Accuracy of Whole-Body Fluorine-18-FDG PET for the Detection of Recurrent or Metastatic Breast Carcinoma

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This study assessed the diagnostic accuracy of whole-body PET on a patient and lesion basis using ^{18}F-fluorodeoxyglucose (FDG) for the detection of tumor foci in patients with suspected recurrent or metastatic lesions of breast carcinoma. **Methods:** Whole-body FDG-PET imaging was performed on 57 patients with a previous history of breast carcinoma who were referred for a clinical suspicion of disease recurrence. Whole-body PET images were scored from 1 (definitely negative) to 5 (definitely positive) by three independent observers, and discrepancies were resolved by a fourth observer. Patients were clinically followed for up to 24 mo to assess the accuracy of PET diagnosis by biopsy, follow-up imaging and other diagnostic tests. **Results:** PET scans showed that there were 41 sites indicating recurrent or metastatic disease in 29 patients. There were 38 sites in 28 patients that showed no evidence for malignant disease. On a patient basis, with scores 4 or 5 considered to be positive, sensitivity and specificity were 93% and 79%, respectively. The corresponding positive and negative predictive values were 82% and 92%. On a lesion basis, with scores 4 or 5 considered to be positive, the sensitivity was 85% and specificity 79%. The area index in receiver operating characteristic analysis was 0.91 for patient-based analysis and 0.88 for lesion-based analysis. To determine the cause for false-negative and false-positive findings more precisely, false-negative lesions with scores of 3 or lower and false-positive lesions with scores of 4 or higher were analyzed. Bone metastases had a significantly larger proportion of false-negative lesions than other nonosseous malignant sites ($p < 0.05$). False-positive lesions were due to muscle uptake ($n = 5$), inflammation ($n = 4$), blood pool activity in the great vessels ($n = 2$), bowel uptake ($n = 1$) and unknown causes ($n = 6$). **Conclusion:** The whole-body FDG-PET scan is a useful diagnostic test for detecting recurrent or metastatic lesions of breast carcinoma. However, the sensitivity for metastases to bone appears to be lower than that to other organs. Specificity may be improved by more strict attention to patient preparation and better recognition of physiologic skeletal muscle or artifactual uptakes.

Key Words: whole-body PET; breast cancer; fluorine-18-fluorodeoxyglucose

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Breast cancer is the most common malignancy among women in North America and is the leading cause of death in women between the ages of 40 and 55. PET with ^{18}F-fluorodeoxyglucose (FDG) has been applied clinically in patients with breast cancer. Clinical studies have shown that FDG-PET is a useful test for differentiating malignant from benign breast masses and staging evaluation of newly discovered breast cancer (*1–10*). FDG-PET also has been used to evaluate the tumor's response to chemotherapy; a significant reduction in tumor metabolism has been shown to indicate a good response to chemotherapy and precedes any decrement in tumor size (*11–14*).

The follow-up of patients after primary therapy is important in detecting locally recurrent disease that is still amenable to curative therapy. The benefit of early detection of distant metastases has not been established, and recurrent, disseminated breast cancer is generally considered to be incurable (*15*). However, recent clinical trials of high-dose chemotherapy showed an increased number of long-term survivors by 10%–20% (*16*). These data may emphasize the need for a better method to detect early metastatic breast cancer.

Whole-body PET imaging generates tomographic images of the entire body, permitting screening for occult metastases. This study was undertaken to evaluate the diagnostic accuracy of PET imaging for the detection of recurrent or metastatic breast carcinoma in patients suspected of having recurrent or metastatic disease after primary therapy.

MATERIALS AND METHODS

Patients

The study group consisted of 57 female patients (range 30–80 yr; mean age 55 yr) with breast carcinoma who underwent primary surgery with or without adjuvant chemotherapy or radiation therapy and were referred to the University of California, Los Angeles (UCLA) PET center from October 1990 to October 1995 with a clinical suspicion of disease recurrence. The mean time interval between the diagnosis of breast cancer and the PET scan was 4 yr (range 1 mo to 17 yr 9 mo). To avoid artifacts secondary to decreased tumor FDG activity from treatment effects, we excluded patients who underwent chemotherapy or radiation therapy within 3 mo before the PET scan. Lesions that were already biopsied or known to have recurrent disease before the PET scan were excluded from the analysis. Five patients had a blood glucose level above 110 mg/dl before the PET scan (113, 118, 160, 198 and 289 mg/ml). Among these, four patients had been diagnosed with diabetes.

All patients had undergone a history and physical examination as well as multiple laboratory and imaging evaluations. Confirmation of positive diagnosis of breast cancer was based on a biopsy of the lesion, a lesion with classic morphological characteristic for tumor detected on two or more conventional imaging studies and follow-up clinical and radiographic data for at least 6 mo after the FDG-PET scan. This confirmation was done by reviewing all available medical charts and records on each patient. PET abnormalities that resolved without treatment were considered to be false-positive lesions. Absolute validation of PET abnormalities is one of the difficulties of whole-body studies; therefore, the requirement of at least 6 mo of careful clinical follow-up was

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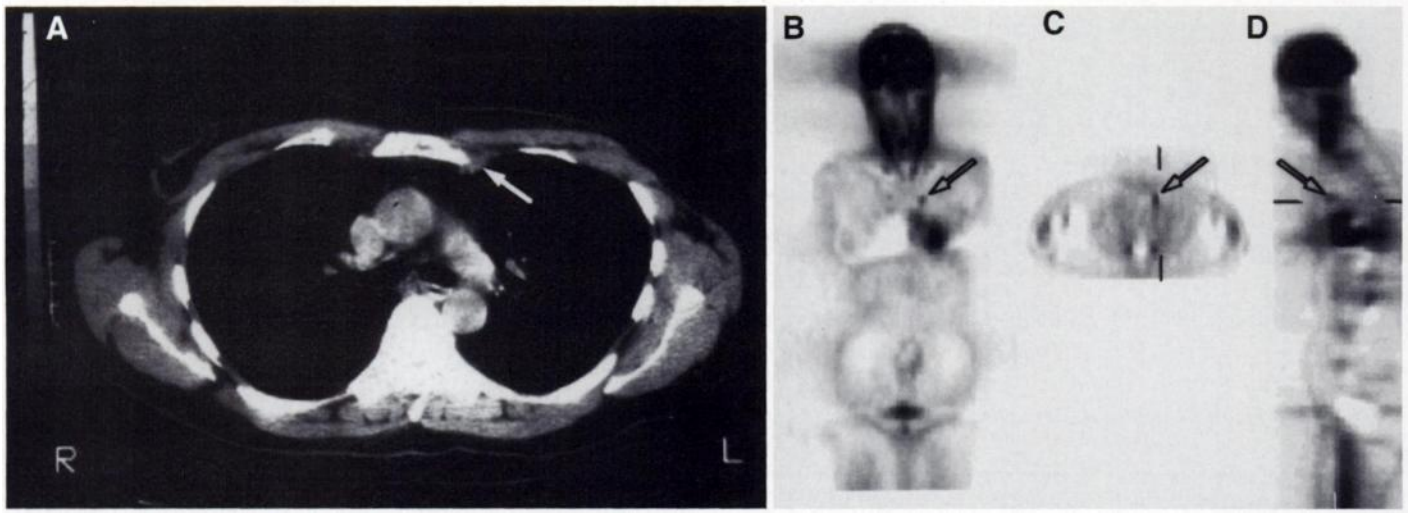

FIGURE 1. A 43-yr-old woman with breast cancer. (A) Chest CT scan shows 1-cm-sized left internal mammary lymph node enlargement. PET scan was done to evaluate the significance of the lesion and the presence of other metastatic lesions. (B) Coronal, (C) transaxial and (D) saggital FDG-PET images show focal uptake in the corresponding lesion. Fine-needle aspiration confirmed the metastatic carcinoma. Note the increased uptake of both sternocleidomastoid muscle and heart.

included in the study so that indeterminate lesions could be better characterized with the absence or presence of disease progression.

PET Imaging

All patients were instructed to fast for at least 6 hr before PET imaging. Patients were given a bolus injection of 10–15 mCi (370–555 MBq) of FDG produced at the biochemical cyclotron facility at UCLA. The method of labeling 2-deoxyglucose with ^{18}F has been described previously (*17*). After a 40-min uptake period following the injection of FDG, we acquired PET data as described below. During the time between injection and scanning, patients were asked to lie or sit comfortably to avoid uptake into striated muscle. They were asked to urinate immediately before scanning to minimize interference from the FDG accumulated in the bladder.

PET scans were obtained with a PET scanner in the whole-body mode (ECAT 931 and ECAT 961; Siemens/CTI, Knoxville, TN). The data acquisition, processing and performance characteristics of the system have been reported previously (*18,19*). Images of multiple longitudinal bed positions (32 for ECAT 931 and 6–8 for ECAT 961) were obtained so that the total effective z-axis field of view spanned from the patient's head to midthigh. Each bed position was imaged for 4 min on the 931 scanner and 6 min on the 961 scanner. Because of the additional time required in performing transmission scans at each bed position, no attenuation correction was performed in this study. Of the 57 patients, 38 patients were studied using the ECAT 931 from October 1991 to July 1994, whereas the remaining PET were obtained on the ECAT 961 scanner from August 1994 to October 1995.

Image Analysis

Images of two-dimensional transaxial, coronal and sagittal views were evaluated by visual inspection on a high-resolution display monitor (Sun workstation) with Siemens/CTI software by three independent observers. The observers were informed of the clinical reason pertinent to the PET study; however, they did not know the results of the final true lesion status. PET images were scored from 1 to 5 (1 = definitely negative, 2 = probably negative, 3 = possibly positive, 4 = probably positive and 5 = definitely positive) for the individual patient or lesion. Any discrepancies were solved by a fourth observer who was aware that a discrepency existed but was not informed of the specifics of the discrepancy.

The sensitivity, specificity, positive predictive value, negative predictive value and receiver operating characteristic (ROC) analysis of whole-body PET imaging using the METZ software (*20*) was determined on a patient-by-patient basis and a lesion-by-lesion basis. A lesion site was defined as any anatomical area with a clinical, radiological or PET imaging abnormality suggesting the possibility of breast recurrence or metastasis. It should be noted that there were many anatomical sites that were negative by all imaging studies and that these sites were not included in the data analysis. Therefore, the analysis was biased toward positive lesions.

Statistical Analysis

Statistical analysis was performed using Fisher's exact test. A p value <0.05 was considered statistically significant.

RESULTS

The primary clinical indication, for which whole-body PET scans were obtained on each patient, was as follows: suggestive symptoms in 10 patients, mass lesions in 10 patients, increased tumor markers in 13 patients, abnormal mammograms in 5 patients, abnormal bone scans in 4 patients and other radiological abnormalities in 8 patients. In 7 patients, no specific clinical and laboratory abnormalities suggesting metastasis were identified.

By using clinical, pathological and radiological information, we established the diagnosis of 83 reference sites in 57 patients. Examples of positive FDG-PET scans are shown in Figures 1 and 2. Twenty-nine patients were confirmed to have recurrent or metastatic breast cancer, and 28 patients were without evidence of recurrence. If scores of 4 (probably positive) or 5 (definitely positive) were considered to be positive for malignancy, PET correctly identified 27 of 29 patients with disease and 22 of 28 without disease, resulting in sensitivity and specificity of 93% and 79%, respectively. The corresponding positive and negative predictive values were 82% and 92%. If scores 3 (possibly positive) through 5 were regarded as positive, the sensitivity and specificity were 93% and 61%, respectively. In 27 of 57 patients (48%), the scores of all three observers were identical. In 22 of 57 patients (38%), a score from one observer deviated one score grade from the other two observers, and in 8 of 57 patients (14%), a score from one observer deviated more than one score grade from the other observers.

In a lesion-based analysis, 35 of 41 malignant sites were scored as 4 or 5. This resulted in a sensitivity of 85% for the detection of malignancy. Of the 39 benign sites, 31 were

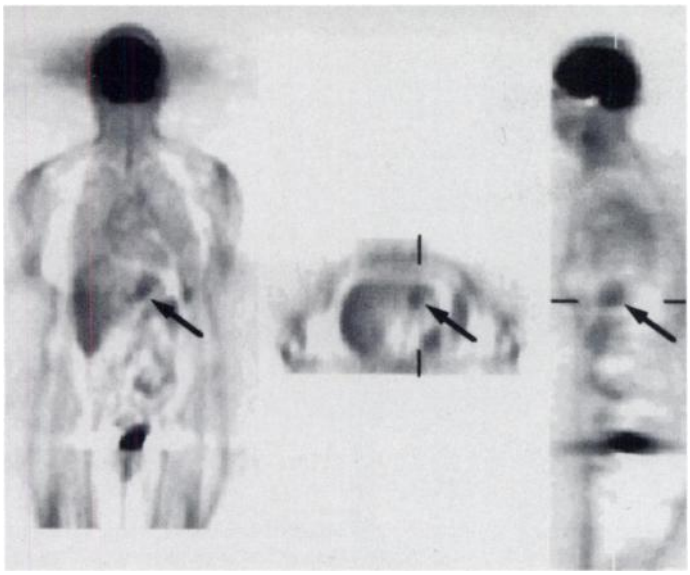

FIGURE 2. A 56-yr-old woman with increased CEA and CA 15-3, 2 yr after surgery. An abdominal CT scan was negative. FDG-PET was done 7 days after the abdominal CT scan. Coronal FDG-PET scans showed increased uptake in the left lobe of liver. A liver biopsy confirmed the metastatic breast carcinoma.

assigned a score from 1 to 3, resulting in a specificity of 79%. If an abnormal PET finding was defined by a score of 3–5, the sensitivity increased to 90% (37 of 41) and the specificity decreased to 54% (21 of 39). In Table 1, the findings of whole-body FDG-PET were analyzed according to the involved organs. Because of the relatively small number of reference sites for each involved organ, we did not conduct statistical comparisons between individual organs. However, bone metastases had a substantially larger proportion of false-negative lesions than other malignant sites when a score of 4 or 5 was regarded as a positive scan: sensitivity was 69% (11 of 16) in bone metastasis versus 96% (24 of 25) in nonosseous metastasis ($p < 0.05$). If scores of 3 or higher were regarded as positive, the false-positives in lymph node sites were significantly higher than other sites: specificity of 13% versus 79% for other sites ($p < 0.05$). If scores of 4 or higher were regarded as positive, the false-positives were reduced: specificity of 60% versus 92% in other sites ($p < 0.001$).

The positive predictive value for lesions was 62% (8 of 13) for a score of 4 and 90% for a score of 5 (27 of 30), respectively. The negative predictive values for scores of 1–3 were essentially identical: 83% (10 of 12), 85% (11 of 13) and 83% (10 of 12), respectively. The corresponding area indexes in ROC analysis were 0.91 for patient detection and 0.88 for lesion detection.

To further evaluate the causes resulting in false-negative or false-positive studies, we reviewed in more detail misdiagnosed lesions with scores of 3 or lower and benign sites with scores of 3 and higher (Table 2). False-negative lesions included five bone metastases and one small breast focus. Of these, three bone lesions and one breast lesion showed mildly increased uptake (scores of 2–3). Of two definitely negative lesions, a lumbar spine lesion was not detected by other imaging studies but was confirmed to be positive for malignancy on a follow-up PET scan done 2 mo later.

TABLE 2
Analysis of False-Negative Sites (Positive Criterion: Score ≥ 4)

Site	No.	Reason
Bone	2	Two definitely negative lesions (score 1) L-spine: very small lesion; all imaging studies were false-negative left ilium lesion
Bone	3	Ischium, pubic bone, and L-spine lesion (score 2–3)
Breast	1	Stage T1 lesion, left outer hemisphere (score 2)
Total	6	

Score 1 = definitely negative; 2 = probably negative; 3 = possibly positive; 4 = probably positive and 5 = definitely positive.

False-positive lesions, based on the more sensitive criteria of scores of 3 or higher, were similarly reviewed (Table 3). Except for one false-positive case attributable to an inflammatory lesion, the specific underlying causes for false-positive findings were not easily confirmed. Both physiological and artifactual FDG uptake (*7,21*) probably contributed to false-positive studies. False-positives were thought to be most likely due to muscle uptake in five sites, inflammation in four sites, blood pool activity of the great vessels in two sites and bowel uptake in one other site. In six lesions, no likely cause for the false-positive uptake could be identified. Examples of false-positive studies are shown in Figures 3–5.

There were five patients with increased fasting blood glucose levels of more than 110 mg/dl (113, 118, 160, 198 and 289 mg/dl). Four of them had a history of diabetes. Two of the patients were injected with a small dose of regular insulin because of high blood glucose levels of 198 and 289 mg/dl. Three of the hyperglycemic patients had true-negative studies, and one had a true-positive study. One patient with a glucose level of 118 mg/dl had false-positive results because of perihilar pulmonary uptake.

DISCUSSION

FDG-PET has been used to detect recurrent or metastatic lesions in ovarian cancer (*21–24*), colorectal cancer (*25–29*),

TABLE 1
Sensitivity and Specificity of Whole-Body FDG-PET Imaging in the Detection of Recurrent or Metastatic Lesions of Breast Cancer

	Malignant lesions			Benign lesions		
Site	No.	Positive ≥ 3	Positive ≥ 4	No.	Negative ≤ 2	Negative ≤ 3
Bone	16	13	11	7	6	7
Lymph node	8	8	8	18	5	12
Breast	6	5	5	5	4	4
Lung	4	4	4	3	2	2
Chest wall	3	3	3	2	2	2
Liver	2	2	2	1	1	1
Others	1	1	1	7	5	7
Total	40	36	34	43	25	35
	Sensitivity	90%	85%	Specificity	58%	81%

TABLE 3
Analysis of False-Positive Sites (Positive Criterion: Score ≥ 3)

Site	No.	Reason
Breast	1	Seroma, pathology proved
Lymph node	5	Muscle uptake: sternocleidomastoid, serratus anterior, scalene, longus coli
Lymph node	1	Thyroiditis
Lymph node	2	Blood pool activity of great vessles: faint bilateral hilar uptake
Lymph node	4	Unknown cause
Lung	1	Radiation pneumonitis
Lung	1	Unknown cause
Spleen	1	Unknown cause, diffuse uptake
Bone	1	Osteoarthritis
Abdomen	1	Intestinal uptake
Total	18	

head and neck cancer (*30,31*), lung cancer (*32,33*) and melanoma (*34,35*). Sensitivity ranging from 58% to 100% and specificity ranging from 81% to 100% have been reported in these tumors. Common causes of false-positive findings for malignancy are inflammation and some benign tumors. We know of no previous studies that have been published to examine the diagnostic accuracy of whole-body FDG-PET imaging in breast cancer. In this study, we found that PET is a useful test in evaluating recurrent and or metastatic lesions in postsurgical breast cancer patients.

Among the six malignant lesions that were assigned a PET score of less than 4, two were evaluated by PET interpreted as being possibly positive for malignancy. In a study by Wahl et al. (*11*), a relatively low sensitivity of FDG-PET scans in the detection of metastatic bony lesions was found also. This may have been due partly to attenuation of tumor activity by bone mass. In nonosseous metastatic lesions, the sensitivity of 96% was obtained by lesion-based analysis, even with the stringent criteria of requiring a score of 4 or higher to indicate a positive finding. The high sensitivity of PET for nonosseous lesions would make the combination of a whole-body PET and whole-body bone scans an effective tumor survey for most tissues throughout the body in patients suspected of having recurrent or metastatic breast cancer.

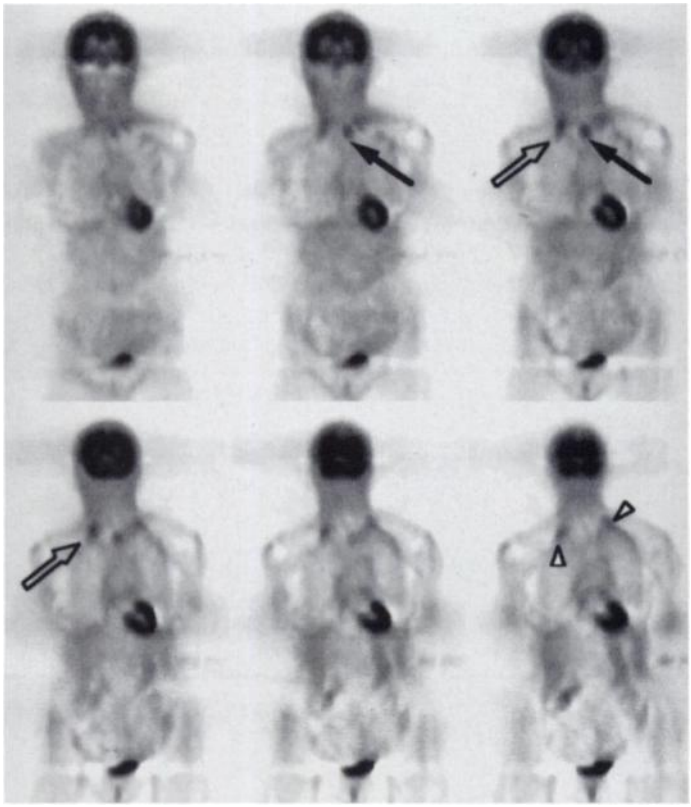

FIGURE 3. False-positive PET scan due to muscle uptake. PET scan shows bilaterally increased uptake of upper thoracic region. Chest CT scan was negative. The patient was clinically free of disease. Because of the location, bilaterality and the shape of uptake, this was concluded to be the uptake in the serratus anterior muscle.

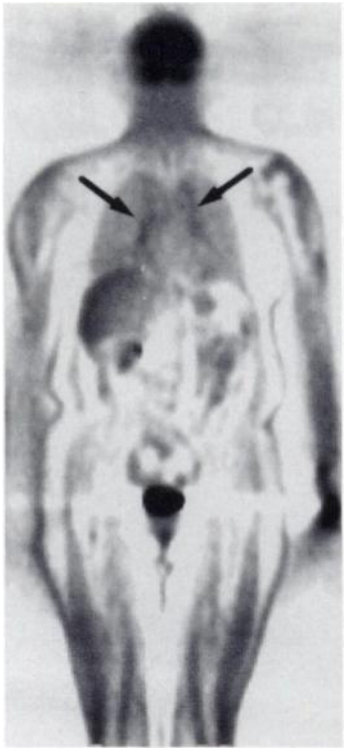

FIGURE 4. Bilateral hilar uptake as a cause of false-positive study. This activity was considered to be due to blood pool activity in great vessels because increased activity in both femoral blood vessels suggested the presence of significant blood pool radioactivity and the oblong shape of left hilar activity appeared to be descending the aortic blood pool.

Of the 18 false-positive lesions found when the less specific criterion of a score greater than 3 was regarded as evidence of malignancy, the most common anatomical sites were lymph node beds in the axilla and neck. Reasons for high false-positives in lymph nodes may include: lesions not definitely associated with large visceral organs being misclassified as lymph nodes; any suspicious lesions in the neck being misclassified because of the high index of suspicion for metastases in this location and increased muscle uptake mimicking lymph node lesions (*21*). By close anatomical correlation with the pattern of neck FDG uptake and other imaging studies, we could identify five false-positive uptakes attributable to muscles

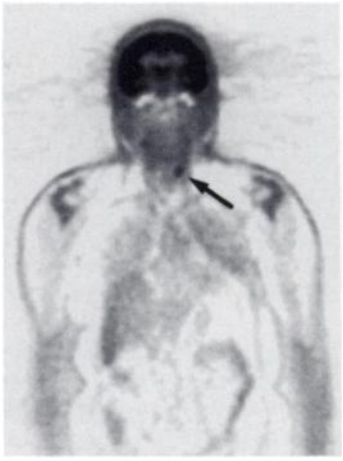

FIGURE 5. False-positive PET scan with unknown etiology. Coronal section of the neck shows increased activity there. Magnetic resonance image of brachial plexus was repeatedly negative. Follow-up PET scan done 1 yr later also showed the same uptake. The patient was without evidence of disease for 1 yr 7 mo. This lesion was considered to be a false-positive lesion with unknown reason.

(Fig. 3): sternocleidomastoid, scalene, serratus anterior and longus coli. These muscles are involved in the movement of head, neck and scapula. FDG uptake in muscle has been described and is well-known. Not only muscle activity during whole-body scanning, but also physical activity before and immediately after injection of FDG has been suggested to increase muscle uptake (*21*). To avoid increased muscle uptake, patients should be in a comfortable and relaxed recumbent position before, during and after injection of FDG. This is particularly important when clinical concern is the involvement of lymph nodes in the neck or mediastinum. More strict attention to patient preparation and awareness of potential skeletal neck muscle uptake will improve the specificity of FDG-PET scanning.

Other troublesome findings included bilateral mild perihilar uptake (Fig. 4). This was likely caused by blood pool activity of perihilar vessels as evidenced by the bilaterality and increased activity in both femoral blood vessels in the same patients (suggesting the presence of significant blood pool activity). Not surprisingly, nonmalignant inflammatory lesions (including one patient with thyroiditis and another patient with bowel inflammation) also were scored as positive.

Compared with most other PET studies for other cancers, this study demonstrated a relatively low specificity on a lesion basis. This was largely due to a high false-positive rate of malignant lymph node assignments, as mentioned previously. More strict attention to patient preparation, recognition of artifactual uptakes and information on clinical history including the presence of inflammatory disease may improve the specificity in future studies.

This study design had some limitations. Obtaining histological proof of all lesions could not be carried out ethically. In patients with possible multiple metastatic lesions, the histology of one or two sites was confirmed to justify systemic chemotherapy, and only those lesions were included in the analysis. Another limitation is that not all regions were prospectively examined with other conventional imaging studies. A third limitation is related to the retrospective nature of this study and producing a referral bias such that only more difficult cases (not resolved by conventional imaging) were referred for PET. From a technical perspective, attenuation correction of the images would provide a more accurate representation of the tracer distribution. A prospective study is in order to further evaluate the role of PET in imaging in postsurgical breast cancer management.

CONCLUSION

Whole-body FDG-PET scans are a sensitive diagnostic test for the detection of recurrent or metastatic lesions of breast carcinoma. Sensitivity for metastasis to bone is lower than for other tissues. More strict attention to patient preparation and better recognition of physiological or artifactual uptake will likely improve specificity in future studies.

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