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Combined ^{18}F-Fluoride and ^{18}F-FDG PET/CT for Evaluation of Malignancy: Results of an International Multicenter Trial

In this issue of *The Journal of Nuclear Medicine,* Iagaru et al. report an international, multicenter trial that compared coinjected ^{18}F-fluoride and ^{18}F-FDG PET/CT imaging with separate ^{18}F-fluoride and ^{18}F-FDG PET/CT scans in 115 patients with cancer (*1*). In the cohort of patients included in this trial, both ^{18}F-fluoride and combined ^{18}F-fluoride and ^{18}F-FDG PET/CT scans detected more skeletal metastases in 48 subjects than did ^{18}F-FDG alone, 29 of whom had no skeletal disease detected on ^{18}F-FDG scans. ^{18}F-FDG PET/CT scans detected extraosseous metastases in 48 patients. The combined ^{18}F-fluoride/^{18}F-FDG scans missed 3 lung nodules in 2 subjects and skull lesions in a further 2 subjects, but in none of these was overall staging affected.

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The results of this trial confirmed the previously reported feasibility of imaging coinjected ^{18}F-fluoride and ^{18}F-FDG (*2,3*), highlighting the potential time and cost savings that could result from this approach without significant loss of diagnostic accuracy compared with performing separate scans. The investigators are therefore to be congratulated in performing a multicenter, multinational trial and achieving their aim of showing the noninferiority of the combined-scan approach.

The optimum method for imaging bone metastases is unresolved, and although nuclear medicine methods have been at the clinical forefront for some decades with bone scintigraphy, limitations have been recognized, particularly with regard to poor diagnostic specificity for staging and limited sensitivity and specificity for monitoring treatment response. Novel, nonnuclear medicine techniques such as whole-body diffusion-weighted MR imaging are now being actively investigated in this field. Preliminary data suggest that measuring restricted diffusion of water molecules in bone metastases may be a sensitive method for detecting skeletal disease as well as for monitoring early changes due to therapy (*4*). However, it is not yet clear how well this methodology works across different cancers and different forms of treatment, and further studies and comparisons with other imaging are required.

In parallel, PET offers tumor-specific (e.g., ^{18}F-FDG, ^{11}C, or ^{18}F-choline) or bone-specific (e.g., ^{18}F-fluoride) tracers. It is important that the different aspects of bone metastasis biology that diffusion-weighted MR imaging and tumor-specific and bone-specific PET techniques report be understood, as it is possible that the different biologic mechanisms involved may make certain methods better for metastasis detection than for assessing treatment response and vice versa.

Diffusion-weighted MR imaging is a whole-body imaging technique that derives its signal from the restriction of water molecule movement in highly cellular tissues such as tumors (*5*). Images are quantifiable by measuring the apparent diffusion coefficient, and there is thus the possibility of quantifying changes in cellularity (i.e., cytotoxicity) that occur as a result of successful treatment. Tumor-specific tracers such as ^{18}F-FDG and ^{11}C/^{18}F-choline reflect underlying metabolic changes in cancer, and it is assumed that most of the signal derives from the tumor cells themselves and that in skeletal metastases there is little, if any, contribution from bone cells. We and others have also noted in the past that ^{18}F-FDG PET appears to be less sensitive for detecting sclerotic metastases in breast cancer (*6,7*). A low sensitivity, compared with ^{99m}Tc-methylene diphosphonate scintigraphy (*8*) or ^{18}F-fluoride PET (*9*), has also been noted in prostate cancer, in which bone metastases are predominantly osteoblastic. The reason for this finding is uncertain. but it may reflect a relatively small tumor volume in sclerotic metastases that are dominated by a reactive sclerosis in the bone. In addition, in the posttherapy setting, in which responding bone metastases tend to become more sclerotic, a low level of ^{18}F-FDG activity may reflect reduced tumor cell viability and volume (*10*). In contrast, ^{18}F-fluoride is a bone-specific PET tracer that reflects bone blood flow and osteoblastic activity similar to other bone-specific nuclear medicine tracers such as ^{99m}Tc-methylene diphosphonate (*11*). Therefore ^{18}F-fluoride uptake within a lesion predominantly reflects local osteoblastic activity that occurs as a primary or secondary effect to metastatic tumor cells rather than the activity of tumor cells themselves.

With this in mind, it is important to recognize that there are 2 main applications for imaging bone metasta-

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ses: first, detecting disease with high sensitivity at initial staging to guide appropriate subsequent treatment, and second, monitoring the effects of therapy in a timely fashion so that patients who are not responding to treatments that are often associated with side effects can be changed to more effective treatment. Treatment response monitoring of bone metastases is even more relevant now that effective second-line treatments are available either as nonspecific systemic therapy or as agents specifically targeting bone (*12,13*).

Although the study by Iagaru et al. (*1*) demonstrated the feasibility and noninferiority of a combined ^{18}F-fluoride/^{18}F-FDG injection approach, it is not possible to accurately determine the ability of the method to answer the 2 clinical scenarios posed above for the following reasons. Forty-one of the 115 patients included in the study were being investigated for bone metastases from prostate cancer, and 23 of the 48 patients who showed more lesions with combined ^{18}F-fluoride/^{18}F-FDG PET had prostate cancer. Although we know that ^{18}F-fluoride PET/CT performs well in detecting the metastases from prostate cancer that are primarily osteoblastic (*14*), ^{18}F-FDG PET shows relatively poor sensitivity compared with conventional bone scintigraphy and ^{18}F-fluoride PET (*8,9*). For this reason, ^{18}F-FDG PET is not used frequently for assessing skeletal or nodal/visceral metastases from prostate cancer, and one could argue that adding ^{18}F-FDG to ^{18}F-fluoride will rarely give additional information. Both ^{18}F- and ^{11}C-choline tracers are being used more frequently for detecting metastatic disease in prostate cancer (*15,16*), and in the future the investigation of combined ^{18}F- or ^{11}C-choline with ^{18}F-fluoride would certainly be of interest in this group of patients, as some potential synergy from the 2 tracers has previously been reported (*17*). For staging of other cancers, the combination of ^{18}F-fluoride and ^{18}F-FDG will be most relevant in tumors that are typically ^{18}F-FDG–avid.

We should also note that 83% of the patients enrolled in the study by Iagaru et al. (*1*) were referred to determine the subsequent treatment strategy rather than for staging. Of the 48 patients in whom ^{18}F-fluoride/^{18}F-FDG showed more lesions than ^{18}F-FDG alone, 26 had received prior chemotherapy. It is in this group that the differences in tracer mechanisms may be important. Of course, it is not possible to differentiate ^{18}F-fluoride signal from ^{18}F-FDG signal within a skeletal lesion on a combined static scan, and on a functional level we are unable to determine the pathologic process we are imaging (i.e., tumor metabolism vs. bone osteoblastic activity). It is likely that these processes frequently do not change in parallel. Although we might expect the cytotoxic effects of successful chemotherapy to reduce uptake of ^{18}F-FDG in tumor cells quite rapidly, any reduction in ^{18}F-fluoride uptake may be delayed by ongoing osteoblastic mechanisms of repair in the bone.

Although the study is reassuring in that there is no significant loss of sensitivity for detecting skeletal metastases, there remain unanswered questions regarding the specificity of ^{18}F-fluoride uptake after treatment, and it is unclear what this means with regard to tumor viability or the requirement for further treatment in these patients. In other words, does an ^{18}F-fluoride–positive, ^{18}F-FDG–negative metastasis after treatment contain viable tumor cells or just treatment-induced bone sclerosis after successful therapy? Therefore, the combined ^{18}F-fluoride/^{18}F-FDG scan would potentially be limited in the ability to give information on tumor viability after treatment and may therefore not be a suitable approach for treatment response assessment. As well as cytotoxic chemotherapy, endocrine, bisphosphonate, and targeted therapies could potentially show differential treatment effects with bone and tumor-specific tracers.

As noted by Iagaru et al. (*1*), an undoubted advantage from the combined injection of ^{18}F-FDG and ^{18}F-fluoride is the potential to reduce radiation exposure to patients when compared with separate scans or when combined with ^{99m}Tc-methylene diphosphonate bone scintigraphy plus ^{18}F-FDG PET/CT. As well as the convenience to patients in having combined, rather than separate, ^{18}F-FDG and ^{18}F-fluoride PET/CT scans, there are potential cost savings for health-care systems, although these savings may vary from country to country.

In the future, as well as refining some of the technologic aspects of this interesting approach (e.g., optimum injected activities of each tracer), further work may clarify some of the other unanswered questions across a range of cancers in the staging and treatment response settings. There will undoubtedly be interest in combining injections of other tracers that reflect tumor and bone metabolism, particularly with the advent of PET/MR imaging, in which there is the potential to reduce radiation doses further and to simultaneously explore other aspects of tumor and bone biology.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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