Misinterpretation of ^{18}F-FDG Studies in Oncology

TO THE EDITOR: The survey finding by Karantanis et al. (*1*) of perceived greater "overinterpretation" than "underintepretation" of ^{18}F-FDG PET/CT studies in oncology on the part of referring physicians is supported by data from a prior report in *The Journal of Nuclear Medicine* by Biggi et al. (*2*). This work showed a better failure-free survival (FFS) rate in patients with Hodgkin disease and positive interim PET scans interpreted locally than in patients judged to have positive scans by a central reading group. The FFS rates for patients with negative scans were identical between local and central interpreters. Therefore, the discrepancy in the FFS rates in patients with positive interim scans can be accounted for only by overinterpretation, that is, false-positive interpretations, on the part of the local interpreters.

In fairness to local interpreters, there is more pressure on them clinically than on central interpreters whose opinions are not used in caring for the patients. There is arguably more pressure when it is known that a result will be used to guide further decisions on treatment.

My own impression of this is that because of the relative consequences, many interpreting physicians are more worried about missing a cancer than having a false-positive result. A missed cancer can progress to the detriment of the patient and with liability risk to the interpreting physician, whereas overcalls are often never discovered because therapy goes forward with apparent success and everyone is happy. From this standpoint, the data from Biggi et al. are unique and eye-opening because outcomes were tracked over time, revealing the impact of overinterpretation, which does not come without medical and financial costs. If we are to use the results of PET/CT in oncology to guide risk-adapted therapy, the interpretations must be accurate.

In the context of international telemedicine, we have seen a similar phenomenon with pathology interpretations. In one case of a lesion falsely diagnosed as cancer, we asked the originating pathologist about his interpretation. He was quite candid and said the patient was a VIP. He was not sure of the diagnosis and had no local expert to consult. He reasoned that if he called the lesion benign, and it turned out to be cancer, his position would be in jeopardy. On the other hand, if he called the lesion cancer, the treatment was certain to be successful and all parties would be satisfied with the outcome.

Equally interesting is the observation of Hicks (*3*) in the accompanying perspective. Hicks notes that he has seen cases in which he has made a positive finding only to be overruled by a negative biopsy result but with disease becoming manifest later in the same area. He posits the likelihood of pathologic sampling errors but with the surgeon left thinking the PET scan was a false-positive.

An article by Haseebuddin (*4*) in the same issue of *JNM* as Biggi's report sheds important light on Hick's observation. Haseebuddin's work provides data on FFS in patients with prostate cancer studied with ^{11}C-acetate for lymph node staging. Patients with "false-positive" PET scans demonstrated higher rates of failure than those judged to have had true-negative scans. Again, having outcome data is pivotal in considering the possible explanations. It is most likely that the discrepancy in FFS rates between true-negative and false-positive PET scans is due to surgical or pathology sampling errors—disease was present but missed on biopsy. However, another intriguing possibility is that PET scans with various agents might actually become positive before histopathologic criteria for cancer are met. Since we have always taken histopathology as the gold standard, this possibility has not been substantively considered or studied.

Perhaps it is time to challenge the gold standard.

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The Impact of Image Reconstruction Bias on PET/CT ^{90}Y Dosimetry After Radioembolization

TO THE EDITOR: We read with great interest the paper entitled "The Impact of Image Reconstruction Bias on PET/CT ^{90}Y Dosimetry After Radioembolization" (*1*). In this paper, Tapp et al. showed that commercial software that truncates the negative pixels (resulting from random-coincidence correction) can display a significant positive bias in ^{90}Y PET imaging. We would like to bring some additional information to the attention of readers and PET system manufacturers.

We were also confronted by this problem while developing a correction method for the spurious-coincidence contamination occurring in ^{86}Y PET imaging (*2*): directly subtracting the estimated spurious-coincidence sinogram from the 511–511 keV true-coincidence sinogram (i.e., prompt minus delayed coincidences) resulted in numerous negative pixel values due to the high fraction of spurious coincidences generated by the multiple γ cascades present in ^{86}Y decay (*3*). Afterward, truncating these negative pixels before ordered-subsets expectation maximization reconstruction ended up in significant bias. Additional smoothing of the spurious-coincidence sinogram only partially improved the reconstruction.

Initially, we tried to take into account the estimation of spurious coincidences by adding it to the projection estimate in the denominator of the iteration step, which can be schematically written as

$$A^{n+1} = A^n \times \frac{1}{\tilde{c}I} \times \tilde{c}\frac{S}{cA^n + S_{sc}}, \text{Algorithm 1}$$

where A^n is the activity image estimate at step n, I the identity image, c the projection matrix, S the measured true-coincidence sinogram, and S_{sc} the estimation of the spurious-coincidence sinogram. The operation +,— is performed ray-sum by ray-sum, and the operation × is performed voxel by voxel. Although this method preserves the reconstructed voxel positivity in an elegant, natural way, we observed that Algorithm 1 no longer correctly converges when the estimated term S_{sc} becomes too large (data not published). In ^{86}Y PET imaging, this was especially the case for corpulent patients. This method is currently implemented in the Gemini TF PET system (Philips) for correction of scatter and random coincidences (*4,5*). Care should thus be taken when imaging low-^{90}Y specific activity with this lutetium yttrium oxyorthosilicate–based system (*6*).

Finally, we decided to remove the negative pixels from the subtracted sinogram by transferring to them an appropriate number of counts from neighboring positive pixels (a detailed description of the method has been published (*2*)). The rationale of this strategy is that Poisson noise is characterized mainly by high-spatial-frequency positive–negative fluctuations. This transfer of counts was performed in a special way that avoids artifact generation in the reconstructed image. Phantom and patient studies showed that this method prevents bias in ^{86}Y PET imaging (*2*). The method could also be evaluated in ^{90}Y imaging with PET systems, allowing separated prompt- and random-coincidence acquisitions such as the one used by Tapp et al. (*1*).

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Erratum

In the article "In Vivo PET Imaging Demonstrates Diminished Microglial Activation After Fingolimod Treatment in an Animal Model of Multiple Sclerosis" by Airas et al. (*J Nucl Med.* 2015;56:305–310), the author line neglected to mention that Laura Airas and Alex M. Dickens contributed equally to the work. The authors regret the error.