



# Unexpected Focal Hypermetabolic Activity in the Breast: Significance in Patients Undergoing $^{18}\text{F}$ -FDG PET/CT

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**OBJECTIVE.** We describe the significance of detecting focal areas of hypermetabolism in the breast in patients undergoing PET/CT for reasons other than for breast cancer detection or staging.

**CONCLUSION.** When evaluated, almost all of the abnormal foci detected in the breast subsequently proved to be breast carcinoma, specifically infiltrating ductal carcinoma.

**T**he role of  $^{18}\text{F}$ -FDG PET in the evaluation of patients with suspected or established cancer has undergone rapid growth over the past 5 years because of the high sensitivity and specificity of PET in detecting areas of malignant potential over other imaging techniques [1]. Historically, one of the major drawbacks of PET has been the inability to precisely localize areas of potential abnormalities within the body. This problem has recently been resolved with the development of in-line PET/CT scanners that allow precise anatomic mapping of areas of increased glucose metabolism [2, 3]. Results of several published studies found that the use of in-line PET/CT scanners improves diagnostic accuracy compared with PET or CT alone or when both studies are compared side by side [4–6].

As the use of PET/CT continues to grow, previously unsuspected areas of disease are being detected. In most cases, the finding of focal areas of hypermetabolic activity should prompt further investigation until an explanation is found [7]. In this article, we describe the significance of detecting focal areas of hypermetabolism in the breast in patients undergoing PET/CT for reasons other than for breast cancer detection or staging. When evaluated, almost all of the abnormal foci detected in the breast subsequently proved to be breast carcinoma, specifically infiltrating ductal carcinoma.

## Materials and Methods

A total of 1,339 whole-body PET/CT examinations were performed from January 1, 2004, to September 30, 2004. Each patient scanned during this period was included in the Scottsdale Medical Imaging patient PET/CT database using Microsoft

Access. This study received institutional review board approval. Two-hundred forty-one patients (18%) were excluded from this retrospective analysis because of a known diagnosis or a history of breast cancer. Among the remaining 1,098 patients, 565 were males (51.5%) and 533 (48.5%) were females. Of the females, 1.1% (6/533) had unexpected (incidental) focal hypermetabolic activity in the breast tissue. None of the males had incidental hypermetabolic activity. A retrospective review of the clinical findings for the six patients with incidental hypermetabolic activity is presented.

## PET/CT Acquisition

Before imaging, patients were instructed to fast for at least 4 hours. Fasting blood glucose was measured before IV injection of  $^{18}\text{F}$ -FDG: Patients meeting the criterion of a blood glucose level within the 60 to 200 mg/dL range received  $^{18}\text{F}$ -FDG (0.154 mCi/kg or 0.57 mBq/kg) through an antecubital vein in a quiet environment. After injection, patients were instructed to remain in a recumbent position for 1 hour. After having voided, each patient was placed supine on the PET/CT scanner (Discovery LS, GE Healthcare); the field of view was 50 cm, and the full width at half maximum (FWHM) was 6.5 mm.

The CT attenuation data were acquired in the standard fashion at 140 kVp, 80 mAs, a pitch of 1.5:1, a table speed of 15 mm/rotation, and 5-mm slice thickness in a craniocaudal direction while the patient was undergoing tidal breathing. PET emission data were then acquired in a caudocranial direction progressing from the thighs to the orbitomeatal line at 5 minutes per table position. The PET/CT data sets were reconstructed using iterative reconstruction (ordered subset expectation maximum [OSEM]) with attenuation correction applied. The images were displayed on a

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workstation (Entegra, GE Healthcare) in the axial, coronal, and sagittal planes. The Entegra workstation and software provided user-independent image fusion and displayed maximum-intensity-projection (MIP) images for whole-body data review.

The workstation made available on-the-fly standardized uptake value (SUV) calculations by placing a user-defined circular region of interest (ROI) on the attenuation-corrected images resulting in a display of the mean and maximum SUVs. SUV is defined as the amount of  $^{18}\text{F}$ -FDG activity in an ROI per gram of tissue according to the following formula:  $\text{SUV} = \text{activity} / \text{mL tissue (decay corrected)} / \text{injected dose} / \text{body weight}$ . All PET/CT studies were interpreted separately by three nuclear medicine radiologists with 26 years of combined experience in the interpretation of PET scans. Activity in the breast was considered suspicious if the  $^{18}\text{F}$ -FDG activity displayed a focal area of increased uptake with SUVs greater than the opposite breast or mediastinum.

## Results

### Patient Population

There were 1,098 patients who met the criteria for inclusion in this study. Approximately 51.5% were males and 48.5% percent were females. The mean age of the group was 62 years (SD, 13 years; range, 8–98 years). The mean ages of males and females were almost identical: men, 62.1 years (SD, 13 years; range, 19–93 years) and women, 61.6 years (SD, 13 years; range, 8–98 years). No males had unexpected hypermetabolic foci in the breast; therefore, only female patients were included in the subsequent analyses.

A total of 533 females who underwent PET/CT for whole-body oncology imaging from January 1, 2004, to September 30, 2004, were included in this retrospective study. Six patients were identified as having unexpected uptake in the breast. The ages of the six women in this study ranged from 44 to 72 years (mean, 62.8 years; SD, 10.5 years). All patients were asymptomatic and were being evaluated for other reasons. Four of the six patients were undergoing imaging for evaluation of a solitary pulmonary nodule. One patient was being evaluated for lung cancer restaging, and the other was being evaluated for Hodgkin's lymphoma (Table 1).

### Evaluation of Hypermetabolic Activity in the Breast

All six patients were noted to have focal areas of increased activity in the breast with an average maximum SUV ( $\text{SUV}_{\text{max}}$ ) of 3.5 (SD, 1.3; range, 2.3–5.5). The mean SUV ( $\text{SUV}_{\text{mean}}$ ) had an average of 2.5 (SD, 0.8; range, 1.2–3.4). The average lesion size was 1.5 cm (SD, 0.8; range, 1.0–2.5 cm) (Figs. 1–3). Four of the hypermetabolic foci were in the right breast and two in the left. Of the six patients, five were discovered to have infiltrating ductal carcinoma that was confirmed by tissue sampling. All five women with breast carcinoma had undergone conventional anatomic evaluation with mammography, sonography, or MRI before undergoing the biopsy that had been prompted by the PET/CT results. The sixth patient had a percutaneous biopsy 1 month before PET/CT, which proved to be a fibroadenoma. The lesion biopsied was in the region where positive PET/CT findings were seen.

## Discussion

An estimated 700,000 clinical PET patient studies were performed in the United States in 2003, a 58% increase from 2002 [7]. This explosive growth is attributed to two factors: the higher sensitivity and specificity of  $^{18}\text{F}$ -FDG PET compared with CT or MRI for the detection and staging of cancer, heart disease, and neurologic abnormalities [8]; and the reduction in economic barriers that had made PET untenable in most of the past century. As a result, the use of PET and now PET/CT has become the fastest-growing segment of the nuclear medicine marketplace [9]. The ability to not only produce accurate CT-based attenuation maps for attenuation correction but also keep the patient in the same position for acquisition of the two data sets used for image fusion of the PET data onto the CT-generated maps are the main advantages of PET/CT over PET [10]. There is also accumulating evidence suggesting that PET/CT can provide additional information above and beyond PET alone [4–6]. This advantage of PET/CT over PET has been related more to the diagnostic certainty of lesion characterization and location rather than to an improvement in the resolution of the PET scanners themselves [11].

The ability to accurately map areas of abnormal glucose metabolism has been helpful in evaluating areas of incidentally detected foci of hypermetabolic activity [12]. In this article, we describe the high rate of breast carcinoma detected in women who have PET/CT scans showing unexpected hypermetabolic foci within the breast. Five (83%) of six patients with hypermetabolic activity detected incidentally in our series had proven infiltrating ductal carcinoma. The sixth patient was found to have a fibroadenoma in the region of hypermetabolic uptake on PET/CT. Nevertheless, the data from this study indicate the need for an aggressive workup of any patient who is found to have incidental areas of increased glucose metabolism on  $^{18}\text{F}$ -FDG PET/CT.

Breast cancer is the most common cancer in women in the United States. The lifetime risk of breast cancer is approximately one in eight American women [13]. Clinical examination and diagnostic imaging are essential for evaluating the breast. The efficacy of  $^{18}\text{F}$ -FDG PET for diagnosing, staging, restaging, and monitoring therapeutic response in patients with breast cancer has been evaluated. These data suggest that the diagnostic utility of  $^{18}\text{F}$ -FDG PET is limited in the detection of small, less than 1 cm, primary breast tumors [10].

**TABLE 1: Patient Characteristics, Standardized Uptake Values (SUVs), and Pathology Results of Unexpected Hypermetabolic Areas in the Breast**

Patient		Indication for PET/CT	Lesion Size (cm) <sup>a</sup>	SUV		Pathology
No.	Age (y)			Mean	Maximum	
1	61	Solitary pulmonary nodule	1.8	3.0	3.8	IDC
2	60	Solitary pulmonary nodule	2.2	2.7	3.2	IDC and DCIS
3	69	Solitary pulmonary nodule	1.1	1.2	2.0	IDC
4	44	Lung cancer restaging	1.0	3.4	5.5	IDC
5	72	Hodgkin's lymphoma	2.5	2.9	4.0	IDC
6	71	Solitary pulmonary nodule	0.5	1.8	2.3	Fibroadenoma
Average	62.8		1.5	2.5	3.5	
SD	10.5		0.8	0.8	1.3	

Note—IDC = infiltrating ductal carcinoma, DCIS = ductal carcinoma in situ.

<sup>a</sup>Based on pathologic measurements of the lesion.

## Focal Hypermetabolic Activity in the Breast on PET/CT

PET has superiority over conventional imaging in detecting distant metastases, evaluating recurrent disease, and monitoring therapeutic response. Newer-generation PET scanners with advanced crystal technologies have theoretically improved resolutions down to 3 mm at FWHM; however, these resolutions still do not match the spatial resolutions of the current screening techniques of mammography and sonography or MRI. Thus, a screening  $^{18}\text{F}$ -FDG PET/CT for breast cancer is not appropriate with the current generation of whole-body scanners and should be discouraged whenever possible. Although emerging research has shown the usefulness of PET in the management of breast carcinoma, to our knowledge, scant literature exists regarding the importance of a hypermetabolic focus in the breast as an incidental finding in women undergoing PET/CT for other reasons.

Interpretations of incidental findings of hypermetabolic activity must be specific to each

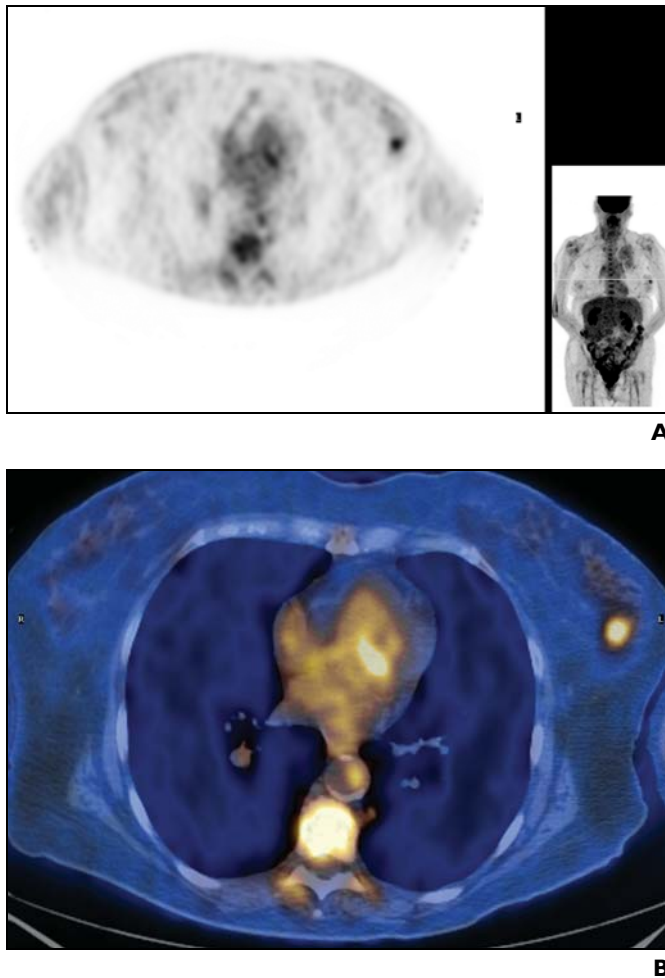
organ, taking into account its unique structure, metabolism, and function. For example, PET/CT of the lung may show areas of hypermetabolic focus that may or may not be malignant. Compared with the lung, the breast is less likely to be involved in infectious or inflammatory disease. Nevertheless, the results from our study are not entirely surprising given the high sensitivity and specificity of  $^{18}\text{F}$ -FDG PET for the detection of lesions larger than 1 cm.

The patients in this retrospective review underwent  $^{18}\text{F}$ -FDG PET/CT evaluation for potential cancer detection and staging in regions other than the breast. The percentage of women without a history of breast carcinoma who showed hypermetabolic foci on PET/CT was 1.1% (six of 533 patients) in the population evaluated over the study time period, whereas the total percentage of breast cancer was 0.94% (five of 533 patients).

In addition, all of the breast cancers detected in this study were infiltrating ductal carcinoma.

It is known that not all breast cancer histologies have similar hypermetabolic potential. Buck and colleagues [14] showed  $^{18}\text{F}$ -FDG localization was significantly higher in ductal carcinoma than in lobular carcinoma (mean tumor-to-background ratio, 17.3 vs 6.5, respectively). Crippa et al. [15] also showed that the median SUV was markedly higher in infiltrating ductal carcinomas than in lobular carcinomas (SUV, 5.6 vs 3.8, respectively).

The average  $\text{SUV}_{\text{max}}$  in our population was  $3.5 (\pm 1.3)$ . The reason for a lower SUV compared with published data could be related to our small number of cases, differences in imaging techniques, and the use of CT for attenuation correction, which may have altered SUV values compared with typical transmission sources of germanium-68 [16]. In addition, breast density and hormonal status can alter  $^{18}\text{F}$ -FDG uptake, factors that were not accounted for in our population [17]. In this study, only one patient was classified as



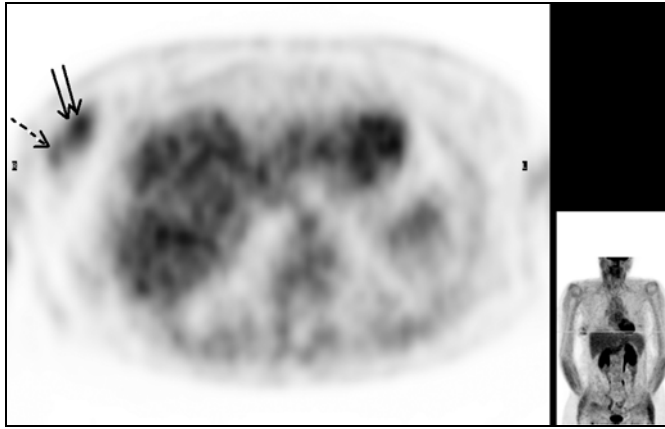
**Fig. 1**—72-year-old woman (patient 5 in Table 1) with infiltrating ductal carcinoma being evaluated for Hodgkin's lymphoma.

**A**, Axial PET image shows focal area of increased metabolism (maximum standardized uptake value = 4.0) in left breast, lateral to midline.

**B**, PET/CT fusion image shows hypermetabolic focus corresponds to ill-defined asymmetric soft-tissue density.

**C**, MR image shows 2.5-cm lesion (arrow) corresponding to PET/CT abnormality.





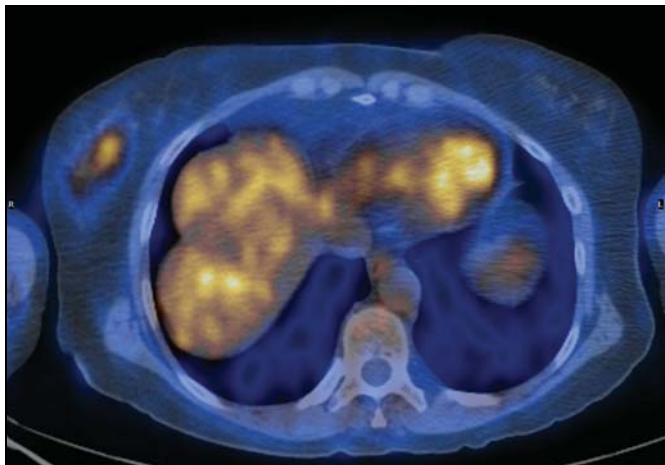
A

**Fig. 2**—60-year-old woman (patient 2 in Table 1) with infiltrating ductal carcinoma and ductal carcinoma in situ (DCIS) scanned for evaluation of solitary pulmonary nodule.

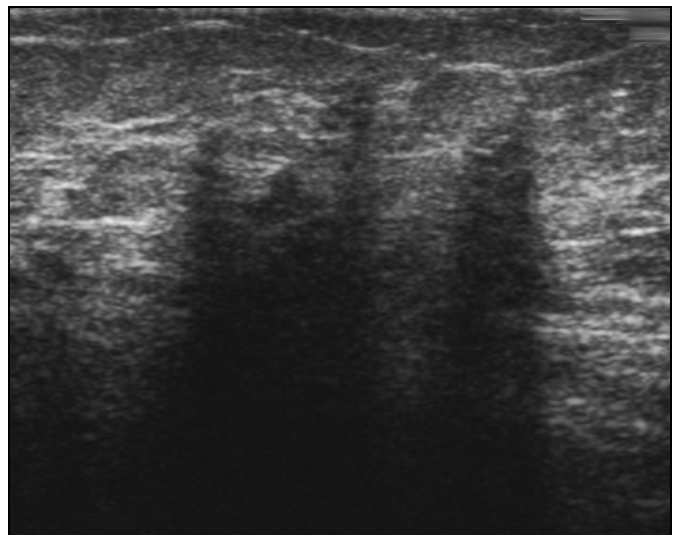
**A**, Axial PET image shows a low level of metabolism (*dashed arrow*) in right breast with more intense and focal metabolism (*solid arrows*) in lower outer quadrant of right breast. Maximum standardized uptake value of focal area of hypermetabolic activity is 3.2.

**B**, PET/CT fusion image shows most intense focus to be associated with ill-defined CT density on lower outer quadrant of right breast in 7-o'clock position.

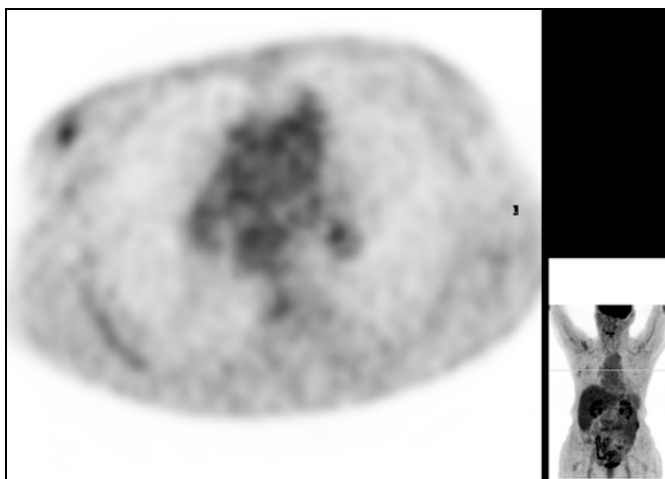
**C**, Sonogram shows 1.1-cm area of abnormal shadowing at 7-o'clock position of right breast. Mammogram (not shown) was remarkable for pleomorphic calcifications (BI-RADS category 4). Diffuse activity on PET surrounding focal hypermetabolic region corresponded to DCIS. Tumor measured 2.2 cm at time of surgery.



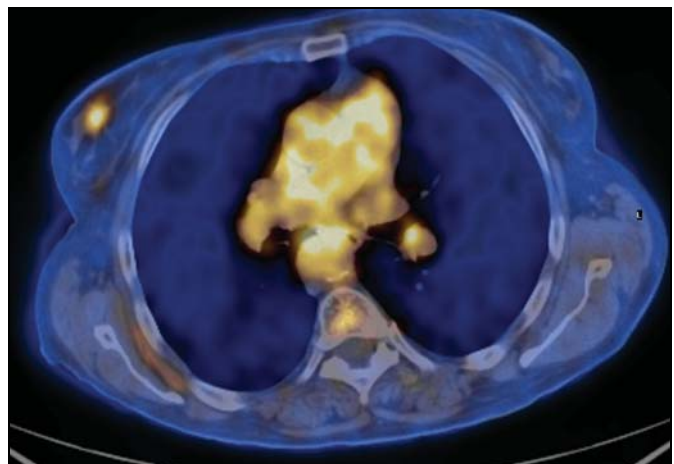
B



C



A



B

**Fig. 3**—71-year-old woman (patient 6 in Table 1) with fibroadenoma who was being evaluated for solitary pulmonary nodule.

**A**, Axial PET image shows very small focus of hypermetabolic activity in right breast (maximum standardized uptake value = 2.3).

**B**, PET/CT fusion image locates lesion centrally in right breast, superior and lateral to nipple. Biopsy revealed fibroadenoma (images not shown).

## Focal Hypermetabolic Activity in the Breast on PET/CT

having a benign explanation (false-positive) for the hypermetabolic activity. Whether the hypermetabolic focus in that patient was related to the fibroadenoma or postsurgical inflammatory change is uncertain.

Follow-up clinical information was not available for this population of women; therefore, the number of women who had breast cancers that remained undetected on PET/CT is not known—which is a limitation of this study. Such information would have been useful to better understand the negative predictive value of PET/CT in our population. Therefore, a negative PET/CT scan should not be used to exclude breast cancer entirely based on the results of this investigation. Indeed, the current generation of PET/CT scanners has reduced sensitivity in the detection of subcentimeter breast cancers. That, in combination with the variable metabolic potential of breast cancers of different histologies, makes the use of the current generation of PET or PET/CT scanners unacceptable for breast cancer screening or for the evaluation of equivocal breast lesions smaller than 1 cm.

In conclusion, unexpected focal areas of hypermetabolic activity discovered in the breast at the time of PET/CT with  $^{18}\text{F}$ -FDG are associated with a high likelihood of infiltrating ductal carcinoma. Therefore, any suspicious activity discovered in the breast on PET/CT should be evaluated until a diagnosis is found.

## References

1. Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. *J Nucl Med* 2001; 42:[suppl]:1S–93S
2. Beyer T, Townsend DW, Brun T, et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med* 2000; 41:1369–1379
3. Wahl RL. Why nearly all PET of abdominal and pelvic cancers will be performed as PET/CT. *J Nucl Med* 2004; 45[suppl]:82S–95S
4. Bar-Shalom R, Yefremov N, Altman H, et al. The clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. *J Nucl Med* 2003; 44:1200–1209
5. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003; 348:2500–2507
6. Cohade C, Osman M, Leal J, Wahl RL. Direct comparison of  $^{18}\text{F}$ -FDG PET and PET/CT in patients with colorectal carcinoma. *J Nucl Med* 2003; 44:1797–1803
7. IMV Medical Information Division, Inc. 2003 PET census market summary report. Des Plaines, IL: IMV Medical Information Division, Inc. November 1, 2004, pp. 1–141
8. Kostakoglu L, Agress H Jr, Goldsmith SJ. Clinical role of FDG PET in evaluation of cancer patients. *RadioGraphics* 2003; 23:315–340
9. Czernin J, Schelbert H. PET/CT imaging: facts, opinions, hopes, and questions. *J Nucl Med* 2004; 45[suppl]:1S–3S
10. McDonough MD, DePeri ER, Mincey BA. The role of positron emission tomographic imaging in breast cancer. *Curr Oncol Rep* 2004; 6:62–68
11. Kamel IR, Cohade C, Neyman E, et al. Incremental value of CT in PET/CT of patients with colorectal carcinoma. *Abdom Imaging* 2004; 29:663–668
12. Agress H Jr, Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. *Radiology* 2004; 230:417–422
13. Web site for Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Age adjusted rate of breast cancer 1997–2001: all ages, < 65, and 65+. Available at: www.seer.cancer.gov. Accessed April 2004
14. Buck A, Schirrmester H, Kuhn T, et al. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. *Eur J Nucl Med Mol Imaging* 2002; 29:1317–1323
15. Crippa F, Seregni E, Agresti R, et al. Association between [ $^{18}\text{F}$ ]fluorodeoxyglucose uptake and postoperative histopathology, hormone receptor status, thymidine labeling index and p53 in primary breast cancer: a preliminary observation. *Eur J Nucl Med* 1998; 25:1429–1434
16. Dizendorf E, Hany TF, Buck A, et al. Cause and magnitude of the error induced by oral CT contrast agent in CT-based attenuation correction of PET emission studies. *J Nucl Med* 2003; 44:5732–5738
17. Vranjesevic D, Schiepers C, Silverman DH, et al. Relationship between  $^{18}\text{F}$ -FDG uptake and breast density in women with normal breast tissue. *J Nucl Med* 2003; 44:1238–1242