The Application of Positron Emission Tomographic Imaging With Fluorodeoxyglucose to the Evaluation of Breast Disease

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Positron emission tomography (PET) is a computer-aided tomographic imaging technique that uses positron-emitting compounds to trace biochemical processes of tissue, and construct images based on them. The authors applied a whole-body PET imaging technique to patients with breast masses or mammographic abnormalities using the isotope 2-[F-18]-fluoro-2-deoxy-D-glucose (FDG), in a clinical trial to evaluate the feasibility of using PET to identify primary breast cancer, axillary lymph node involvement, and systemic metastases, before surgical resection. Fourteen patients have been entered on this study, 10 of whom proved to have breast cancer. Positron emission tomography correctly predicted the nature of 12 of the 14 primary breast lesions, and correctly determined the lymph node status of 11 of the 14 patients. The authors conclude that PET with FDG has potential as a diagnostic modality for detection of primary breast cancer, particularly in the patient with radiodense breasts by conventional mammography, and that it has potential for the preoperative identification of axillary lymph node metastases.

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POSITRON EMISSION TOMOGRAPHY (PET) is an imaging technique that produces images reflective of the biochemical activities of tissue. Positron emission tomography, like x-ray computed tomography and magnetic resonance imaging, employs computer-based image reconstruction techniques to produce tomographic images. In contrast to both computed tomography and magnetic resonance imaging, which produce anatomic images based on the physical characteristics of the imaged tissue, PET produces images based on the accumulation, distribution, and metabolism of the administered positron-emitting compound, processes that reflect the biochemistry of the imaged tissue.[1-3]

More than 30 years ago, Warburg[4] observed that malignant tissue was characterized by a high rate of glycolysis. This biochemical characteristic of malignancy can be exploited in tumor imaging using PET with 2-[F-18]-fluoro-2-deoxy-D-glucose (FDG), a positron-emitting isotope that is taken up by normal membrane glucose transport mechanisms. Because the first PET scanners were constructed for brain scanning, initial PET FDG studies in malignancy focused on the study of tumors in the central nervous system.[5,6] More recently, the development of whole-body PET scanners has made possible the imaging with FDG of tumors of other primary sites, including head and neck,[7] lung,[8] breast,[9-12] melanoma,[13] colon,[14,15] and extremity sarcomas.[16,17] These initial studies have suggested that PET with FDG can image otherwise undetectable solid tumors outside the brain, and in some cases may provide quantitative estimates of tumor glycolytic rates that correlate with more traditional indicators of proliferative activity.

The diagnosis and treatment of breast cancer present several challenging clinical problems that may be addressed by PET with FDG. These are clinical problems of major significance; breast cancer is the most common malignancy in women in the United States, with an annual incidence of more than 70 per 100,000, resulting in more

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than 40,000 deaths per year. Screening to facilitate diagnosis, identification of patients with biologically aggressive primary tumors, lymph node involvement, or metastatic disease, and early determination of chemotherapy response remain important issues both in patient care and clinical research in breast cancer, issues that might be addressed using metabolic imaging.

Because of the potential advantages of imaging based on glycolytic rate over imaging based on radiodensity, PET with FDG may complement mammography in the early diagnosis of breast cancer, particularly in women with fibrocystic and radiodense breasts, and in addition may discriminate benign from malignant masses and detect occult axillary and distant metastatic disease. If feasible and effective, such a diagnostic tool might improve the results of efforts to diagnose and treat breast cancer. In a prior report of PET with FDG in patients with known primary or metastatic breast cancer, 10 of 10 primary breast cancers, and 15 of 15 metastases were imaged.[12] Two primary breast tumors in patients with negative mammograms and fibrodense breast tissue were visualized by PET. Four previously unsuspected lymph node metastases were detected. No previous attempt to use whole-body PET with FDG in patients suspected of having breast cancer, examining the ability of FDG PET to distinguish benign from malignant lesions and to detect occult axillary metastases before pathologic confirmation, has been reported.

To further study the potential of PET with FDG to detect primary breast cancer and to predict the results of breast biopsy and axillary dissection, we initiated a trial of FDG PET, using a whole-body imaging technique, in patients presenting with an abnormal mammogram or a palpable breast mass, and correlated the results with the mammographic and pathologic findings.

Materials and Methods

Entry criteria requisite for participation in the clinical trial included: (1) female sex, between the ages of 18 and 70 years, (2) a history of a mammographic abnormality or palpable breast mass, (3) persistence of the breast mass or mammographic abnormality at the time of study entry, and (4) candidacy for surgical resection, including axillary dissection, if indicated. All patients entered in this study signed an informed consent approved by the Human Subjects Protection Committee of the UCLA School of Medicine. Mammograms were obtained and reviewed for all consenting patients. All patients had physical examinations, mammography, and PET scans before excisional biopsy. If found to have breast cancer, patients were treated with surgery, radiotherapy, and adjuvant chemotherapy or hormonal therapy, as deemed appropriate by the treating physician. No treatment decisions were based on the results of the PET scan.

The labeling of 2-deoxyglucose with ^{18}F in the 2 position to produce the positron-emitting glucose analog FDG was performed at the on-site biomedical cyclotron facility at UCLA using the method described by Barrio et al.[18] The whole-body imaging approach employed has been described in detail previously.[19] Briefly, 10 mCi sterile FDG was injected intravenously as a bolus to each patient 40 minutes before the initiation of imaging. Patients were imaged on an eight-ring, 15-image plane, Siemens/CTI 931/08-12 PET system (Knoxville, TN) in a series of imaging sequences encompassing the entire body in incremental steps. The imaging time in our protocol for a whole-body acquisition was 64 minutes. After reconstruction with software written at UCLA on a Vaxstation 3200 computer (Digital Equipment Corp., Maynard, MA), 32 two-dimensional, transaxial, coronal, and sagittal projection images were generated from each acquisition set. Reconstructed images were displayed on a high-resolution monitor using a Macintosh computer (Apple Computer, Inc., Cupertino, CA) and image display software developed at UCLA.

PET FDG scans were obtained before excisional breast biopsy. The breast, axillary areas, and the rest of the body were examined on the PET scans of all patients. Increased localized FDG uptake, as compared with surrounding tissue, by visual inspection was considered abnormal, and interpreted as suspicious for a malignant process. All PET interpretations were performed blinded to the pathologic findings at biopsy or surgery.

Results

Fourteen patients have undergone PET imaging with FDG before excisional biopsy or definitive surgical resection on this protocol (Table 1). Three patients had palpable breast masses without mammographic abnormalities, three patients had abnormal mammographic findings in the absence of a palpable mass, and eight patients had both abnormal physical and mammographic findings. Three patients had palpable, enlarged axillary lymph nodes. One patient had received multiple courses of systemic chemotherapy treatment before PET imaging. Pathologic examination showed that 10 patients had infiltrating ductal carcinoma of the breast, and that seven of these cancers were associated with axillary lymph node involvement. Four patients had benign breast lesions.

Of the 10 patients with breast cancer, eight had areas of increased FDG uptake in the breast, interpreted as consistent with primary cancer and corresponding to the abnormal mammographic finding or palpable mass. Examples of representative PET scans from three of the patients are shown in Figures 1 through 3. One patient with multiple small foci of infiltrating ductal carcinoma involving most of the breast did not show focal increased FDG uptake. The remaining patient with a false-negative

TABLE 1. *Pathologic and PET Results*

Patient	Physical Examination Findings	Mammogram Findings	Primary Site		Axilla Lymph Nodes	
			Pathologic Finding	PET	Pathology	PET
1	Breast mass, no palpable nodes	Nodular density suspicious	Benign	Negative	Not done	Negative
2	Breast mass, no palpable nodes	Calcifications suspicious	Carcinoma	Positive	Negative	Negative
3	Breast mass, no palpable nodes	Radiodense breast negative	Benign	Negative	Not done	Negative
4	No breast mass, palpable nodes	Nodule and calcification suspicious	Carcinoma	Negative	Positive (n = 7)	Positive
5	No breast mass, no palpable nodes	Calcifications negative	Benign	Negative	Not done	Negative
6	Breast mass, no palpable nodes	Nodular density suspicious	Carcinoma	Positive	Negative	Negative
7	No breast mass, no palpable nodes	Nodular density suspicious	Carcinoma	Positive	Negative	Negative
8	Breast mass, no palpable nodes	Radiodense breast negative	Carcinoma	Positive	Positive (n = 4)	Negative
9	Breast mass, palpable nodes	Nodular density suspicious	Carcinoma	Positive	Positive (n = 27)	Positive
10	Breast mass, palpable nodes	Nodular density suspicious	Carcinoma	Positive	Positive (n = 9)	Positive
11	Breast mass, no palpable nodes	Dense breast negative	Carcinoma	Negative	Positive (n = 1)	Negative
12	Breast mass, no palpable nodes	Nodular density suspicious	Carcinoma	Positive	Positive (n = 12)	Positive
13	Breast mass, no palpable nodes	Nodular density suspicious	Carcinoma	Positive	Positive (n = 12)	Negative
14	Breast mass, no palpable nodes	Nodular density suspicious	Negative	Negative	Not done	Negative

Results of physical examination, mammography, positron scan, and histologic examination of the breasts and axillae of 14 women evaluated for breast masses or abnormal mammograms. Negative refers to an interpretation consistent with a benign process; positive or suspicious refers to an interpretation consistent with a malignant process.

PET examination had a lesion composed largely of intraductal carcinoma with some areas of focal invasion. The smallest primary tumor that has been identified by PET with FDG in this study to date has been $1.0 \times 0.7 \times 0.3$ cm, visualized on mammogram as calcification without a mass. All four patients with benign breast lesions had no focally increased FDG uptake in the breast, and had PET scans interpreted as consistent with benign disease. One of these patients had a diffuse pattern of periareolar FDG uptake bilaterally and was found to have mastitis clinically, as well as a fibroadenoma pathologically. Another patient with a fibroadenoma had FDG uptake in her tonsils and one cervical lymph node, and was found to have tonsillitis associated with an upper respiratory tract infection. The remaining two patients with benign breast biopsies had no areas of unusual FDG uptake.

Of the seven patients with pathologic axillary lymph node involvement, four had axillary FDG uptake interpreted as consistent with metastatic involvement (Figs. 1 through 3), including one of the patients whose primary tumor was not detected by PET (Fig. 1). The three patients with cancer who did not have axillary lymph node involvement, and the four patients who had benign breast lesions, all had negative FDG studies in the axillary region.

None of the 11 patients with breast cancer demonstrated unsuspected localized FDG uptake that would indicate possible distant metastatic disease. One patient with a medial primary breast lesion showed localized FDG uptake consistent with internal mammary lymph node involvement (Fig. 3). Because this patient had axillary lymph node involvement, internal mammary lymph node dissection was not indicated, and thus was not performed. With a median follow-up of 9 months, none of these patients have relapsed with metastatic disease.

Mammography identified eight of the 10 cancers as suspicious for malignancy. Both patients with false-negative mammograms had radiodense breasts. In one of these cases, PET correctly predicted that the breast contained cancer. Mammography correctly identified one of the two patients who were ultimately proven to have false-negative PET scans as having a lesions as suspicious for malignancy. Mammography interpreted one of the benign breasts lesions as suspicious for malignancy; PET was interpreted as negative for this patient (Table 1).

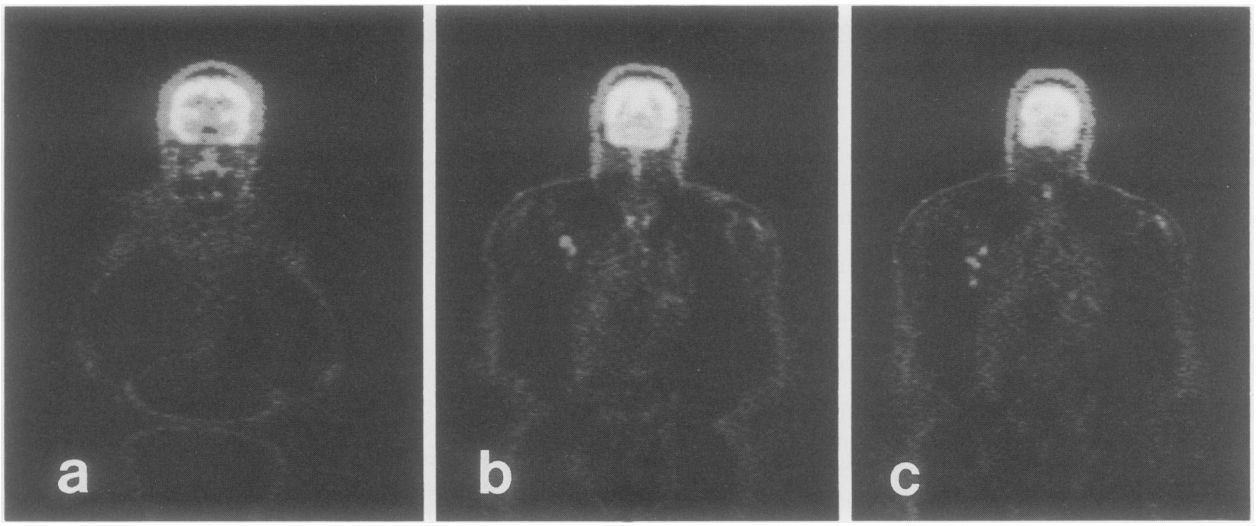

FIG. 1. Three coronal views of the whole-body positron scan from patient 4, who had abnormal mammogram findings and clinically palpable lymph nodes in the right axilla. (A) The PET did not detect the primary breast lesion, but (B and C) the areas of focally increased right axillary uptake are visible in two different coronal views.

Discussion

Despite recent advances in screening, diagnosis, and treatment, breast cancer remains a common malignancy associated with a high case mortality rate. One approach to improving the outcome for patients with breast cancer has been early detection, using physical examination and mammography.[20] Mammography has a reported sensitivity as high as 90%,[21] and its use has been reported to result in more than a 30% reduction in breast cancer mortality rates.[22] One technical limitation of mammography has been a loss of sensitivity in radiodense breasts, including breasts with significant spontaneous fibrocystic changes as well as fibrosis due to radiotherapy. The increasing use of breast-conserving therapy for breast cancer with quadrantectomy and radiotherapy has resulted in an increase in the number of women at risk for developing cancer in radiodense breasts. Hence, a diagnostic test that images based on differences in metabolism rather than radiodensity merits study as a adjunct to mammography,

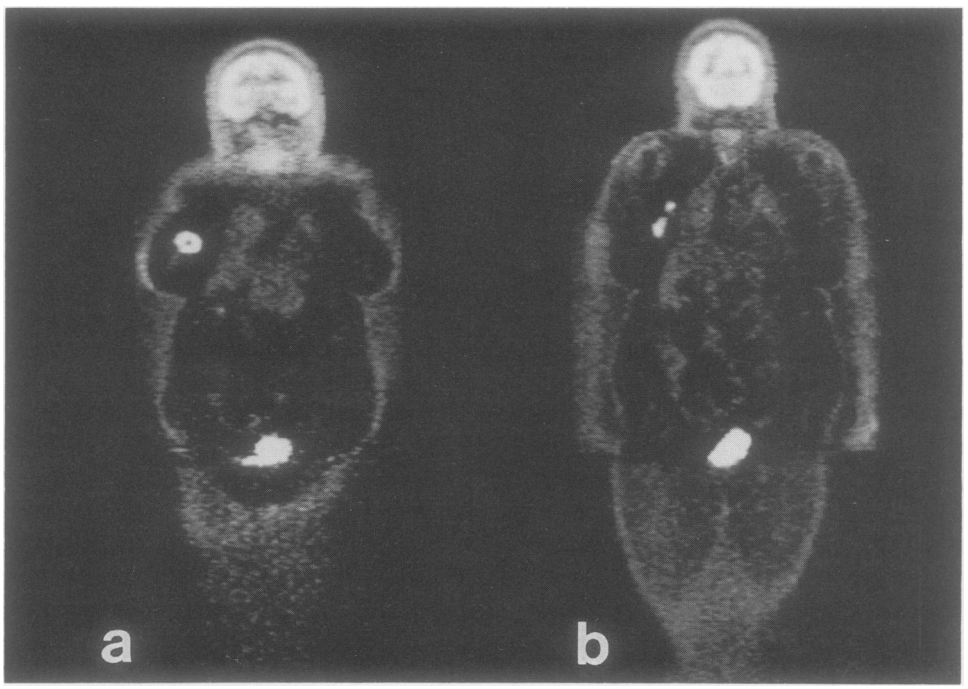

FIG. 2. Two coronal views of the whole-body positron scan from patient 10, who had a large primary tumor and clinically palpable axillary lymph nodes. (A) In these PET images, the breast lesion imaged as a focal area of increased glycolytic activity in the right breast. The center region of this lesion is dark in comparison to the periphery, indicating a low glycolytic rate in this area consistent with necrosis. (B) The right axillary lymph nodes are visible in a more posterior coronal view.

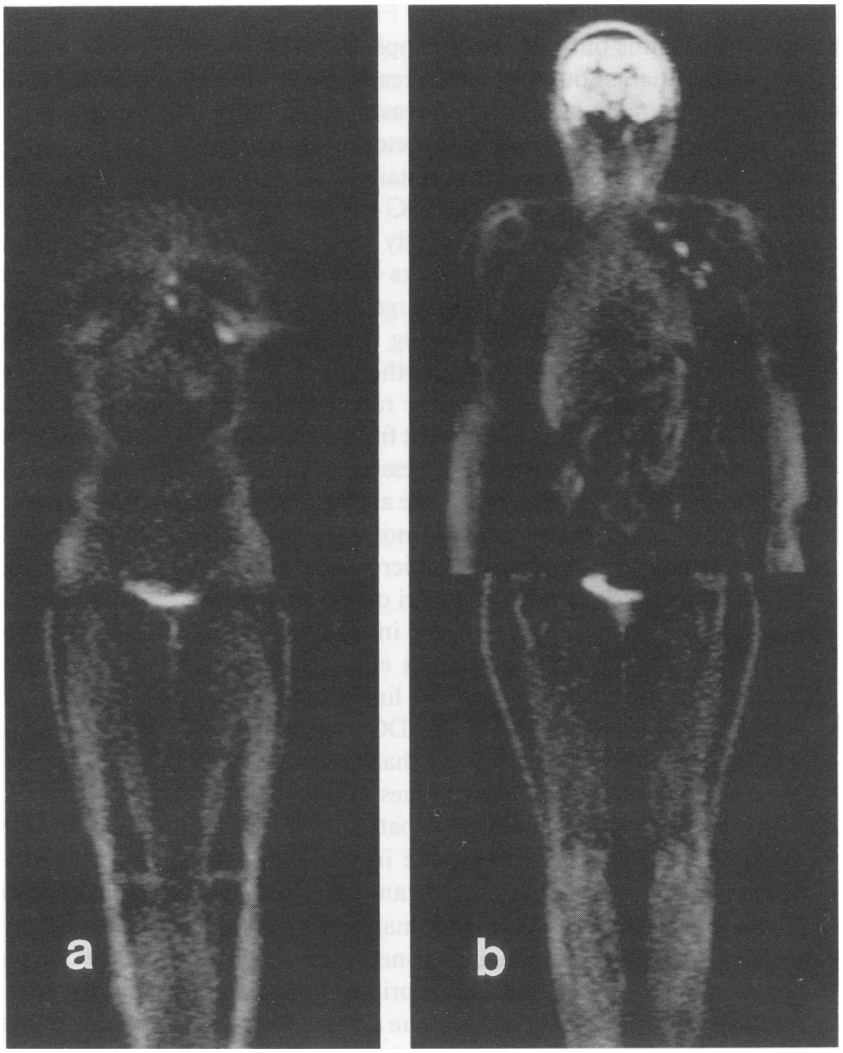

FIG. 3. Two coronal views of the whole-body positron scan from patient 12, who had a left medial breast lesion that was detected by PET. (A) In addition to this primary lesion, internal mammary chain lymph nodes showed increased uptake in the same coronal view. (B) Increased activity consistent with metastatic involvement in axillary lymph nodes was shown in a more posterior coronal view.

both in the detection of breast cancer and in the discrimination of benign from malignant breast lesions. Moreover, the whole-body PET technique has the possible advantage of providing information with respect to the axillary lymph node status, and occult distant metastatic disease. This information may be valuable in further refining decisions regarding initial treatment for those women found to have breast cancer.

This study is the first to prospectively evaluate the feasibility of using whole-body PET imaging with FDG to detect and determine the nature of primary breast lesions in a series of patients with an abnormal mammogram or breast mass, before biopsy. In this preliminary series, PET using FDG accurately distinguished benign from malignant pathology in 12 of 14 cases (86%) in the primary site. In the case of one of the two false-negative scans, pathologic examination of the breast showed diffuse microscopic foci of malignant cells throughout the breast. It is possible that the tumor-to-background uptake ratio of FDG in each of these foci was insufficient to result in a localized abnormal uptake of the tracer material detectable with our methodology. The pathology from the other tumor associated with a false-negative FDG PET showed predominantly intraductal cancer with microscopic foci of invasive elements. It is conceivable that the glycolytic rate of *in situ* breast cancer is not sufficiently different from normal breast tissue to permit PET detection by our technique, although further experience with PET and confirmatory biochemical studies in intraductal breast cancer is required. In the remaining 12 cases, including one patient with radiodense breasts and a negative mammogram, focally increased uptake in the breast lesion was noted, and interpreted in a blind fashion as consistent with malignancy. These data suggest that PET with FDG has promise as an adjunct to mammography in the preoperative evaluation of breast disease. Because this study was done in women already identified as having a breast mass or an abnormal mammogram, it is not possible to comment on the potential role of PET with FDG in the early detection of breast cancer in the general population.

Positron emission tomography with FDG correctly determined the status of the axillary lymph nodes in seven of 10 (70%) patients found to have breast cancer; in the four patients found to have benign breast disease, PET of the axillary lymph nodes was interpreted as benign, although confirmatory tissue was not obtained. To date, we have encountered no false-positive FDG PET scans of the axilla. Of the three patients with a falsely negative axillary PET scan, one had received six courses of intensive chemotherapy treatment because of a large primary lesion and a fine-needle aspirate confirming the presence of breast cancer. It is possible that chemotherapy resulted in a decrease in the glycolytic rate in the rate in the cancer cells to a level not sufficiently different from surrounding normal lymphoid tissue to permit successful PET imaging. In the remaining two patients, with one and four involved axillary nodes, microscopic foci of tumor were present in involved nodes. As in the case of microscopic primary cancer, it is possible that the small foci of tumor in these nodes had aggregate glycolytic activity insufficient to permit detection by the PET techniques employed in this study. Further studies will define the limits imposed by tumor size on the power of PET with FDG to detect breast cancer in various tissues; it is likely that this power will depend in part on the PET techniques employed. The data do demonstrate that, in some patients, PET with FDG can detect axillary lymph node involvement preoperatively. This in itself is an important observation.

The numbers in our series are too small to permit valid conclusions regarding the actual false-negative and false-positive rates for PET with FDG in primary or axillary breast cancer, or PET's diagnostic value relative to mammography. Our results are similar to those in the recent study with PET FDG in 12 patients with known, advanced breast cancer reported by investigators at the University of Michigan.[12] In that series, all 10 primary breast cancers were detected, including those in two patients with radiodense breasts and negative mammography. These patients had large primary tumors (median, 6 cm; smallest, 3 cm); axillary lymph node involvement was correctly detected in three patients. Although the results are similar, there were important technical differences between the two studies. The Michigan series employed attenuation corrected transaxial imaging over a limited area at the body. In the Michigan series, images were obtained only at levels of suspected tumor involvement, with acquisition times at each level of 10 minutes for static image data. This methodology would be expected to result in a high sensitivity at the levels scanned, but has the disadvantage of not permitting screening of the rest of the body for unsuspected metastases. The contrasting approach in our study has been to employ a total body scanning technique that allows imaging of the breast, regional lymph nodes, and all sites of potential distant metastases, that is, the whole body. To complete the scanning procedure within a reasonable period, the acquisition time at each level is limited to 2 minutes, and the images are reconstructed without attenuation correction. This approach may result in a decreased sensitivity for PET in sites of suspected disease, but has the advantage of screening all tissues for sites of focally increased glycolytic activity. Hence, the sensitivity and specificity of PET with FDG for primary and axillary breast cancer may be in part dependent on technical variables. Both series confirm that PET with FDG is a promising technique for the diagnosis of primary breast cancer, and may be complimentary to mammography in detecting breast cancer in radiodense breast tissue, where mammography is less sensitive. The unique observation in our study, that PET may have some utility in distinguishing benign from malignant breast masses, is significant, and merits further study.

Currently, whole-body PET is available at a limited number of centers. This fact, coupled with cost, will limit the feasibility of developing PET with FDG as a screening test to be applied to the general population. Further studies may define subgroups of patients in which PET screening could be viewed as feasible and cost effective, and in whom a screening clinical trial would be warranted. These groups might include women with prior breast radiotherapy, women with multiple breast masses with several negative biopsies in the past, and women with severe fibrocystic disease.

Beyond breast cancer detection in the radiodense breast, and the nonsurgical evaluation of breast disease, there are interesting practical implications in our data. Our experience suggests that PET with FDG can detect axillary lymph node involvement before operation in some patients with breast cancer; if this can be confirmed and the procedure further refined in subsequent clinical trials, PET may come to play a role in the selection of patients for axillary dissection and for preoperative adjuvant chemotherapy. Furthermore, the demonstration that primary breast cancer can be imaged by PET means that quantitative PET techniques should be applicable to these tumors. In addition to the qualitative analytical techniques used in this study, kinetic models permit the quantitative analysis of PET data, yielding accurate numerical estimates of tumor glycolytic rate. In some tumor systems, the degree of the increase in metabolic rate has been shown to correlate with the rate of tumor growth.[23] Quantitative PET can metabolically grade tumors noninvasively, as has been demonstrated in studies of brain tumors.[24–26] In gliomas, the glycolytic rate measured by PET with FDG has been shown to be predictive of clinical outcome.[27–29] More recent studies suggest that a high glycolytic rate as measured by a high tumor FDG uptake may be predictive

of the aggressive clinical behavior in meningiomas,[27] pituitary tumors,[27] and sarcomas[30] or of a high proliferative activity in breast cancer,[31] and head and neck tumors.[32] In studies now in progress, tumor glycolytic rate, as quantified noninvasively by PET with FDG, is correlated with the hormonal receptor, flow cytometry, and oncogene data now gathered routinely on breast cancers, and used to predict clinical outcome and to guide adjuvant therapy. If the rate of glycolysis correlates with these proven predictors of tumor behavior, PET with FDG will become a powerful tool in breast cancer research. Finally, our data demonstrate that PET with FDG using the whole-body technique is feasible in patients presenting with localized breast cancer. Our group has previously demonstrated that PET with FDG using our whole-body technique can detect systemic metastases in patients with breast cancer.[10] In this application, PET has the potential to detect occult metastases, possibly sparing patients unnecessary surgeries or providing previously unobtainable response data during adjuvant chemotherapy.

Beyond the implications of the data presented here, PET imaging holds additional potential in breast oncology.[33] Studies suggest that the accelerated glycolytic rate of tumors decreases after exposure to radiation or cytotoxic agents,[34,35] but remains higher than normal tissue in instances in which viable tumor cells persist.[12,36] A previous report has suggested that breast cancer glycolytic rates, as measured by PET, change after systemic treatment before any physical change in tumor size.[37] Because PET can detect these early and quantitatively small changes in metabolic rate, PET may be an effective tool for assessing the early response to treatment both in micrometastatic and gross disease. Using PET with FDG, it may be possible to identify chemotherapy-unresponsive patients early, and to change their treatment plans, avoiding unnecessary complications from ineffective treatments. In clinical research into new cancer treatments, the ability to make repeated quantitative measurements of metabolic parameters in tumors *in vivo* may enhance our results, and the speed with which we achieve them. Finally, qualitative observation and quantitative analysis of glycolytic rate as measured by PET with FDG is only a beginning in the application of PET to oncology. Using other isotopes, it may be possible to base *in vivo* studies of tumor tissue on rates of blood flow, oxygen consumption, protein synthesis, nucleic acid synthesis, and other metabolic parameters.[33] This potential has far-reaching implications for clinical research and patient care in oncology.

We conclude that PET with FDG has potential for the study of primary breast cancer, and that it may be complimentary to mammography in this role. In addition, PET has promise in the detection of axillary lymph node involvement. Further studies of PET with FDG in primary breast cancer are warranted, to further define its role in this clinical setting.

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