

¹⁸F-FDG Uptake and Breast Density in Women with Normal Breast Tissue

TO THE EDITOR: We read the article by Vranjesevic et al. (1) with great interest and concur with their conclusions. This article points out an important advantage of ¹⁸F-FDG PET over other techniques: the high contrast that it provides between normal and malignant tissues. This contrast is achieved by minimal uptake of ¹⁸F-FDG in the normal breast, compared with uptake in cancer tissue, which is commonly hypermetabolic. The advantageousness of ¹⁸F-FDG PET is particularly true for normal, dense breast tissue, for which early diagnosis of malignant lesions by conventional imaging modalities such as mammography is difficult.

Breast cancer is the most common cancer in women, with approximately 182,000 new cases diagnosed each year in the United States. Screening with conventional mammography along with thorough physical examination is a sensitive method for the early detection of breast cancer. However, mammography does have several limitations in clinical practice. Mammography is moderately sensitive for detecting breast lesions, but its positive predictive value, 35.8%, is low (2). Diagnosis can also be difficult in young women with dense breasts and in those who have implants or have undergone surgery or irradiation to the breast tissue (2). Other imaging modalities, such as CT and MRI, have high sensitivity but low specificity in diagnosing breast cancer. Scintimammography has been used for the detection of nonpalpable breast lesions with promising results, and a recent metaanalysis of the published data has suggested that scintimammography may be useful as an adjunct to mammography and physical examination in the diagnosis of breast cancer (3). ¹⁸F-FDG PET has been compared with scintimammography and was found superior for identifying involved axillary lymph nodes and equal to scintimammography for identifying the primary breast lesion (4). ¹⁸F-FDG PET is a well-established methodology for differentiating benign from malignant tumors, including breast tumors (5).

Increased breast density is considered an independent risk factor for developing breast cancer. Vranjesevic et al. demonstrated that despite significantly higher ¹⁸F-FDG uptake in dense breasts than in nondense breasts, breast density is unlikely to affect the accuracy of ¹⁸F-FDG PET in detecting breast cancer, as peak standardized uptake value (SUV) in dense breasts never exceeded 1.5 (1). We assessed physiologic uptake in normal breast tissue by qualitative visualization and quantitative SUVs.

Thirty-three patients with histologically proven breast carcinoma were reviewed. The median age was 52.6 y (range, 32–79 y). Twenty-one patients had grade 3 or 4 mammographic density (dense breast), and 12 patients had grade 1 or 2 mammographic density (nondense breast), according to the lexicon criteria of the American College of Radiology. All mammographic studies were obtained within 4–6 wk before the ¹⁸F-FDG PET scan. All patients fasted for a minimum of 4 h and were verified to have a normal serum glucose level (less than 150 mg/dL) before the administration of ¹⁸F-FDG (5.2 MBq [0.14 mCi]/kg) through a peripheral vein. Sequential overlapping emission scans of the neck, chest, abdomen, and pelvis were acquired on a dedicated PET scanner (Allegro; Philips Medical Systems) 60 min after the administration of ¹⁸F-FDG.

SUVs for ¹⁸F-FDG were calculated for the contralateral normal breast in 24 patients with unilateral lesions and for normal breast tissue remote from the malignant lesion in 9 patients with bilateral lesions. For this purpose, 12 × 12 mm (9 pixels) circular regions of interest were placed over the area of highest ¹⁸F-FDG activity in the normal breast tissue. Peak and average SUVs were obtained from the normal areas of the 2 groups and were compared for statistically significant differences using the Student *t* test.

The peak and the average SUVs were 0.99 ± 0.20 and 0.82 ± 0.19 , respectively, for the normal tissue of dense breasts and 0.82 ± 0.23 and 0.66 ± 0.24 , respectively, for the nondense breasts. Both the peak and the average SUVs of normal dense breasts were significantly higher than those of normal nondense breasts ($P = 0.003$ and 0.003 , respectively). The highest peak SUVs were 1.3 and 1.2 for the normal dense breast and normal nondense breast, respectively. However, the peak SUVs for both dense and nondense breast tissues were well below 2.5, a widely used cutoff value for malignancy.

Although our SUVs were slightly higher than those of Vranjesevic et al., our results showed a significant difference between the dense and nondense normal breast tissues. Similar to their data, our peak SUVs were well below the cutoff values for malignancy. These data further confirm that although dense breasts may have a higher uptake, the accuracy of ¹⁸F-FDG PET studies in diagnosing malignant breast tumors will not significantly be affected by the varying uptake of ¹⁸F-FDG in surrounding normal tissues.

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REPLY: We appreciate the comments of Kumar et al. on our article (1). Kumar et al. confirm our finding that normal breast

tissue exhibits low glucose metabolic activity. This is in agreement with our suggestion that breast cancer detectability with ^{18}F -FDG PET is unlikely to be altered by breast density.

In contrast to PET, the sensitivity of mammography for breast cancer detection is strongly affected by breast density. In women with dense and very dense breasts, the sensitivity is only 59% and 30%, respectively (2). This low sensitivity is of particular concern because breast density is an independent risk factor for breast cancer (3). One can conclude from the available literature that women with dense breasts or with scars and implants are underserved by mammography.

The sensitivity of ^{18}F -FDG PET for breast cancer detection in a screening population with a low likelihood for breast cancer has not been established. In addition, larger studies need to determine the accuracy of ^{18}F -FDG PET for breast cancer detection in women with suggestive mammography findings.

What we know thus far is that infiltrating ductal carcinoma exhibits increased glycolytic activity, whereas lobular cancers tend to exhibit low or no ^{18}F -FDG uptake (4). In addition, small, invasive carcinomas and carcinoma in situ cannot reliably be detected with ^{18}F -FDG PET (5). Histologic tumor type, growth pattern, and tumor cell proliferation rates, among others, determine the degree of ^{18}F -FDG uptake (6)

Benign disease entities that can exhibit increased ^{18}F -FDG uptake include adenoma, angiomyolipoma, foreign body granuloma, fatty cell necrosis, papilloma, and others. Thus, no clear cutoff point between benign and malignant breast lesions can be established despite the low background activity of normal breast tissue, and one should not expect the sensitivity or specificity of ^{18}F -FDG PET for breast cancer detection to be close to 100%.

Despite these limitations, the sensitivity of ^{18}F -FDG PET for breast cancer detection in women with dense and very dense breasts is likely higher than that of mammography (4). Thus, PET can be useful as an additional diagnostic modality even if its accuracy is only around 70%.

The work initiated by Alavi's group is important and will provide additional data for defining the role of ^{18}F -FDG PET for breast cancer detection in women with dense and very dense breasts.

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PET Tracers for Osteosarcoma

TO THE EDITOR: Thanks to Dr. Winfried Brenner et al., and *The Journal of Nuclear Medicine*, for publishing the excellent continuing education article on imaging of osteosarcoma with PET (1).

I have a correction and a comment. The brief discussion of non- ^{18}F -FDG PET tracers leaves the reader with the impression that non- ^{18}F -FDG tracers have been used only in animal studies. In fact, as the title of the authors' reference 41 implies, studies with ^{13}N -labeled amino acids had been performed on patients with osteosarcoma and soft-tissue sarcomas several years before the first clinical use of ^{18}F -FDG in these tumors. Studies using ^{13}N -(L)-glutamate included pretherapy planar imaging studies (2,3) and quantitative follow-up studies that correlated the histologic extent of residual viable tumor with changes in ^{13}N uptake (4). A review published in 1984 included PET images of ^{13}N -(L)-glutamate and ^{18}F -sodium fluoride in osteosarcoma (5).

The use of amino acids natively labeled with short-lived positron emitters offered several advantages to the pediatric patient population, including rapid enzymatic synthesis, rapid tumor localization (minutes as opposed to hours with ^{18}F -FDG), and very low radiation exposure. Unfortunately, the early enthusiasm for ^{13}N and ^{11}C tracers was soon dampened because of the scarcity of hospital-based cyclotrons. If PET scanners and on-site production facilities continue to proliferate, perhaps a place will be found for non- ^{18}F -FDG PET tracers for osteosarcoma.

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REPLY: We appreciate the comments and additional information provided by Dr. Reiman regarding our review article on PET imaging of osteosarcoma (1).

When searching PubMed, the online service of the National Library of Medicine, for PET tracers besides ^{18}F -FDG and ^{18}F -fluoride ion (^{18}F) that have been applied to osteosarcoma, we retrieved experimental studies using ^{18}F -labeled monoclonal antibodies (2), ^{18}F -fluoromisonidazole (3), ^{18}F -labeled Arg-Gly-Asp (RGD)-containing glycopeptide (4,5), ^3H -thymidine (3), and PET

imaging of p53 transcriptional activity (6). Although we used various search terms on PubMed, the study by Sordillo et al. (7) was the only patient study we found, and the studies mentioned by Dr. Reiman did not surface. Thus, we are grateful for this information on human studies with ^{13}N -(L)-glutamate—information that gives us a more complete overview of PET imaging of osteosarcoma.

We also would like to use Dr. Reiman's comments on successful sarcoma imaging with ^{13}N - and ^{11}C -labeled compounds to encourage the application of non- ^{18}F -FDG PET tracers. When PET scanners with on-site cyclotron facilities become more ubiquitous and shipping of ^{18}F -labeled compounds to satellite PET devices is available, both new and "old" tracers should be applied in patient studies to investigate their potential for individualized risk evaluation. The use of a PET tracer such as ^{13}N -(L)-glutamate, ^{13}N -methionine, ^{18}F -fluorothymidine, ^{11}C -acetate, ^{11}C -verapamil, ^{18}F -misonidazole, or ^{18}F -annexin, to name just a few, could give detailed insight into biologic features such as amino acid metabolism, cell proliferation, multidrug resistance 1-induced chemotherapy resistance, tumor hypoxia, and apoptosis. This additional information will assist physicians in choosing the best available therapy for an individual patient and in tailoring follow-up to the specific case. Such an individualized approach will further improve patient outcome and will also allow knowledge of molecular imaging to be applied clinically and help nuclear medicine continue to evolve as a modern specialty in the fast-growing field of sophisticated diagnostic procedures.

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