraphy after a tracer dose of radiolabeled mAbs. This does not mean that a patient cannot benefit from RIT, as Britton postulates (*1*). In my patient experiencing a complete response after RIT, no uptake of ^{99m}Tc-epratuzumab was observed in known lymphoma sites on scintigraphy (*3*). Still, this patient was selected for treatment because of positive CD22 antigen expression on histologic material from his lymphoma. Even on scintigraphy after treatment with ^{186}Re-epratuzumab, the lymphoma could not be detected, but a complete response was observed (*3*). Scintigraphy, however, can be used to exclude patients from further treatment: not because visual assessment of scintigraphy does not show lymphoma uptake but because the radiopharmaceutical has an unfavorable biodistribution. If uptake of the radiopharmaceutical is observed only in the bone marrow, it may be wise not to treat the patient because of the severe myelotoxicity or even myeloablation that may result (*3*).

Second, tumor dosimetry is not used for dosing radiolabeled mAbs since doing so would suggest that a clear dose–response relationship exists and that we know which absorbed dose is minimally needed to induce a response. Neither the former nor the latter holds true. A wide variety of tumor doses was reported, ranging from 0.6 to 243 Gy in cases of treatment with ^{90}Y-ibritumomab (*4*) and from 0.4 to 18 Gy after treatment with ^{131}I-tositumomab (*5*), but no correlation was found between doses and response to treatment (*5,6*). Because the mAbs themselves can induce responses, even absorbed doses as low as 4 Gy are associated with responses to treatment (*7*). Therefore, tumor dosimetry is of limited value in planning RIT of patients with NHL.

Taking into account the fact that RIT consists of a combination of treatment with mAbs and radionuclide therapy, I do not see a dilemma with respect to the approach to be followed. There is neither an exclusively nuclear medicine approach nor a strictly oncologic approach: RIT is a multidisciplinary treatment modality, using doses of radiolabeled antibodies and radionuclides as determined by safe and sound clinical trials. It is time for nuclear medicine physicians and oncologists to implement this new treatment in routine clinical practice.

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REPLY: In response to the letter by Dr. Postema, I reiterate my concern that radionuclide β-therapy is not being assessed by prior radionuclide γ-imaging. He cites a case in which a patient responded although the results of prior imaging and posttherapy dose imaging were negative. Surely Dr. Postema does not think that the patient's response was due to radiation. The logical procedure when pretherapy imaging results are negative in a patient with a disease with a high degree of antigen expression would be to give unlabeled antibody therapy. Whether by antibody-dependent cellular cytotoxicity, ADCC, complement-dependent cytotoxicity, CDC, or human idiotype 2 formation, unlabeled antibody therapy may be effective in up to half of non-Hodgkin's lymphoma patients, as is stated in his own review (*1*). Clinical and legal justification of radionuclide therapy requires evidence of uptake of the proposed radionuclide therapy agent, and he should be in a position to make his multidisciplinary team aware of this to avoid unjustified radiation, isolation, or expense in the treatment of a patient with non-Hodgkin's lymphoma.

Oncologists are trying to individualize their therapy through determining a range of genetic markers for each patient. We in nuclear medicine are able to individualize treatment by prior imaging as proof of uptake. Positive imaging does not "suggest that a clear dose–response relationship exists." It is just common sense that no uptake predicts no therapeutic effect *due to radiation*. It does not exclude other beneficial actions of the antibody. The relationship between tumor dose and response in radioimmunotherapy may thus be explained. When the carrier is relatively inert, such as with ^{131}I MIBG, a more direct dose–response relationship is evident. It is our duty to protect patients from unnecessary therapeutic radiation, just as it is our duty to point out the safety of our diagnostic studies in adults. These are basic principles resulting from the "J"-shaped response to radiation (*2*).

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