FDG-PET/CT Compared with Conventional Imaging in the Detection of Distant Metastases of Primary Breast Cancer

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ABSTRACT

Purpose. Evidence from studies with small numbers of patients indicates that ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) accurately detects distant metastases in the staging of primary breast cancer. We compared the sensitivity and specificity of PET/CT and conventional imaging (CT, ultrasonography, radiography, and skeletal scintigraphy) for the detection of distant metastases in patients with primary breast cancer.

Patients and Methods. We performed a retrospective review that identified 225 patients with primary breast cancer seen from January 2000 to September 2009 for whom PET/CT data were available for review. Imaging findings were compared with findings on biopsy, subsequent imaging, or clinical follow-up. Sensitivity and specificity in the detection of distant metastases were calculated for PET/CT and conventional imaging. Fisher's exact tests were used to test the differences in

sensitivity and specificity between PET/CT and conventional imaging.

Results. The mean patient age at diagnosis was 53.4 years (range, 23–84 years). The sensitivity and specificity in the detection of distant metastases were 97.4% and 91.2%, respectively, for PET/CT and 85.9% and 67.3%, respectively, for conventional imaging. The sensitivity and specificity of PET/CT were significantly higher than those of conventional imaging ($p = .009$ and $p < .001$, respectively). Eleven cases of distant metastases detected by PET/CT were clinically occult and not evident on conventional imaging.

Conclusion. PET/CT has higher sensitivity and specificity than conventional imaging in the detection of distant metastases of breast cancer. A prospective study is needed to determine whether PET/CT could replace conventional imaging to detect distant metastases in patients with primary breast cancer. *The Oncologist* 2011;16:1111–1119

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INTRODUCTION

Breast cancer patients with large tumors ($\geq T3$) have a >8.3%–15.1% risk for distant metastasis [1–3]. The National Comprehensive Cancer Network recommends the following types of imaging for staging of locally advanced breast cancer at the time of diagnosis: chest radiography (CXR), mammography, breast ultrasonography as necessary, and optional additional studies as indicated by symptoms—breast magnetic resonance imaging (MRI); skeletal scintigraphy (SS); computed tomography (CT), ultrasonography, or MRI of the abdomen; CT, ultrasonography, or MRI of the pelvis; and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan [4]. However, these conventional imaging modalities have limitations with respect to the precise detection of distant metastases from breast cancer [5].

Several previous studies have examined the role of whole-body FDG-PET in breast cancer staging [6–9]. In breast cancer, FDG-PET may detect recurrence and allow for accurate determination of the spread of disease [10]. Conventional imaging plus FDG-PET may lead to the detection of unexpected metastases on initial staging [9]; however, the role of FDG-PET in women with breast cancer remains undefined [6].

Previous studies have shown that FDG-PET/CT is more sensitive than conventional imaging in the detection of distant metastases from breast cancer [11–15]. However, those studies had small numbers of patients [11–15]. Further confirmation of the value of PET/CT in the detection of breast cancer distant metastases is needed.

We hypothesized that distant metastases are detected more accurately by PET/CT than by conventional imaging in the initial staging of breast cancer. We tested this hypothesis using data from a large number of patients ($n = 225$) from a single institution.

METHODS

Patients

We retrospectively identified patients with breast cancer diagnosed at The University of Texas MD Anderson Cancer Center from January 1, 2000, to September 30, 2009, for whom the reports of PET/CT scans ordered for staging of primary breast cancer were available for review. To identify these patients, we used a prospectively maintained database managed by the Department of Breast Medical Oncology at our institution. Patients who had undergone systemic therapy (i.e., chemotherapy or endocrine therapy) before PET/CT were excluded. During the study period, 8,510 patients were newly diagnosed with primary breast cancer. Of these, 225 had PET/CT data available for review

and were included in our study. The MD Anderson Institutional Review Board reviewed and approved this study.

General Approach to Imaging

At MD Anderson, recommended imaging evaluations for primary staging of clinical stage II or stage III breast cancer are CXR, SS, and CT of the abdomen. Recommended imaging evaluations for patients with locally advanced or stage IV breast cancer are CXR, SS, CT of the abdomen, and consideration of PET/CT. In addition, PET/CT is considered for patients with equivocal or suspicious findings on conventional imaging, and PET/CT is routinely performed as part of primary staging for patients with inflammatory breast cancer.

PET/CT Imaging

^{18}F -FDG-PET/CT was performed using one of the following: Siemens ECAT HR with dedicated CT (Siemens/CTI, Knoxville, TN), GE Discovery ST 8-slice PET/CT, GE Discovery STE 16-slice PET/CT, GE Discovery RX 16-slice PET/CT, or GE VCT 64-slice PET/CT (General Electric Medical Systems, Milwaukee, WI) scanner. Normal fasting blood glucose levels <150 mg/dL were a standard requirement for imaging in all patients. Patients fasted for at least 6 hours before the ^{18}F -FDG injections. An i.v. injection of 555–740 MBq (15–20 mCi) of ^{18}F -FDG was administered, and 60–90 minutes later, two- or three-dimensional emission scans were acquired at 3–5 minutes per bed station. PET images were reconstructed using standard vendor-provided reconstruction algorithms. Noncontrast CT was used for attenuation correction and diagnosis and acquired in helical mode with tube current modulation (120 kV, 300 mA, 0.5-second rotation) from the vertex or base of the skull to the mid thigh, calf, or toes during quiet respiration at a 3.75-mm slice thickness. Images were viewed on GE Advantage 4.2–4.4 workstations (General Electric Medical Systems). Maximum standardized uptake value, a semiquantitative measure of FDG uptake, was most commonly reported.

Conventional Imaging

We defined conventional imaging as CXR, SS, and CT of the chest, abdomen, or pelvis. The CT studies of the chest, abdomen, or pelvis were performed with i.v. contrast agent. In general, MRI in the patients in our series was used to provide additional information about previously identified metastases rather than to screen for distant metastases. Therefore, we did not include MRI among the conventional imaging studies compared with PET/CT.

Image Interpretation and Confirmation of Distant Metastasis

Our study was a retrospective chart review. According to the normal operating procedures of our institution, each conventional imaging or PET/CT study was interpreted by an attending physician who was board certified in diagnostic radiology, nuclear medicine, or both fields. The analysis performed in this study was based on these interpretations of the imaging studies. The interpreting physicians had full access to all prior imaging studies and to the patient's medical record. The interpretations of the prior imaging studies were available in a picture archiving computer system immediately as audio reports and were transcribed within 24 hours of dictation.

The presence or absence of distant metastases was determined on the basis of histopathologic findings or subsequent imaging findings (e.g., MRI, ultrasonography, or plain radiography). If no distant metastases were confirmed on these studies, the presence of distant metastases was determined on the basis of clinical follow-up with a minimum duration of 2 years. Suspected distant metastases were confirmed tumor progression by conventional imaging or PET/CT or MRI while patients were followed.

Imaging findings were considered positive for metastasis when the radiologist concluded that a metastasis was suspected or that there was an indeterminate abnormality and more imaging studies were needed. Imaging findings were considered positive for benign disease when the radiologist concluded that there was no evidence of metastasis or that an abnormality was most likely benign.

On conventional imaging and PET/CT, abnormalities potentially representative of distant metastasis were examined with regard to their basic imaging characteristics and for interval change. The radiologists and nuclear medicine physicians at our cancer center have expertise in the appearance of metastatic disease on their respective imaging modalities; a detailed explanation of the imaging characteristics of all potential types of metastases on each imaging modality is not possible here because of space limitations. In the absence of the standard imaging findings indicating metastatic disease, metastatic disease was not reported.

Additionally, lesions were evaluated for change between studies. The timing of imaging follow-up was at the discretion of the attending medical oncologists, all of whom were board certified in medical oncology. Lesions that progressed or responded in a fashion typical of metastatic disease were further evaluated with sequential imaging studies to confirm whether they did in fact represent metastases. Criteria used to evaluate interval change included the Response Evaluation Criteria in Solid Tumors for solid lesions on conventional imaging [16], the PET Response Criteria in

Solid Tumors for PET/CT [17], and the MD Anderson criteria for bone lesions [18–20].

Statistical Methods

Sensitivity and specificity were determined on the basis of number of patients, not number of lesions. McNemar's test was used to test differences in the accuracy (sensitivity and specificity) between PET/CT and conventional imaging. A p -value $< .05$ was considered significant. The analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC).

RESULTS

Patients

Patient characteristics are summarized in Table 1. The median follow-up time for the 225 patients in the study after initial diagnosis of breast cancer was 26.7 months (range, 1–68 months). The reasons for performing PET/CT were equivocal or suspicious findings on conventional imaging (116 patients), locally advanced breast cancer (98 patients), to rule out primary cancer (seven patients), unknown (two patients), and patient request (two patients).

Distant Metastasis Rate and Patient Outcomes as per Distant Metastasis

The numbers of patients with and without distant metastases, as well as the outcomes of patients in these two groups, are summarized in Figure 1. Seventy-eight patients were judged to have distant metastases on the basis of histological confirmation (27 patients), subsequent imaging (30 patients), or clinical follow-up (21 patients). One hundred forty-seven patients were judged not to have distant metastases. Of these, 56 patients were initially suspected of having metastases on the basis of PET/CT alone (eight patients), conventional imaging (43 patients), or both PET/CT and conventional imaging (five patients), but were judged not to have distant metastases on the basis of histological confirmation (10 patients), subsequent imaging (28 patients), or clinical follow-up (18 patients). The median follow-up time for the 18 patients with distant metastases ruled out on the basis of clinical follow-up was 42 months (range, 24–68 months).

Of the 147 patients judged not to have distant metastases, no patients died during follow-up, 20 patients relapsed, and 127 patients remained progression free. The sites of relapse in the 20 patients with relapse were local lymph node ($n = 4$), distant lymph node ($n = 3$), bone ($n = 4$), brain ($n = 4$), lung ($n = 4$), and liver ($n = 4$) (some patients had relapse at more than one site).

Table 1. Patient characteristics			
Characteristic	<i>n</i> of patients (<i>n</i> = 225)	Characteristic	<i>n</i> of patients (<i>n</i> = 225)
Mean age at primary tumor diagnosis	53.4 yrs	Stage	
Primary tumor classification		I	19 (8.4%)
T0, Tis		II	40 (17.8%)
N1	5	IIIa	6 (2.6%)
N2	1	IIIb	28 (12.4%)
N3	1	IIIc	54 (24.0%)
T1		IV	78 (34.7%)
N0	20	Estrogen receptor status	
N1	6	Positive	134 (59.6%)
N3	3	Negative	87 (38.7%)
T2		Unknown	4 (1.7%)
N0	17	Progesterone receptor status	
N1	21	Positive	101 (44.9%)
N2	1	Negative	121 (53.8%)
N3	15	Unknown	3 (1.3%)
T3		HER-2 status	
N0	3	Positive	71 (31.5%)
N1	7	Negative	108 (48.1%)
N3	5	Unknown	46 (20.4%)
T4a-c		Nuclear grade	
N0	4	I	5 (2.2%)
N1	2	II	66 (29.3%)
N2	4	III	146 (64.9%)
N3	19	Unknown	8 (3.6%)
T4d		Local therapy before PET/CT	
N0	4	Yes	20 (8.9%)
N1	20	No	205 (91.1%)
N2	5		
N3	62		
Metastasis status			
M0	147 (65.3%)		
M1	78 (34.7%)		

Abbreviations: HER-2, human epidermal growth factor receptor 2; PET/CT, positron emission tomography/computed tomography.

Conventional Imaging

Findings on conventional imaging are summarized in Table 2. The utility of conventional imaging in the detection of distant metastases from breast cancer is outlined in Table 3. On conventional imaging, 115 patients (51%) had suspected distant metastases, and 67 (58%) of these 115 patients were judged positive for distant metastases. The sensitivity of conventional imaging in the detection of distant metastases was 85.9% and the specificity was 67.3% (Table 3).

PET/CT

On PET/CT, 136 patients were not suspected of having distant metastases. Two of those patients actually had distant metastases as indicated by biopsy (one of two) or subsequent imaging (one of two). The sensitivity of PET/CT in the detection of distant metastases was 97.4% (Table 3). One of the two patients with false-negative PET/CT findings had a bone metastasis that was suggested by bone scan and confirmed by MRI. That patient had no disease pro-

Figure 1. Flowchart on follow-up after diagnosis in 225 patients.
Abbreviations: CI, conventional imaging; PET/CT, positron emission tomography–computed tomography; Pts, patients; TN, true negative; TP, true positive.

Table 2. Conventional imaging rates and findings						
Imaging test	Done	Not done	% of patients	Suspected metastases	True positive	False positive
Chest radiography	225	0	100.0	14	9	5
Skeletal scintigraphy	199	26	88.4	59	37	22
Chest CT	113	112	50.2	40	28	12
Abdominal CT	189	36	84.0	54	39	15
Abdominal ultrasonography	10	215	4.4	3	1	2
Pelvic CT	50	175	22.2	15	13	2

Abbreviation: CT, computed tomography.

Table 3. Sensitivity and specificity of PET/CT and conventional imaging						
	Distant metastasis by PET/CT			Distant Metastasis by Conventional Imaging		
	+	–	Total	+	–	Total
Distant metastasis						
+	76	2	78	67	11	78
–	13	134	147	48	99	147
Total	89	136	225	115	110	225
	Sensitivity	97.40%		Sensitivity	85.90%	
	Specificity	91.20%		Specificity	67.30%	

Abbreviations: PET/CT, positron emission tomography/computed tomography.

gression over a follow-up time of 26 months. The other patient with false-negative PET/CT findings had mediastinal pleural metastasis suggested by CT of the chest and confirmed by cytology. That patient experienced progression of disease after 11 months.

On PET/CT, 89 patients had suspected distant metasta-

ses. Thirteen of these 89 patients did not actually have distant metastases as indicated by biopsy (one of 13), additional imaging (four of 13), or clinical follow-up (eight of 13). The specificity of PET/CT in the detection of distant metastases was 91.2% (Table 3).

In the 13 patients with false-positive PET/CT findings, the sites of false-positive findings on PET/CT were bone ($n = 7$), ovary ($n = 3$), lung ($n = 2$), mediastinal lymph node ($n = 1$), and liver ($n = 1$), with some patients having multiple false-positive sites. None of the 13 patients with false-positive PET/CT findings had a recurrence, and all were alive at a median follow-up time of 23.2 months. In seven of the 13 patients with false-positive PET/CT findings, systemic therapy was given as though there was stage IV disease.

Sensitivity and Specificity of PET/CT and Conventional Imaging

The sensitivity of PET/CT (97.4%) was significantly higher than the sensitivity of conventional imaging (85.9%) ($p = .009$). The specificity of PET/CT (91.2%) was significantly higher than the specificity of conventional imaging (67.3%) ($p < .001$).

We also analyzed sensitivity and specificity in three different subgroups of patients in our series. First, we excluded the 25 patients with stage IV disease at presentation prior to primary staging. In the remaining 200 patients, the sensitivity and specificity of PET/CT were 96% and 91%, respectively, and those of conventional imaging were 84% and 67%, respectively. There was a significant difference in accuracy between PET/CT and conventional imaging ($p < .001$) (supplemental online Table S1). Second, we limited the analysis to patients without stage IV disease at presentation who had locally advanced breast cancer ($n = 134$). In this group, the sensitivity and specificity of PET/CT were 98% and 90%, respectively, and those of conventional imaging were 83% and 85%, respectively (supplemental online Table S2). Again, there was a significant difference in accuracy between PET/CT and conventional imaging ($p = .0411$). Third, we limited the analysis to patients without stage IV disease at presentation who had early breast cancer ($n = 66$). In this group, the sensitivity and specificity of PET/CT were 91% and 93%, respectively, and those of conventional imaging were 91% and 38%, respectively (supplemental online Table S3). There was again a significant difference in accuracy between the two diagnosis methods ($p < .001$).

Cases Detected by FDG-PET/CT and Not by Conventional Imaging

In 15 patients, PET/CT findings suggested distant metastases that were not suspected on the basis of conventional im-

aging findings, and these PET/CT findings prompted administration of systemic therapy for presumed stage IV disease. In other words, in 15 patients, the results of PET/CT changed the clinical management. In 11 of those patients, distant metastases were confirmed by subsequent biopsy or conventional imaging studies (Table 4). However, in the other four patients, distant metastases were not confirmed by subsequent biopsy or imaging. The follow-up durations in these four patients were 12 months, 24 months, 26 months, and 25 months.

Performance of PET/CT and Conventional Imaging by Disease Site

Table 5 shows the performance of PET/CT compared with conventional imaging in the detection of metastases in bone, in lymph nodes in the chest, in the lungs, and in the liver.

Fifty-six patients in our study had bone metastases. PET/CT detected bone metastases in 55 of those patients, failed to detect bone metastases in one of those patients, and incorrectly suggested bone metastases in seven patients. SS detected bone metastases in 38 patients, failed to detect bone metastases in 12 patients (six patients did not undergo SS), and incorrectly suggested bone metastases in 21 patients. The sensitivity and specificity of PET/CT for detecting bone metastases were 98% and 96%, respectively, compared with 76% and 86%, respectively, for SS.

Twenty-five patients in our study had metastases in the lymph nodes of the chest, and 14 patients had lung metastases. The only chest or lung metastasis not detected by PET/CT and detected by chest CT was a lesion of the mediastinal pleura. PET/CT detected two mediastinal nodal metastases and one hilar nodal metastasis not detected by chest CT.

Twenty patients in our study had liver metastases. Both PET/CT and abdominal CT accurately detected liver metastases in all cases. PET/CT incorrectly indicated liver metastases in one patient, and abdominal CT incorrectly indicated liver metastases in nine patients. In the detection of liver metastases, the sensitivity and specificity of PET/CT were 100% and 99%, respectively, compared with 100% and 95%, respectively, for CT.

DISCUSSION

To our knowledge, this is the largest study to date investigating the application of PET/CT for the detection of distant metastases in the primary staging of breast cancer. Seventy-eight (35%) of the 225 patients in our study had distant metastases at the time of initial staging. In the detection of such metastases, PET/CT was superior to conventional imaging in terms of both sensitivity and specificity.

Table 4. Cases with distant metastases detected by PET/CT but not detected on conventional imaging

Case No.	Conventional Imaging	Site of metastasis	n of Mets	Biopsy	Confirm by Imaging	Survival	Follow-up time for survival, mos	PD	Time to PD, mos	Site of PD ^a	Treatment
1	CXR, BUS, MMG, BMRI, SS, CCT,	Bone	2	No	MRI	Alive	30	Yes	10	Same	
2	CXR, BUS, MMG, BMRI, SS, CCT, ACT, PCT	Bone	1	No	MRI	Alive	39	No	–	–	H+Z
3	CXR, BUS, MMG, BMRI,	Bone	Multiple	No	MRI	Alive	31	Yes	18	Other	
4	CXR, BUS, MMG, SS, CCT, ACT, PCT	LN (Hilary)	1	Yes	No	Dead	52	Yes	15	Same	
5	CXR, BUS, MMG, SS, CCT, ACT, PCT	Bone, lung	1	No	MRI	Dead	31	Yes	24	Same	
6	CXR, BUS, MMG, SS, CCT, ACT,	Bone	Multiple	No	No	Alive	20	Yes	9	Same	
7	CXR, BUS, MMG, SS, CCT, ACT,	LN (mediastinal)	1	No	No	Dead	20	Yes	10	Same	
8	CXR, BUS, MMG, SS, ACT,	LN (mediastinal)	1	No	CT (Anigo)	Alive	67	Yes	11	Same	
9	CXR, BUS, MMG, SS,	Lung, bone, LN	Multiple	Yes	No	Alive	19	Yes	10	Same	
10	CXR, BUS, MMG, SS,	LN (opposite side)	Multiple	Yes	No	Alive	20	No	–	–	AI
11	CXR, BUS, MMG, ACT, AUS	LN (neck), bone	Multiple	No	No	Dead	17	Yes	10	Other	

^aSame indicates same as the initial site of distant metastases; other indicates another site.
Abbreviations: ACT, abdominal CT; AI, aromatase inhibitor; BMRI, breast MRI; BUS, breast ultrasonography; CCT, chest CT; H, trastuzumab; LN, lymph node; Mets, metastases; MMG, mammography; PCT, pelvic CT; PD, progressive disease; PET/CT, positron emission tomography/computed tomography; Z, zoledronic acid.

Table 5. Comparison of PET/CT and conventional imaging at individual sites of metastasis

Site of metastasis	n of Patients with Mets at site	PET/CT				Conventional imaging ^a				NA
		TP (sensitivity)	FN (1 – sensitivity)	TN (specificity)	FP (1 – specificity)	TP (sensitivity)	FN (1 – sensitivity)	TN (specificity)	FP (1 – specificity)	
Bone	56	55 (98%)	1 (2%)	162 (96%)	7 (4%)	38 (76%)	12 (24%)	128 (86%)	21 (14%)	6
Thoracic lymph nodes (N4)	25	24 (96%)	1 (4%)	199 (99%)	1 (1%)	13 (81%)	3 (19%)	95 (98%)	2 (2%)	9
Lung	14	14 (100%)	0 (0%)	209 (99%)	2 (1%)	9 (90%)	1 (10%)	95 (92%)	8 (8%)	4
Liver	20	20 (100%)	0 (0%)	204 (99%)	1 (1%)	20 (100%)	0 (0%)	160 (95%)	9 (5%)	0

^aBone scintigraphy for bone imaging, chest CT for N4 lymph nodes and lung imaging, and abdominal CT for liver imaging.
Abbreviations: CT, computed tomography; FN, false negative; FP, false positive; Mets, metastases; NA, not available; PET/CT, positron emission tomography/computed tomography; TP, true positive.

PET/CT detected metastases not seen on conventional imaging in 11 (14%) of the 78 patients. Accurate detection of distant metastases is important for a number of reasons. In a patient with distant metastases, surgical removal of the primary breast tumor may not be indicated. In addition, if bone metastases are detected, they can be treated systemically with a bisphosphonate in order to reduce or prevent a skeletal-related event. Solitary metastases in other or-

gan sites might be better treated with combined-modality therapy.

Our study strongly supports the conclusions of previous studies that have shown that PET/CT is more accurate than conventional imaging for the detection of distant metastases [11–13, 15, 21]. Previous studies have shown that PET or PET/CT may be superior to SS for the detection of bone metastases [22–28]. Our results indicated that PET/CT was

superior to SS in the detection of bone metastases. On the basis of the previous studies and our study, PET/CT could replace SS as the initial modality for detection of bone metastases in the staging of newly diagnosed breast cancer. However, because our study was not designed to compare these two modalities, prospective studies are needed to confirm these observations.

Recently, Mahner et al. [29] suggested that FDG-PET could potentially detect distant metastases in primary breast cancer patients with sufficiently high accuracy to replace conventional imaging techniques. On the basis of our results, we speculate that, for the detection of distant metastases from breast cancer, PET/CT is superior to conventional imaging in terms of accuracy.

As previously mentioned, for 15 patients in this study, systemic therapy was changed on the basis of PET/CT findings of stage IV disease. In 11 of those patients, distant metastases were confirmed, but in the other four patients, distant metastases were not confirmed. The systemic therapy for presumed stage IV disease in those four patients may have been unnecessary and inappropriate.

Our study has limitations. First, this study was retrospective. Our data were collected from patients' medical records, and therefore this study suffers from the various biases associated with any retrospective study, including the possibility of selection bias with respect to insurance status and socioeconomic status. Second, not all of the patients underwent the full battery of conventional imaging evaluations. This may have diminished the efficacy of conventional imaging for detecting distant metastases. Third, scans were reviewed as part of standard clinical practice and not blinded to the results of other scans. Fourth, histopathologic findings were not available for all areas of suspected distant metastases because clinicians tended to avoid biopsy in patients with multiple suspected metastases, par-

ticularly when findings on additional imaging were highly suggestive of metastatic disease and treatment needed to be expedited in the face of rapidly progressive disease. In the patient with presumed false-negative findings on PET/CT who did not undergo biopsy, we do not have a definitive answer regarding whether or not the patient actually had distant metastases. Nevertheless, our finding that 10 of 37 patients with suspected distant metastases who underwent biopsy had benign findings on biopsy clearly shows that clinicians must perform a biopsy to confirm suspected distant metastasis.

In summary, our study demonstrates that, for the detection of distant metastases of breast cancer, PET/CT is superior to conventional imaging in terms of sensitivity and specificity. Given our results, a large, prospective study in which PET/CT readers are blinded to the results of conventional staging studies is warranted to confirm the hypothesis that FDG-PET/CT can replace conventional imaging in the evaluation of metastatic disease in primary breast cancer patients.

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