Combined ^{18}F-FDG and Fluoride Approach in PET/CT Imaging: Is There a Clinical Future?

TO THE EDITOR: We read with interest the recent article by Iagaru et al. (*1*) that examined the feasibility of combined ^{18}F-FDG and ^{18}F-fluoride PET/CT in the management of patients with cancer. We congratulate the authors for their well-conducted study and would like to share our views on this promising approach. As mentioned by the authors, Hoegerle et al. (*2*) previously explored a similar approach with PET methodology in a prospective study that investigated 30 patients with various malignancies who underwent combined ^{18}F-FDG and ^{18}F-fluoride PET. The result was compared with that of the control group comprising 30 patients who underwent only ^{18}F-FDG PET. These authors concluded that combined ^{18}F-FDG and ^{18}F-fluoride PET is an advanced metabolic imaging approach for the evaluation of cancer. There are certain obvious methodologic differences between the previous study and the present one: The previous study adopted PET, which was the predominant modality at that time, whereas the present study used PET/CT fusion imaging. In the present study, the same patients underwent separate ^{18}F-fluoride PET/CT and ^{18}F-FDG PET/CT and combined ^{18}F-FDG–^{18}F-fluoride PET/CT scans; that is, a total of 3 scans were performed on each patient, whereas in the previous study, 2 different patient groups were tested with 2 different scans. Though the first study was conducted in 1998, there was apparently no further endeavor until the present study, a decade later, to investigate the potential of this 2-in-1 dual-tracer approach to PET.

This thought-provoking approach raises certain important questions in a logical mind with regard to clinical applicability. The foremost obvious question is what the potential clinical indications will be for this approach. Defining the clinical situation in which the combined study will be of advantage over conventional ^{18}F-FDG PET/CT or the ^{18}F-fluoride technique appears to be of great importance. One can foresee promise for skeletal metastatic lesions, an application in which ^{18}F-FDG PET demonstrates limited sensitivity. This application would include detection of osseous metastatic lesions in malignancies such as prostate or thyroid carcinoma. However, one must be aware of certain practical issues that might be associated with the combined ^{18}F-FDG–^{18}F-fluoride approach: first, one must remember the great potential of ^{18}F-FDG in detecting and evaluating marrow metastases—a potential that rivals MRI in this context (*3*). It is perceivable that this advantage of ^{18}F-FDG might be compromised in the combined ^{18}F-FDG–^{18}F-fluoride approach when there is normal skeletal uptake of fluoride that can obscure an abnormal ^{18}F-FDG–avid focus in the bone marrow. Also, as observed in this pilot study, therapy with bone marrow–stimulating agents can induce intense ^{18}F-FDG uptake in the skeleton that can hamper the interpretation of ^{18}F-fluoride uptake. In addition, after administration of systemic or hormonal therapy, the osseous flare with ^{18}F-fluoride may prove to be a confounding factor in the assessment of therapeutic response in ^{18}F-FDG–concentrating skeletal lesions. The metabolic flare with ^{18}F-FDG after systemic or hormonal therapies, on the other hand, is relatively short-lived and is an advantage in treatment monitoring with ^{18}F-FDG PET (*4*). These factors are important in routine clinical PET and must be considered before this approach can be recommended in this scenario. As the authors rightly indicate, the use of skeletal ^{18}F-fluoride uptake as a surrogate for anatomic localization of an abnormal focus of ^{18}F-FDG is no longer valid in the present era of PET/CT fusion imaging. The above having been said, the combined approach, if used appropriately, can be of substantial value in certain specific situations, and these potential clinical indications for this powerful technique must be defined precisely by the user community to render this approach clinically viable and efficient.

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TO THE EDITOR: The April 2009 issue of the journal contains a paper on the combined use of ^{18}F-FDG and ^{18}F-fluoride for dual detection of soft-tissue and skeletal metastatic disease (*1*). There are 2 comments that I feel should be made about this paper.

First, the authors state "Combining ^{18}F and ^{18}F-FDG in a single PET/CT scan for cancer detection has not been reported to date." Although it is technically true that this is the first paper to be published that has reported combined ^{18}F-FDG and ^{18}F-fluoride imaging with a combined PET/CT scanner, it is slightly disingenuous not to mention until well into the "Discussion" section of the manuscript that these agents have been used in

combination with PET-only scanners for more than a decade. The impression given is that it is a novel concept to combine the 2 agents into a single study. It is not.

Second, the authors use a "bone mask" with which to "separate" skeletal uptake, assumed to be attributable to the ^{18}F-fluoride, from the soft-tissue uptake attributable to ^{18}F-FDG. They state "We successfully separated the metabolic skeletal uptake and allowed interpretation of the ^{18}F and ^{18}F-FDG tissue distribution, even though the 2 tracers were administered at the same time." This is nonsense. The authors acknowledge that "bone marrow–stimulating therapy" and soft tissue abutting bone, and therefore being included in the bone mask, may confound this separation by including some ^{18}F-FDG in the skeletal images. However, it is well established that osteoblastic and osteolytic lesions display different uptake patterns with ^{18}F-FDG, with lytic lesions in bone demonstrating high ^{18}F-FDG uptake (*2*). Indeed, Cook and Fogelman have previously reported the combined use of ^{18}F-FDG and ^{18}F-fluoride in numerous publications and texts (*3,4*). Further, from a purely scientific point of view, their assertion could be substantiated only if they performed both separate and simultaneous PET scans with the 2 tracers to see how many lesions were seen in the skeleton with ^{18}F-FDG.

It is disappointing to see such a flawed and naïve piece of work published in what is an otherwise excellent journal.

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REPLY: We read the letter to the editor by Dr. Dale Bailey regarding our recently published article (*1*). We strongly disagree with the ideas expressed by Dr. Bailey for the reasons listed below.

In regard to the first objection raised by Dr. Bailey, we reaffirm that our work is indeed the first report that we know of on the use of combined PET/CT to image the distribution of combined ^{18}F-fluoride and ^{18}F-FDG for evaluation of malignancy. The reference by Hoegerle et al. (*2*) cited in our discussion is the only previously published report we know of on the combined administration of ^{18}F-fluoride and ^{18}F-FDG followed by PET (no CT). However, that administration was performed to anatomically localize ^{18}F-FDG uptake based on the preferential skeletal uptake of ^{18}F-fluoride, not to evaluate soft-tissue and skeletal lesions in a single imaging examination. Furthermore, in the study by Hoegerle et al. the images obtained after combined administration of ^{18}F-fluoride and ^{18}F-FDG were not compared with separate ^{18}F-fluoride and ^{18}F-FDG scans for each subject. Instead, 30 patients underwent only ^{18}F-FDG PET, whereas a different 30 patients underwent combined ^{18}F-FDG and ^{18}F-fluoride PET. The key value of CT could not be studied by Hoegerle et al. since at that time combined PET/CT scanners were not available. We performed a detailed prospective clinical study in which each patient had an ^{18}F-fluoride study alone, an ^{18}F-FDG study alone, and a cocktail ^{18}F-fluoride–^{18}F-FDG study. This approach required 3 PET/CT scans for each patient and was critical to moving forward in validating the utility of our novel strategy.

Related to the statement that our text ("We successfully separated the metabolic skeletal uptake and allowed interpretation of the ^{18}F and ^{18}F-FDG tissue distribution, even though the 2 tracers were administered at the same time.") is "nonsense," we simply disagree. Perhaps we could have made it clearer that certain focal skeletal uptake of ^{18}F-fluoride or ^{18}F-FDG, in conjunction with CT abnormalities, denotes osseous metastases. We do not think this will be a universal approach for cancer detection (as we discussed in the paper), but the approach will certainly work in selected patients. It was exactly "from a purely scientific point of view" that we did we perform both separate and simultaneous PET scans with the 2 tracers in all subjects. Based on the visual analysis and comparison of these 3 separate scans, we noted that only 1 skull lesion seen on an ^{18}F-fluoride scan was missed on the corresponding combined ^{18}F-fluoride–^{18}F-FDG scan, whereas all lesions seen on ^{18}F-FDG PET/CT were also detected on the ^{18}F-fluoride–^{18}F-FDG scans. Thus, we concluded that the visual analysis alone (without the aid of a bone mask) of the combined ^{18}F-fluoride–^{18}F-FDG PET/CT allowed for accurate evaluation of the scans in this selected population with known cancers referred for detection of the extent of disease before therapy.

The other references cited by Dr. Bailey (*3,4*) do not report the combined administration of ^{18}F-fluoride and ^{18}F FDG but the different patterns of skeletal metastases, facts that we agree on and that are not disputed by our work.

We certainly hope that others who took the time to read our article in detail will in fact find it a detailed, rigorous prospective study. We look forward to multicenter clinical trials to further explore the advantages and limitations of our ^{18}F-fluoride–^{18}F-FDG cocktail approach to PET/CT imaging.

We also read the letter to the editor from Dr. Basu and want to thank him and his coauthor for their attention to our article and their comments. Just as we did in our paper, they also raise the challenging issue of determining the appropriate indications for the combined ^{18}F-fluoride–^{18}F-FDG PET/CT scan. We think that this approach will work for the initial staging of patients recently diagnosed with cancer, before initiation of treatment. Thus, the issues of bone marrow activation due to