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Breast Cancer

Defining the Role of PET–CT in Staging Early Breast Cancer

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ABSTRACT

Introduction. **Currently, there is a lack of data on the role of combined positron emission tomography–computed tomography (PET–CT) in the staging of early invasive primary breast cancer. We therefore evaluated the role of ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET–CT in this patient population.**

Methods. **We prospectively recruited 70 consecutive patients (69 women, one man; mean age, 61.9 ± 8.1 years) with early primary breast cancer for staging with ^{18}F-FDG-PET–CT. All PET–CT images were interpreted by two readers (independently of each other). A third reader adjudicated any discrepancies. All readers had ≥5 years of specific experience. Ethics board approval and informed consent were obtained.**

Results. **The mean clinical follow-up was 22.7 ± 12.6 months. The primary tumor was identified with PET–CT in 64 of 70 patients. Of the unidentified lesions, surgical pathology revealed two intraductal carcinomas, one invasive tubular carcinoma, and three invasive lobular carcinomas. Undiagnosed multifocal breast disease was shown in seven of 70 patients. PET–CT identified avid axillary lymph nodes in 19 of 70 patients, compared with 24 of 70 confirmed during surgery. There were four patients who were axillary node positive on PET but had no axillary disease at surgery.**

Five patients were reported with avid metastases. Two of those patients were treated for metastatic disease (nodal, lung, and liver in one and bone metastases in the other) following further imaging and clinical assessment. In the other three patients, lesions (lung, $n = 1$; pleural, $n = 1$; paratrachael node, $n = 1$) were subsequently diagnosed as benign lesions.

Conclusion. **Integrated ^{18}F-FDG-PET–CT may have a role in staging patients presenting with early breast cancer.** ***The Oncologist*** 2012;17:613–619

INTRODUCTION

Breast cancer is a common disease with a highly variable outcome [1], and therefore accurate tumor staging is important. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) has been shown to be helpful in the staging of many malignancies [2]. This reflects PET's inherent sensitivity over other imaging modalities [3]. However, the role of PET in the staging of primary breast cancer is less clear and there is only limited evidence, as recently highlighted [4]. Initial studies showed the potential for PET in this respect, but most studies were from stand-alone scanners [5–8], and there is recognition that data from PET–computed tomography (CT) is needed [9]. PET–CT over stand-alone PET has shown added value for many malignancies [10, 11], and such findings have also been suggested for breast cancer [12]. These findings are intuitive; the CT component aids localization of PET findings, whereas it may identify soft tissue and bone changes beyond the spatial resolution of radionuclide imaging [13]. The role of ^{18}F-FDG-

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PET–CT in recurrent breast cancer and in treatment response is recognized [14–16], and the use of PET–CT to phenotype breast cancer by imaging metabolic flow relationships has been shown [17, 18].

Current recommendations do not incorporate the routine use of ^{18}F-FDG-PET–CT for staging primary breast cancer [2]. However, the direct scientific evidence to support this recommendation is limited. There have been prospective investigations with ^{18}F-FDG-PET–CT in patients with advanced primary breast cancer [19, 20] and in high-risk or recurrent patients [21–23]. Other studies combined whole-body ^{18}F-FDG-PET–CT with PET–CT mammography [24] or compared diffusion-weighting magnetic resonance imaging (MRI) and PET–CT [25], but the data were obtained in patients with known metastatic disease.

The lack of evidence for the role of PET–CT in primary breast cancer has also led to a recent call for more research [4]; this is particularly true for early disease. Subsequent retrospective data suggesting that PET–CT may indeed have a role in breast cancer staging have recently become available, which further highlighted the need for prospective investigations [26]. Here, we present the findings from a prospective study investigating the role of ^{18}F-FDG-PET–CT in the staging of patients with early primary breast carcinoma.

Materials and Methods

Patients

We prospectively recruited 70 consecutive eligible consenting patients (69 women and one man; mean age, 61.9 ± 8.1 years) with early primary unilateral invasive breast cancer for ^{18}F-FDG-PET–CT staging. Eligibility included patients with primary tumors sized 1.0–3.5 cm (mean size, 2.1 ± 0.7 cm) as measured on imaging. Patients aged <45 years, pregnant patients, and patients with inflammatory breast carcinoma were excluded. The only other exclusion was patients declining to take part. All patients had undergone triple assessment including mammography, ultrasound, and core biopsy prior to recruitment. These tests were performed before the PET–CT study. The mean time from PET–CT to surgery was 2.4 ± 2.1 weeks. Although some patients at our institutions receive MRI clinically, breast MRI was not part of this study. In this patient cohort, bone scintigraphy, liver ultrasound, and CT were not performed because these patients had early disease.

Axillary node staging was performed using sentinel lymph node scintigraphy (performed after the PET–CT exam) in 59 patients. In nine patients, ultrasound-guided nodal biopsy confirmed metastasis (prior to the PET–CT examination). The remaining two patients had large multicentric lesions with enlarged axillary nodes on ultrasound. However, subsequent axillary clearance showed no metastasis. A clinical and histological profile of the study patients is presented in Table 1 and in supplemental online Table 1.

Ethics board approval and informed consent was obtained.

Table 1. Profile of the patient population

Characteristic	Data	Total
Stage		
T1	34	
T2	30	64 (+ 6 nonavid)
N1	24 (versus 19 on PET–CT)	24 (versus 19 on PET–CT)
Hormone receptor status		
ER$^+$	64	70
ER$^-$	6	
PR$^+$	58	70
PR$^-$	12	
HER-2 status		
Positive	15	70
Negative	49	
Equivocal	6	
Type of tumor		
Ductal carcinoma	45	70
Lobular carcinoma	10	
Tubular	2	
Metaplastic carcinoma	1	
Mixed/nonspecific carcinoma	12	
Grade		
1	12	70
2	33	
3	25	

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; PET–CT, positron emission tomography–computed tomography; PR, progesterone receptor.

PET–CT Imaging

Following 6 hours of fasting prior to examination (ensuring a blood glucose level <10 mmol/L in all patients), images were acquired 1 hour after injecting 200 MBq of ^{18}F-FDG using a dedicated combined PET–64-detector-CT (VCT-XT Discovery; GE-Healthcare Technology, Waukesha, WI). A CT scan was performed (for attenuation correction) using 64-mm × 3.75-mm detectors, a pitch of 1.5, and a 5-mm collimation (140 kVp and 80 mA in 0.8 seconds) from vertex to mid-thigh. Oral but not i.v. CT contrast medium was administered. Maintaining the patient position, an ^{18}F-FDG-PET scan was performed that covered an area identical to that covered by the CT scan. All PET acquisitions were carried out in two-dimensional mode (8 minutes per bed position, compensating for the reduced administered activity, minimizing radiation exposure). Transaxial emission images of 3.27 mm thickness (pixel size, 3.9 mm) were reconstructed using ordered subsets expectation maximization with two iterations and 28 subsets. The axial field of view was 148.75 mm, resulting in 47 slices per bed position. The images were reconstructed as a 128 × 128 matrix.

PET–CT Image Interpretation

PET–CT images were displayed on an Advantage work station (GE Healthcare Technology, Waukesha, WI). On the dual-screen work station, the PET and CT datasets were both displayed as separate but coregistered images and also displayed using color (PET) images fused with CT. All readers had access to all these datasets. All the PET–CT images were interpreted by two readers (independently of each other). A third reader adjudicated any discrepancies. All readers had ≥5 years of specific experience. The only clinical data provided to the readers was primary breast carcinoma. The readers were unaware of the other imaging and histological findings. Both PET and CT images were reviewed by all readers. The PET–CT reporting and acquisitions used current European cancer guideline criteria and standardizations [27].

Histology

Histology was performed as per routine clinical management using the surgically excised specimens (mastectomy in 20 patients and wide local excision in 50 patients).

Statistical Analysis

The population size was determined as 70 using a proportion of $p = 90\%$ and a precision of 6% (in our estimation), including an additional 10%, allowing for incomplete data. Receiver operating characteristic (ROC) curve analysis was performed to identify the ideal standardized uptake value (SUV) threshold for detecting axillary node metastasis. κ statistics were used to assess interobserver variability in the staging of early breast cancer with PET–CT. Sensitivity and specificity were formally calculated (Table 2) for axillary node metastasis calculation. All statistics were performed using SPSS 2011 software (IBM; Armonk, NY).

Results

Primary Tumor

The primary tumor was identified in 64 of 70 patients. The mean maximum SUV (SUV_{max}) in the identified lesions was 6.4 ± 5.6. Of the six unidentified lesions, surgical pathological data revealed two invasive ductal carcinomas, one invasive tubular carcinoma, and three invasive lobular carcinomas (Table 2).

Multifocal Disease

Undiagnosed multifocal disease was shown on PET–CT in seven of 70 patients (Table 3 and Fig. 1). This was not identified by mammography or ultrasound. Multifocal disease was confirmed by histopathology in all cases.

Axillary Lymph Node Staging

All patients were staged using histology as the gold standard. PET–CT identified avid axillary lymph nodes in 19 of 70 patients, compared with 24 of 70 confirmed on histology. There were four patients who were axillary node positive on PET but had no axillary disease at surgery (Table 4). In total, 18 nodes were obtained at surgery and histologically analyzed. The maximum short axis diameter (in mm) in the nodes of these four patients on CT were 6.4, <5, 11.2, and 15.6.

Table 2. Size on imaging and histology of the six tumors not identified by PET–CT

Tumor	Size (cm)	Histology type	Tumor grade
1	1.0	IDC	Low
2	1.0	IDC	Intermediate
3	1.0	ILC	Low
4	1.5	ILC	Intermediate
5	1.1	ITC	Low
6	2.3	ILC	Intermediate

Many of these tumors were at the lower end of the inclusion criteria and thus close to the limits of spatial resolution for PET [33, 34].
Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ITC, invasive tubular carcinoma; PET–CT, positron emission tomography–computed tomography.

Table 3. Location of multifocal disease in the seven patients in whom this was diagnosed on a case-by-case basis

Case (histology)	Location of main tumor	Location of second focus
Case 1 (NST)	Left breast close to nipple	Posterior to main lesion
Case 2 (IDC)	Right lateral	Medial and superficial to the main lesion
Case 3 (IDC)	Right central breast	Adjacent to main mass
Case 4 (IDC)	Left upper outer	Superficial and medial to the main lesion
Case 5 (IDC)	Left upper inner	One lesion medial and a second lesion lateral to the main lesion
Case 6 (IDC)	Left upper outer	Adjacent to the main lesion in the upper outer
Case 7 (IDC)	Right lower inner	Adjacent lesion in inner quadrant and second one in outer

Abbreviations: IDC, invasive ductal carcinoma; NST, nonspecific tumor.

ROC curve analysis revealed an SUV_{max} threshold of 1.4 to maximize the best compromise of sensitivity and specificity.

Extra-Axillary FDG-Avid Foci

Metastatic lesions were reported in five patients. After imaging and clinical assessment, metastatic disease was found in two of 70 patients. One of these patients, aged 75 years with a 2.2-cm intermediate-grade lobular estrogen receptor–positive carcinoma, had widespread avid skeletal disease, which was also identified on CT (Fig. 2). The most avid skeletal lesion had an SUV_{max} of 19.5. The second patient, aged 54 years with a

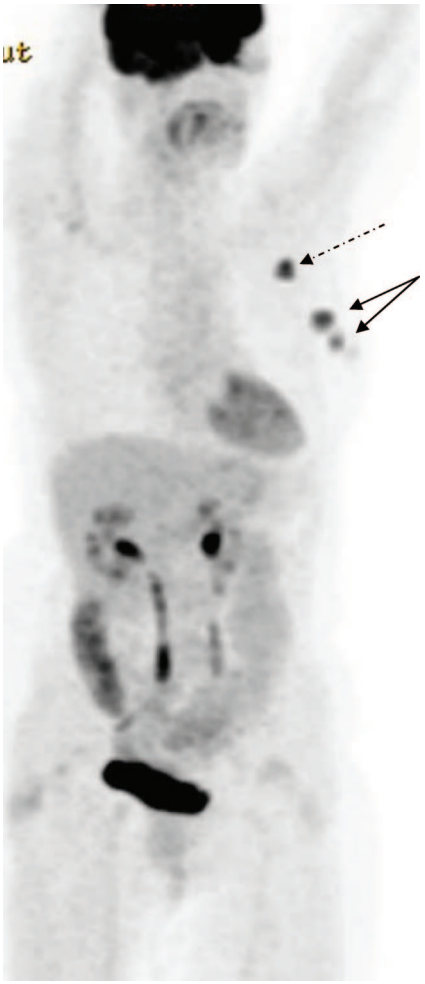

Figure 1. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography of a patient with newly diagnosed primary breast cancer. The maximum intensity projection image shows multifocal disease in the left breast (solid arrows). Avid left axillary nodal uptake is also identified (dashed arrow). No distant FDG-avid disease is identified.

3.5-cm intermediate-grade ductal estrogen receptor–positive carcinoma, had nodal disease above and below the diaphragm with lymph node, liver, and lung nodule (the largest was 7 mm and avid) involvement. The most avid distant lesion in that patient had an SUV_{max} of 6.0.

In the remaining three patients, the lesions were subsequently believed to be benign. In one of those patients, biopsy of a moderately avid pleural nodule revealed a fibroma. In the second patient (treated with trastuzumab), who had a mildly avid lung nodule on PET, follow-up CT showed no identifiable lung nodules and the patient remained disease free 25 months after the PET–CT study. In the last patient, with a moderately avid paratracheal lymph node on PET–CT imaging, clinical follow-up for 31 months showed no evidence of disease recurrence off treatment.

The mean clinical follow-up period was 22.7 ± 12.6 months. To date there is no evidence of false-negative metastatic disease.

Table 4. Axillary nodal PET–CT and surgical histology findings

	PET–CT positive axillary node	PET–CT negative axillary node
No nodal metastasis on histology	4	42
Nodal metastasis on histology	15	9

The sensitivity was 62.5% (95% CI, 40.7%–80.5%) and the specificity was 91.3% (95% CI, 78.3%–97.2%).
Abbreviations: CI, confidence interval; PET–CT, positron emission tomography–computed tomography.

Interobserver Variability

The κ statistic for tumor, node, and metastasis reporting were 0.91, 0.83, and 0.86, respectively.

Discussion

Original, prospective ^{18}F-FDG-PET–CT data from 70 patients with primary early breast carcinoma are presented. Over 95% of the invasive ductal carcinomas were identified on PET–CT, but only one third of lobular carcinomas were identified. In this study, distant PET findings that were reported as metastatic were found in 7% of patients and previously undetected multifocal disease was identified in 9% of patients. Patient breast cancer management was directly affected in nine (13%) patients—two patients with distant metastases and seven patients with multifocal disease. Our findings from early breast cancer mirror the results of ^{18}F-FDG-PET–CT scanning in patients with more advanced primary breast cancer, for which PET–CT was found to impact patient management in 42% [19] and 18% [20] of cases. Given the useful biological correlates of FDG-PET in primary breast cancer [28], there is a need for further assessment of FDG-PET–CT for primary breast cancer.

In this study, ^{18}F-FDG avidity was identified above and below the diaphragm as well as in the skeleton. Extralocoregional metastases alter patient management and provide additional prognostic information. The findings of skeletal metastatic disease also significantly alter the management pathway and again impact prognosis, and thereby aid targeted individualized treatment for the patient [29]. In both these cases, systemic therapy is indicated. In one case in this study, a pleural abnormality detected on PET required additional ultrasound and biopsy to determine the etiology; these showed a benign pleural tumor, illustrating the effort needed to obtain the correct diagnosis. The findings of unidentified multifocal breast disease in seven patients also impacted patient management; these patients require mastectomy instead of wide local excisions. MRI and mammography are useful to diagnose multifocal disease, but their diagnostic accuracy is limited [30]. MRI has nonetheless been shown to be useful in the management of breast cancer with the potential of reducing unnecessary surgery [31, 32].

The performance of ^{18}F-FDG-PET is limited in diagnosing axillary disease because of its failure to detect micrometastases

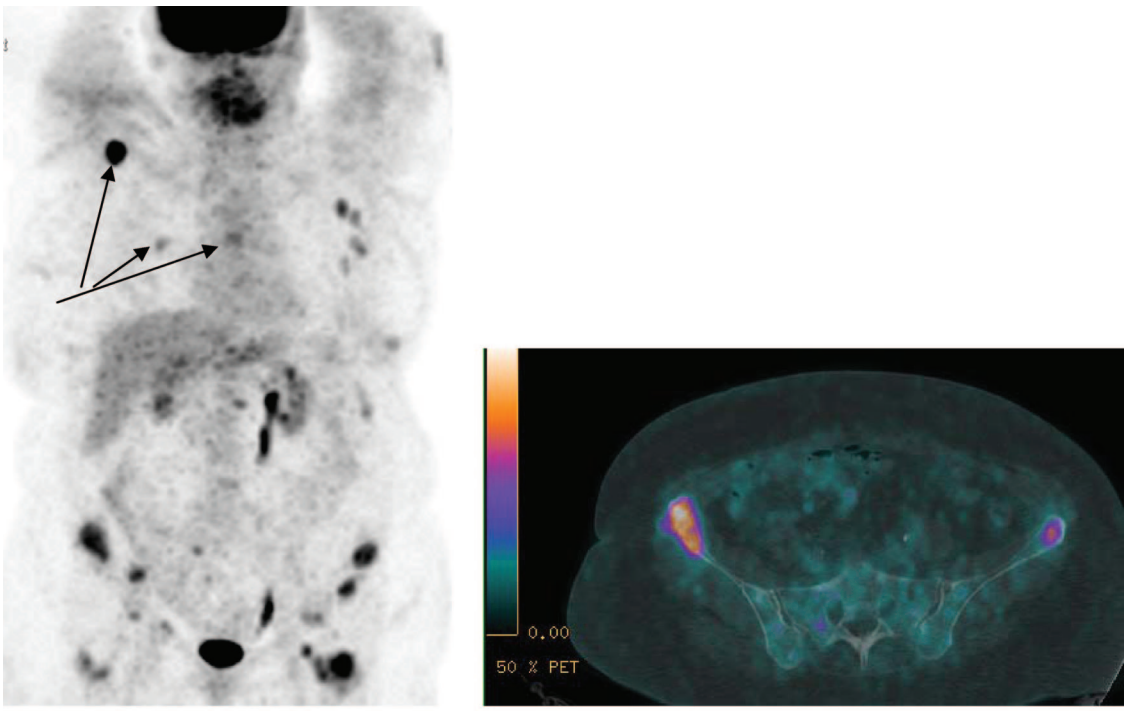

Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (PET–CT) of a patient with newly diagnosed primary breast cancer. The maximum intensity projection image **(A)** shows widespread avid disease including the right scapula, right 6th rib and the T6 vertebra (see arrows). The fused PET–CT image **(B)** shows that focal avidity in the pelvis coregisters to the bony pelvis.

[33]. Both the size of the lesion and the intensity of tracer uptake are important determinants for lesion detectability with PET. Phantom studies show that lesions <5 mm are not reliably detected on PET [33]. Thus, it is not surprising that micrometastases (<2 mm) are not detected, and indeed a recent technology assessment showed that the smallest axillary node detected was 3 mm [34]. One can improve the sensitivity of axillary nodal metastasis detection by reducing the SUV threshold, but this can negatively impact specificity. Therefore, low-grade ^{18}F-FDG nodal uptake may simply represent inflammatory (reactive) changes and thus give rise to false-positive findings. Our findings confirm the presence of both false-negative and false-positive lymph nodes, which is consistent with a large multicenter study using stand-alone PET [34]. The sensitivity and specificity in our study were higher, and this may reflect the contribution of the CT component of PET–CT over PET-only scanners. Compared with a recent health technology assessment, our data showed similar accuracy in diagnosing axillary disease, with high specificity but limited sensitivity [34]. Although PET–CT is limited for axillary staging, a recent study showed that PET/CT may extend the use of sentinel lymph node biopsy over more invasive methods [35].

Generally, conventional imaging modalities such as whole-body CT and liver ultrasound are not routinely used in asymptomatic breast cancer patients with stage 1 or stage 2 disease [7, 36]. Given that the quoted incidence of detectable metastatic disease at the time of breast cancer diagnosis is ~4% [36, 37], then the rationale for such a strategy may be justified. However, the detection of anatomical changes using conventional cross-sectional imaging is less sensitive than the picomolar sensitivity of PET [3]. Moreover, whole-body PET–CT gives the potential of synergistic diagnostic performance by combining the spatial resolution of multidetector CT data with the metabolic sensitivity of PET. Our findings in patients with early breast cancer, along with PET–CT findings in patients with more advanced primary disease [19, 20], confirm that, in many cases, there is potential to change patient management.

In order to evaluate the usefulness of PET–CT for early breast cancer management, many factors need to be assessed. First, the true incidence of ^{18}F-FDG-PET–CT–detectable disease in various stages of primary breast cancer needs to be determined and systematically measured. Then, how this detection alters patient management, survival, and quality of life should be assessed. The anxiety caused by detecting foci of avidity that are later found to be benign should not be overlooked. It should also be appreciated that PET–CT staging may also give important prognostic information, for example, ^{18}F-FDG uptake has been shown to predict survival and angiogenesis in lung cancer patients [38–40]. This type of additional information is needed, but is limited in breast cancer. Second, the cost to patients of undergoing PET–CT needs to be assessed, such as radiation exposure and inconvenience. Finally, the cost of performing ^{18}F-FDG-PET–CT to the health service provider needs to be accurately calculated. These factors are complex, and much more data are needed than presently exist to perform a health technology assessment. There would appear to be need for a prospective, randomized, controlled study

such as the recent COMICE (comparative effectiveness of MRI in breast cancer) study that evaluated MRI staging [30].

Studies of the type undertaken here have inherent limitations. Breast cancer is a heterogeneous disease [1]. In this respect, we were able to obtain a relatively homogeneous cohort in terms of early disease, histology, and lack of presurgical neoadjuvant chemotherapy or radiotherapy. A larger patient population would have been helpful, but this would have significantly increased the recruitment and follow-up periods. It should be appreciated that it is much easier to confirm the presence of metastatic disease than to exclude it. Therefore, a longer follow-up period would have been ideal, but this should be balanced against the need to obtain data that are lacking in the current literature.

Conclusion

We present original prospective data on the use of ^{18}F-FDG-PET–CT in the staging of early breast cancer. In keeping with the limited literature on advanced primary breast cancer, PET–CT was shown to impact cancer management in 16% of patients with early primary breast carcinoma. Given that the current recommendations for primary breast cancer do not routinely advocate the use of PET–CT for staging, our findings highlight the recent call for a randomized, controlled trial to further investigate the role of PET–CT in breast cancer staging [4].

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