The Yield of ^{18}F-FDG PET/CT in Patients with Clinical Stage IIA, IIB, or IIIA Breast Cancer: A Prospective Study

David Groheux[1,2], Sylvie Giacchetti[3], Marc Espié[3], Laetitia Vercellino[1], Anne-Sophie Hamy[3], Marc Delord[4], Nathalie Berenger[1], Marie-Elisabeth Toubert[1], Jean-Louis Misset[3], and Elif Hindié[1,2]

[1]Department of Nuclear Medicine, Saint-Louis Hospital, Paris, France; [2]B2T, Doctoral School, IUH, University of Paris VII, Paris, France; [3]Department of Medical Oncology, Breast Diseases Unit, Saint-Louis Hospital, Paris, France; and [4]Department of Statistical Sciences, IUH, University of Paris VII, Paris, France

The purpose of this study was to prospectively evaluate the role of ^{18}F-FDG PET/CT in patients with stage IIA, IIB, or IIIA breast cancer. **Methods:** During 56 mo, 131 consecutive patients with large (>2 cm) breast cancer and clinical stage IIA, IIB, or IIIA (based on clinical examination, mammography, breast MRI, and ultrasonography) underwent ^{18}F-FDG PET/CT. The nuclear physician was unaware of the results of any other procedure (bone scan, chest radiography, liver ultrasound, or thoracoabdominal CT scan). **Results:** Of the 131 examined patients, 36 had clinical stage IIA (34 T2N0 and 2 T1N1), 48 stage IIB (20 T3N0 and 28 T2N1), and 47 stage IIIA (29 T3N1, 9 T2N2, and 9 T3N2). ^{18}F-FDG PET/CT modified staging for 5.6% of stage IIA patients, for 14.6% of stage IIB patients, and for 27.6% of stage IIIA patients. However, within stage IIIA, the yield was specifically high among the 18 patients with N2 disease (56% stage modification). When considering stage IIB and primary operable IIIA (T3N1) together, the yield of ^{18}F-FDG PET/CT was 13% (10/77); extraaxillary regional lymph nodes were detected in 5 and distant metastases in 7 patients. In this series, ^{18}F-FDG PET/CT outperformed bone scanning, with only 1 misclassification versus 8 for bone scanning ($P = 0.036$). **Conclusion:** ^{18}F-FDG PET/CT provided useful information in 13% of patients with clinical T3N0, T2N1, or T3N1 disease. The yield was more modest in patients with stage IIA. The high yield in the case of N2 disease demonstrates that stage IIIA comprises 2 quite distinct groups of patients.

Key Words: ^{18}F-FDG; PET/CT; bone scan; primary operable breast cancer; stage II breast cancer; stage IIIA breast cancer; work-up, initial staging

J Nucl Med 2011; 52:1526–1534
DOI: 10.2967/jnumed.111.093864

In patients with large but primary operable breast cancer, precise knowledge of the extent of disease is important for adequate management. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend a systematic work-up for operable invasive breast carcinoma including physical examination, bilateral mammogram, and ultrasound with or without breast MRI (*1*). In the case of operable stage IIIA (T3N1M0), additional imaging, including bone scanning (BS), abdominal ± pelvic CT (or ultrasound or MRI), and chest imaging, can optionally be used. ^{18}F-FDG PET or PET/CT are not recommended in current practice (*1*) but can be used in situations in which conventional imaging studies are equivocal or suggestive.

Some authors suggest that PET/CT can provide important information in patients with stage II or III breast carcinoma with the detection of unknown lymph nodes metastases outside axilla levels I and II (infraclavicular, supraclavicular, and internal mammary nodes) and the detection of occult distant metastases. However, most of these series mixed patients with stage II or IIIA carcinoma with others having inflammatory or locally advanced stages IIIB or IIIC breast cancer (*2–6*).

In this prospective study, we focused only on the role of ^{18}F-FDG PET/CT in stage IIA, IIB, and IIIA breast carcinoma. We examined the yield in each specific subgroup.

MATERIALS AND METHODS

This study was performed from May 2006 to December 2010 and enrolled 131 patients with biopsy-proven invasive breast cancer of ≥2 cm and clinical stage IIA (T2N0M0/T1N1M0), IIB (T3N0M0/T2N1M0), or IIIA (T3N1M0/T2N2M0/T3N2M0).

Clinical stage was established after physical examination, mammography, ultrasound of the breast and axilla, and breast MRI. T and N clinical scores were evaluated according to the American Joint Committee on Cancer (AJCC) classification (*7*). T scores were as follows: T1 ≤ 20 mm; 20 mm < T2 ≤ 50 mm; T3 > 50 mm; and T4, tumor of any size with direct extension to the chest wall or to the skin or inflammatory breast cancer. N scores were as follows: N1, metastases to movable ipsilateral level I or II axillary lymph nodes; N2, metastases in ipsilateral level I or II axillary lymph nodes that are clinically fixed or matted or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases; and N3, metastases in ipsilateral infraclavicular (level III axillary) or supraclavicular lymph nodes, or in clinically detected ipsilateral internal mammary lymph nodes with clinically evident axillary lymph node metastases.

After enrollment in this prospective study, all 131 patients underwent a conventional imaging work-up and ^{18}F-FDG PET/CT to search for distant metastases before any treatment.

Received May 30, 2011; revision accepted Jul. 14, 2011.
For correspondence or reprints contact: David Groheux, Service de Médecine Nucléaire, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, 1 Ave. Claude Vellefaux, 75475 Paris Cedex 10, France.
E-mail: dgroheux@yahoo.fr
Published online Aug. 30, 2011.

Exclusion criteria were previous history of breast or other cancer, uncontrolled diabetes mellitus, pregnancy, and age younger than 18 y. The study followed the guidelines of the institutional ethical committee. Most patients received neoadjuvant chemotherapy before surgery and patient-tailored adjuvant treatment.

Conventional Staging

To rule out distant metastases, conventional imaging was performed according to routine practice in our institution (and current practice in France) and comprised BS in all patients, chest examination by radiography or contrast-enhanced CT (CE-CT), and abdominal and pelvic examination by ultrasound or CE-CT.

^{18}F-FDG PET/CT

None of the 131 patients in this series received breast surgery, chemotherapy, or radiotherapy before PET/CT examination. Patients fasted for 6 h. Blood glucose level had to be less than 7 mmol/L. Five megabecquerels of ^{18}F-FDG per kilogram were intravenously injected in the arm opposite to the tumor using a venous line to prevent extravasation. Imaging was performed 60 min after the injection on a PET/CT scanner (Gemini XL; Philips), combining germanium oxyorthosilicate–based PET and 16-slice Brilliance CT components. Patients were allowed to breathe normally. CT and PET data were acquired from mid-thigh level to the base of the skull with the arms raised. No oral or intravenous contrast was used. PET emission counts were collected over 2 min per table position, acquired in a 3-dimensional mode, and reconstructed using a 3-dimensional row-action maximum likelihood algorithm.

PET/CT Interpretation and Staging

PET/CT scans were interpreted by 2 nuclear medicine specialists who had no knowledge of the results of conventional imaging. If the interpretation differed, consensus was reached with the help of a third reader.

Lymph nodes were evaluated in a way similar to the method described by Heusner et al. (*8*). The readers relied on visual assessment of PET images (a well-defined focus, with uptake clearly higher than surrounding background). The location of hypermetabolic lymph nodes on the PET/CT image was noted according to the AJCC seventh classification (*7*). Different areas were considered as follows:

- The axillary area was divided into 3 levels: level I (low axilla), lymph nodes lateral to the lateral border of the pectoralis minor muscle (intramammary lymph nodes were also considered as axillary level I); level II (mid axilla), lymph nodes between the medial and lateral borders of the pectoralis minor muscle (this level also includes the interpectoral [Rotter's] lymph nodes); and level III (apical axilla), lymph nodes medial to the medial margin of the pectoralis minor muscle and inferior to the clavicle (also known as infraclavicular nodes).
- Internal mammary basin.
- Supraclavicular area.

When easily accessible, a biopsy was performed on suspected lymph nodes to confirm involvement.

For distant metastases, form and intensity of ^{18}F-FDG uptake and CT findings were considered altogether. Bone evaluation was performed as described by Nakamoto et al. (*9*). ^{18}F-FDG uptake corresponding to degenerative findings on the underlying CT scan (e.g., on facet articulation) and uptake in a rib fracture in a patient with a history of trauma were considered nonsuggestive. However, high uptake on a classic area of metastasis (e.g., body of a vertebra, pedicle, long bone) was considered malignant even if the CT part showed subtle or no changes, in agreement with the well-known high sensitivity of ^{18}F-FDG PET, compared with CT, for early bone marrow involvement (*9*). For lung evaluation, we considered as suggestive any pulmonary nodules with high ^{18}F-FDG uptake or the presence of multiple small angiocentric nodules on the CT part (even in the absence of an increase in ^{18}F-FDG uptake on attenuation-corrected images). ^{18}F-FDG uptake in the thyroid gland was not considered suggestive of metastasis (but consistent with thyroid nodules or thyroiditis based on the pattern of uptake, whether focal or diffuse). ^{18}F-FDG uptake in an ovary (often representing inflammation after ovulation), or in the uterine cavity, was interpreted according to the timing of the cycle. Diffuse uptake in the bowel tract and brown fat artifacts were also considered benign patterns.

Modification in Staging and in Treatment Planning According to PET/CT

^{18}F-FDG PET/CT findings considered suggestive of malignancy were assessed using surgery, biopsy results, or patient follow-up. For bone foci, MRI was performed instead of biopsy. ^{18}F-FDG PET/CT was not used for the local evaluation of the breast tumor because previous reports demonstrated that PET/CT is suboptimal in comparison to breast MRI (*10*). We considered modification of stage resulting from findings of distant metastasis or lymph node involvement outside classic areas of axillary dissection, with an impact on treatment management.

Statistical Methods

Modifications resulting from PET/CT were evaluated separately for each of the 3 clinical groups (stages IIA, IIB, and IIIA) but also within the subsets of stage IIIA (primary operable T3N1 vs. T2/3N2 disease). A χ^2 test for trends in proportions was performed to test whether modifications in initial staging with PET/CT increased along within the different substages. Staging using ^{18}F-FDG PET/CT was compared with that of the conventional BS approach. We used an exact Fisher test to compare number of misclassified patients for each approach (PET/CT and BS). A *P* value of less than 0.05 was considered statistically significant. Analyses were performed using R 2.12.0 statistical software (The R Foundation for Statistical Computing).

RESULTS

Patient and tumor characteristics are outlined in Table 1.

Stage IIA

Thirty-six patients had clinical stage IIA (34 T2N0M0 and 2 T1N1M0). All primary tumors had clear-cut ^{18}F-FDG uptake (median maximum standardized uptake value [SUVmax], 5.8; range, 1.5–18.8), except in 1 case (a 30-mm, grade 2 invasive ductal carcinoma). The 2 women clinically classified N1 (T1N1M0) had uptake in axillary nodes.

^{18}F-FDG PET/CT upstaged 2 patients (5.5%). Uptake in an internal mammary lymph node (SUVmax, 2.3) was depicted in 1 patient, leading to internal mammary radiation therapy (Fig. 1, upper). The other patient showed

TABLE 1
Patient Demographics and Tumor Characteristics

Characteristic	No. of patients (total n = 131)
AJCC clinical stage and TNM	
IIA	36 (27)
T1N1M0	2
T2N0M0	34
IIB	48 (37)
T2N1M0	28
T3N0M0	20
IIIA	47 (36)
T2N2M0	9
T3N1M0	29
T3N2M0	9
Tumor type	
Invasive ductal carcinoma	114 (87)
Invasive lobular carcinoma	8 (6)
Others	9 (7)
Grade	
1	9 (7)
2	65 (50)
3	53 (40)
Unknown	4 (3)
Estrogen receptor status*	
Positive	82 (63)
Negative	46 (35)
Unknown	3 (2)
Progesterone receptor status*	
Positive	42 (32)
Negative	85 (65)
Unknown	4 (3)
HER2 status	
Positive	30 (23)
Negative	96 (73)
Unknown	5 (4)

*Tumors were considered positive for estrogen receptor or progesterone receptor if >10% of cells showed staining by immunohistochemistry.

Data in parentheses are percentages. Median age of patients was 48 y (range, 26–81 y).

^{18}F-FDG uptake in contralateral supraclavicular lymph nodes (biopsy-confirmed involvement) and mediastinal lymph nodes (confirmed by chest CE-CT). This patient was upstaged to stage IV (distant nodal metastases), and treatment was adapted to the metastatic disease.

^{18}F-FDG PET/CT depicted a primary lung carcinoma in 1 patient.

Stage IIB

Forty-eight patients had clinical stage IIB (20 T3N0 and 28 T2N1). All primary tumors were ^{18}F-FDG–avid (median SUVmax, 7.25; range, 2.2–29). Among the 28 patients who were clinically node-positive, 21 had ^{18}F-FDG uptake in axillary nodes, whereas in 7 patients (25%), PET/CT could not depict nodal involvement.

^{18}F-FDG PET/CT changed staging in 7 patients (14.6%). Internal mammary uptake was seen in 2 patients, initially classified T2N1. These patients were upstaged to N3b (stage IIIC). In another patient, PET/CT depicted an infra-mammary lymph node. ^{18}F-FDG uptake suggestive of distant metastasis was seen in 4 women: 1 with a single liver metastasis, 1 with a solitary pulmonary metastasis, 1 with multiple lung nodules with ^{18}F-FDG uptake and a faint bone focus, and 1 with a bone marrow femoral metastasis (confirmed by MRI).

Stage IIIA

Forty-seven patients had clinical stage IIIA (29 T3N1, 9 T2N2, and 9 T3N2). The primary tumor showed ^{18}F-FDG uptake in 46 cases (median SUVmax, 6.85; range, 1.4–25.9), and no uptake was present in 1 case (a 40-mm, grade 2 invasive lobular carcinoma). In 8 of the 47 patients (17%), PET/CT was unable to detect axillary involvement.

^{18}F-FDG PET/CT changed staging in 13 patients (27.6%). PET/CT revealed N3 lymph nodes (infra- or supraclavicular or internal mammary) in 7 patients (15%) and uptake suggestive of distant metastases in 10 patients (21%) (Fig. 1, lower); 4 of the patients also had N3 lymph nodes. Sites of involvement in the 10 patients with distant lesions were bone (n = 9), liver (n = 2), lung (n = 3), and pleural effusion (n = 1). Chemotherapy was adapted to the metastatic diseases, and some bone lesions were treated by radiation therapy.

Within stage IIIA, the yield was quite different between patients with T3N1 (3/29) and those with N2 disease (10/18; P = 0.0256).

Differences in Yield Between Stages

There were no differences in the yield of ^{18}F-FDG PET/CT between stage IIB and primary operable stage IIIA (T3N1) patients (7/48 vs. 3/29; P = 0.739). Therefore, these 2 groups were merged (Table 2). The overall yield of ^{18}F-FDG PET/CT in patients with stage IIB plus primary operable IIIA (T3N1) was 13% (10/77). In this group, extraaxillary lymph nodes were evidenced in 5 patients and distant metastases in 7 (2 patients had distant metastases and internal mammary nodes).

In conclusion, PET/CT changed staging, with impact on therapeutic management in 5.5% (2/36) of stage IIA patients, in 13% (10/77) of stage IIB plus primary operable stage IIIA patients, and in 56% (10/18) of patients with stage IIIA due to N2 disease (Table 2). The χ^2 test for trend in proportions showed that the PET/CT yield gets higher along these 3 subgroups ($P < 0.0001$).

PET/CT Versus Chest Imaging

All lung nodules and mediastinal lymph nodes detected by chest imaging were also depicted by PET/CT (Table 3). Nevertheless, multiple small nodules in 2 patients of stage IIIA were considered metastases on the basis of the CT part of PET/CT, despite the absence of ^{18}F-FDG uptake. Both these women had additional bone involvement with ^{18}F-FDG uptake. Finally, ^{18}F-FDG PET corrected the diagnosis in 1 patient who had isolated pleural effusion, which was considered benign on CE-CT. However, the PET/CT scan

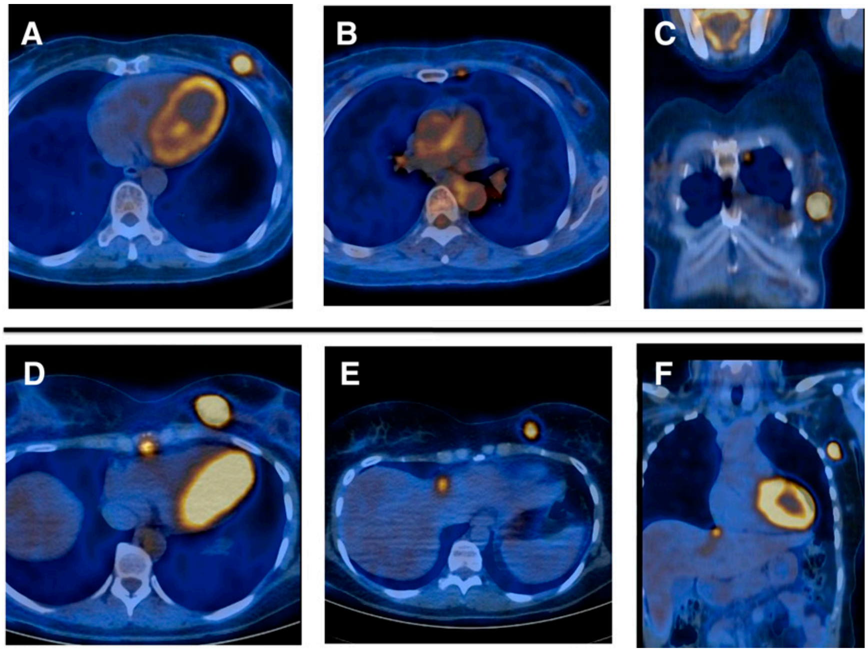

FIGURE 1. ^{18}F-FDG-PET/CT results at initial staging in 2 patients. (A–C) Patient with 40-mm invasive ductal carcinoma of left breast, with clinical T2N0 (stage IIA) disease; ^{18}F-FDG PET/CT shows uptake in primary tumor (A) and evidences internal mammary lymph node (B and C). After PET/CT, cancer was classified T2N2bM0 (stage IIIA). Radiotherapy planning was modified according to PET/CT results to encompass internal mammary basin. (D–F) Patient with 52-mm invasive ductal carcinoma of left breast and movable axillary lymph node (T3N1; clinical stage IIIA). ^{18}F-FDG PET/CT shows uptake in primary tumor (D and E), axillary lymph node (F), and distant metastases to the sternum (D) and liver (E and F). After PET/CT, cancer was classified stage IV. Treatment was adapted to metastatic disease.

showed high ^{18}F-FDG nodular uptake in the effusion, which was interpreted as metastasis and later confirmed by pleural aspiration as malignant.

PET/CT Versus Abdominopelvic Examination

All hepatic metastases detected by ultrasound or CE-CT were also evidenced by PET/CT (Table 3). Moreover, PET/CT helped settle the origin of equivocal liver findings on conventional imaging in 2 patients: one patient from the clinical stage IIB group with a suggestion of hepatic metastasis on CE-CT for whom ultrasound had concluded it was an angioma and another patient for whom CT showed suggestive peritoneal nodules whereas ultrasound and MRI concluded they were accessory spleen nodules. In both cases, PET/CT showed no ^{18}F-FDG uptake, and follow-up confirmed absence of metastases.

PET/CT Versus BS

^{18}F-FDG PET/CT revealed true-positive bone metastases in 11 patients; BS revealed metastases in only 7 (64%) (Table 3). In all 4 patients with negative bone scan results, MRI and follow-up confirmed bone involvement. Two of these 4 women had additional visceral metastases.

Four patients had negative PET/CT results but positive bone scan findings. However, MRI and follow-up concluded that these scan findings were false-positive and due

TABLE 2
Findings with ^{18}F-FDG PET/CT in 3 Different Groups

Characteristic	Stage IIA (n = 36; 34 T2N2 and 2 T1N1)	Stage IIB and primary operable IIIA (n = 77; 20 T3N0, 28 T2N1, and 29 T3N1)	Stage IIIA with N2 disease (n = 18; 9 T2N2 and 9 T3N2)
Overall stage modifications	2 (5.5)	10 (13)	10 (56)
Lymph nodes outside Berg-I and Berg-II axillary levels (% patients)	1 (2.8)	5 (6.5)	5 (27.8)
Internal mammary involvement	1	4	2
Infraclavicular	0	1	3
Supraclavicular	0	0	2
Distant metastases	1 (2.8)	7 (9.1)	7 (38.9)
Bone metastases	0	4	7
Liver metastases	0	2	1
Lung metastases	0	3	2
Other distant metastases	1 (mediastinal lymph node)	0	1 (pleura)

Total number of patients was 131: 36 (27%) stage IIA; 77 (59%) stage IIB plus primary operable IIIA; and 18 (14%) stage IIIA due to N2 disease. Data in parentheses are percentages. Results are expressed on per-patient basis.

TABLE 3
Performance of Conventional Imaging Versus PET/CT in Depicting Distant Metastases in Overall Series of 131 Patients

Type of imaging	Lung metastases	Liver metastases	Bone metastases	Other distant metastases
Total*	5	3	11	2
Chest (chest radiography or CE-CT)	5	—	—	1 (mediastinal lymph node†)
Abdominal (ultrasonography or CE-CT ± MRI)	—	2	—	—
BS	—	—	7	—
PET/CT	5‡	3	11	2 (mediastinal lymph node and pleura)

*Some women had distant metastases in different viscera; overall, 15 patients had metastases.
†Mediastinal lymph nodes were detected by CE-CT but not with chest radiography.
‡In 2 women, lung metastases had no ^{18}F-FDG uptake and were detected only by CT part of PET/CT hybrid imaging.
Results are expressed on per-patient (not per-lesion) basis.

to benign osteoarticular lesions. On the other hand, PET/CT yielded 1 false-positive result: a woman with a T3N1 breast cancer had low ^{18}F-FDG uptake on the body of a dorsal vertebra, which was analyzed as suggestive of bone metastasis. BS was negative, and follow-up confirmed the absence of bone metastasis.

Finally, our data show that PET/CT outperformed BS in adequately classifying patients, leading only to 1 misclassification versus 8, respectively ($P = 0.036$).

DISCUSSION

Some authors suggested that PET/CT can provide important information in patients with stage II or III breast carcinoma (Table 4). However, most of these series mixed primary operable stage II or IIIA carcinoma with other patients having inflammatory or locally advanced stage IIIB or IIIC breast cancer (*2–6*).

We performed PET/CT in 131 consecutive breast cancer patients who were classified as having stage IIA, IIB, or IIIA after primary evaluation with physical examination, mammography, ultrasound of the breast and axilla, and breast MRI. Because of the study design, stage IIA was mostly limited to T2N0 patients (only 2 patients had T1N1). We found additional results with a potential impact on management in 2 of 36 patients (5.5%) with stage IIA, in 7 of 48 patients (14.6%) with stage IIB, and in 13 of 47 patients (27.6%) with stage IIIA. However, within stage IIIA, the yield was specifically high among patients with N2 disease (56%), whereas the yield for patients with primary operable stage IIIA (T3N1) was similar to that of stage IIB patients. When patients with stage IIB and those with primary operable IIIA (T3N1) are considered together, the yield of ^{18}F-FDG PET/CT was 13% (10/77).

PET/CT has little role in assessing T score and multifocality of the breast tumor. ^{18}F-FDG PET/CT also cannot replace axillary dissection or sentinel node biopsy in assessing the axilla in clinical N0 patients (*10,11*). Across 26 studies evaluating PET or PET/CT ($n = 2{,}591$ patients), mean sensitivity was only 63% (*12*). In the present series, some axillary nodal disease depicted by clinical examination or ultrasound was not evidenced on ^{18}F-FDG PET/CT. Besides partial-volume effect, affecting the detection of small tumor deposits, other factors may influence sensitivity. We and others have reported that low tumor grade, estrogen receptor positivity, or lobular carcinoma histology are factors associated with lower ^{18}F-FDG uptake in breast cancer (*13*).

However, findings on ^{18}F-FDG PET/CT scans of regional nodal involvement outside the Berg-I and Berg-II axillary levels traditionally cleared during axillary dissection can affect prognosis and management. ^{18}F-FDG uptake in infraclavicular, supraclavicular, or internal mammary nodes was frequent in our study (Table 2). Our results are in agreement with the results of other series (*2–6,13–15*). It is well known that N3 nodal involvement (stage IIIC) confers poor prognosis (*7*). Detection of extraaxillary lymph nodes may also have a major impact on the locoregional treatment, for example, by defining the target volume for radiotherapy or the extent of the surgical clearance (*2,5*).

Several studies showed PET/CT is useful for detecting occult distant metastases (*2–4,6,14–16*). In our study, all metastatic patients detected by BS were evidenced by PET/CT. Four additional cases were PET/CT-positive and BS-negative. These patients had bone marrow involvement or lytic metastases. Our results are in agreement with the retrospective study from Morris et al. (*17*). Among 163 women, 18 were PET/CT-positive and BS-negative: biopsy and follow-up showed that most of these women had bone metastases. The authors concluded that BS may be avoided in patients undergoing PET/CT (*17*). Other teams advised performing BS in addition to ^{18}F-FDG imaging; they noted that ^{18}F-FDG PET suffers from limited sensitivity in detecting purely sclerotic bone metastases (*18,19*). Yet osteoblastic metastases are visible most of the time on the CT part of PET/CT (even in the absence of ^{18}F-FDG uptake). Our data show that PET/CT outperformed BS in adequately classifying patients, leading to only 1 misclassification versus 8, respectively ($P = 0.036$). However, most of the examina-

TABLE 4
Studies Evaluating ^{18}F-FDG PET/CT for Breast Cancer Staging

Study							Impact of PET/CT results (% per-patient basis)			
Reference	Year	Type	Setting	No. of patients	PET/CT modality	Conventional imaging (modalities performed)	Detection of unknown extraaxillary node metastases	Detection of unsuspected distant metastases	Modification in initial staging	Modification in treatment plan
Groheux et al. (*2*)	2008	Prospective	Stage II or III breast cancer	39	Whole-body PET performed approximately 60 min after ^{18}F-FDG injection; low-dose NE-CT	Mammography (± breast MRI), breast ultrasonography, abdominal ultrasonography (± abdominal CT), chest radiography, or CT, and BS	8	10	18	13
Heusner et al. (*3*)	2008	Retrospective	T1–T3 N0–N+ M0–1 breast cancer	40	Whole-body PET performed approximately 60 min after ^{18}F-FDG injection + additional breast PET acquired 110 min after injection; CE-CT and oral contrast	Breast MRI, axilla ultrasonography, chest radiography, abdomen ultrasonography, and BS	7.5	7.5	NA	12.5
Fuster et al. (*4*)	2008	Prospective	Large (T > 3 cm) and noninflammatory breast cancer	60	Whole-body PET performed approximately 60 min after ^{18}F-FDG injection; NE-CT	Breast MRI, chest CE-CT, liver ultrasonography, and BS	5	8.5	42*	6.5
Yang et al. (*14*)	2008	Retrospective	Inflammatory breast cancer	24	Whole-body PET performed approximately 60–90 min after ^{18}F-FDG injection; NE-CT	Mammography, breast ultrasonography, and MRI	25	38	NA	NA

TABLE 4 (Continued)

Study							Impact of PET/CT results (% per-patient basis)			
Reference	Year	Type	Setting	No. of patients	PET/CT modality	Conventional imaging (modalities performed)	Detection of unknown extraaxillary node metastases	Detection of unsuspected distant metastases	Modification in initial staging	Modification in treatment plan
Carkaci et al. (*15*)	2009	Retrospective	Inflammatory breast cancer	41	Whole-body PET performed approximately 60–90 min after ^{18}F-FDG injection; NE-CT	Mammography, breast ultrasonography or MRI, BS, chest radiography, chest and abdominal CT	SC (15%); IM (22%)	17	NA	NA
Alberini et al. (*16*)	2009	Prospective	Inflammatory breast cancer	59	Whole-body PET performed approximately 60 min after ^{18}F-FDG injection; low-dose NE-CT	Chest radiography, abdominal ultrasonography, BS; if necessary, additional CT investigations were performed	56†	31	NA	NA
Aukema et al. (*5*)	2010	Prospective	Stage II–III breast cancer	60	Whole-body PET performed approximately 60 min after ^{18}F-FDG injection + additional PET of thorax (including breasts and axillae) with patient prone; low-dose NE-CT	Mammography, breast ultrasonography, and breast MRI	17	NA	17	12
Segaert et al. (*6*)	2010	Retrospective	Stage IIB–III breast cancer	70	Whole-body PET performed 75 min after ^{18}F-FDG injection; CE-CT performed during breath-hold at expiration tidal volume	Chest radiography, liver ultrasonography, BS, and breast and axilla ultrasonography	13 (IM)	10	NA	NA

*High percentage of modification in this study can be explained by detection of axillary infiltrated nodes (17%), and PET findings downstaged 12% of patients with suspected metastases on conventional imaging.

†Some retropectoral nodes were considered extraaxillary.

NE-CT = nonenhanced CT; SC = supraclavicular area; IM = internal mammary basin; NA = not available (not stated).

tions were performed with a planar bone scan (not with a SPECT/CT scan). Another limitation of our results is that not all ^{18}F-FDG–avid bone foci were biopsied. In the AJCC staging, imaging is sufficient to classify patients as stage IV (distant metastases) when biopsy is not easy to perform (*7*).

Regarding the pulmonary parenchyma, PET efficiently detects supracentimetric pulmonary nodules. However, because of the partial-volume effect and respiratory movements, PET lacks sensitivity for smaller nodules. In our series, multiple small nodules were considered as metastases even without ^{18}F-FDG uptake. PET/CT obviously had improved sensitivity in comparison to stand-alone PET; nevertheless, free-breathing CT is less efficient than standard diagnostic thoracic CT.

In early experience with PET-alone imaging, positive predictive value was low. Now PET/CT allows for better accuracy. There is also now a progressive shift toward the use of CT contrast agents during PET/CT. The use of contrast agents can further improve PET/CT performance (*3,20*).

NCCN experts recommend against the use of PET or PET/CT in stage II or in stage IIIA primary operable (T3N1) breast cancer. PET/CT can be used if findings at conventional imaging are equivocal. The recommendations against the use of PET are supported by several findings: the high false-negative rate in the detection of breast tumors that are small ($<$1 cm) or of low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability that these patients have detectable metastatic disease, and the high rate of false-positive scan findings. NCCN does not differentiate between PET and PET/CT.

In the present series, all the lesions detected by the conventional imaging approach were also detected with ^{18}F-FDG PET/CT, which showed additional lesions. PET/CT had the clear advantage of examining chest, abdomen, and bone in a single session. Our study shows that ^{18}F-FDG PET/CT has a nonnegligible yield in patients with stage IIB and primary operable stage IIIA. In these patients with T3N0, T2N1, or T3N1 disease, the overall yield was 13%, with a substantial change in management (findings of N3 disease or distant disease). In our series, the yield of PET/CT was quite different between patients with T3N1 (3/29) and patients with N2 disease (10/18). This finding is in agreement with therapeutics recommendations from NCCN experts who segregate stage IIIA into 2 different subgroups: T3N1 patients for whom recommendations are similar to the stage II group and patients with clinical N2 disease for whom recommendations are similar to stage IIIB and IIIC locally advanced breast carcinoma.

CONCLUSION

^{18}F-FDG PET/CT might be helpful in patients with stage IIB and primary operable stage IIIA, in essence, in patients with T3N0, T2N1, or T3N1, modifying stage by finding N3 disease or distant metastases in 13% of patients. These results, if confirmed by other series, might call for a reevaluation of the current NCCN guidelines. However, future prospective studies should also include an evaluation of the cost effectiveness. Other staging examinations (bone scanning, liver ultrasound, chest radiography, or thoracoabdominal CT) are probably less helpful when ^{18}F-FDG PET/CT is performed.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

ACKNOWLEDGMENTS

Professor Jean-Luc Moretti, head of the Department of Nuclear Medicine, passed away on December 21, 2010. This work is dedicated to him. Part of this study was presented at the Society of Nuclear Medicine 2011 annual meeting, Henry B. Gonzalez Convention Center, San Antonio, Texas, June 4–8, 2011. No potential conflict of interest relevant to this article was reported.

REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2. 2011. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
2. Groheux D, Moretti J, Baillet G, et al. Effect of ^{18}F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. *Int J Radiat Oncol Biol Phys.* 2008;71:695–704.
3. Heusner TA, Kuemmel S, Umutlu L, et al. Breast cancer staging in a single session: whole-body PET/CT mammography. *J Nucl Med.* 2008;49:1215–1222.
4. Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol.* 2008;26:4746–4751.
5. Aukema TS, Straver ME, Peeters MTFDV, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. *Eur J Cancer.* 2010;46:3205–3210.
6. Segaert I, Mottaghy F, Ceyssens S, et al. Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. *Breast J.* 2010;16:617–624.
7. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
8. Heusner TA, Kuemmel S, Hahn S, et al. Diagnostic value of full-dose FDG PET/CT for axillary lymph node staging in breast cancer patients. *Eur J Nucl Med Mol Imaging.* 2009;36:1543–1550.
9. Nakamoto Y, Cohade C, Tatsumi M, et al. CT appearance of bone metastases detected with FDG PET as part of the same PET/CT examination. *Radiology.* 2005;237:627–634.
10. Groheux D, Hindié E, Rubello D, et al. Should FDG PET/CT be used for the initial staging of breast cancer? *Eur J Nucl Med Mol Imaging.* 2009;36:1539–1542.
11. Hindié E, Groheux D, Brenot-Rossi I, et al. The sentinel node procedure in breast cancer: nuclear medicine as the starting point. *J Nucl Med.* 2011;52:405–414.
12. Cooper KL, Harnan S, Meng Y, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. *Eur J Surg Oncol.* 2011;37:187–198.
13. Groheux D, Giacchetti S, Moretti JL, et al. Correlation of high ^{18}F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. *Eur J Nucl Med Mol Imaging.* 2011;38:426–435.
14. Yang WT, Le-Petross HT, Macapinlac H, et al. Inflammatory breast cancer: PET/CT, MRI, mammography, and sonography findings. *Breast Cancer Res Treat.* 2008;109:417–426.

15. Carkaci S, Macapinlac HA, Cristofanilli M, et al. Retrospective study of ^{18}F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data. *J Nucl Med.* 2009;50:231–238.
16. Alberini J, Lerebours F, Wartski M, et al. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. *Cancer.* 2009;115:5038–5047.
17. Morris PG, Lynch C, Feeney JN, et al. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. *J Clin Oncol.* 2010;28:3154–3159.
18. Nakai T, Okuyama C, Kubota T, et al. Pitfalls of FDG-PET for the diagnosis of osteoblastic bone metastases in patients with breast cancer. *Eur J Nucl Med Mol Imaging.* 2005;32:1253–1258.
19. Schirrmeister H. Detection of bone metastases in breast cancer by positron emission tomography. *Radiol Clin North Am.* 2007;45:669–676.
20. Dirisamer A, Halpern BS, Flöry D, et al. Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer. *Eur J Radiol.* 2010;73:294–299.