Performance of FDG PET/CT in the Clinical Management of Breast Cancer

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In this analysis, the role of metabolic imaging with fluorine 18 fluorodeoxyglucose (FDG) in breast cancer is reviewed. The analysis was limited to recent works by using state-of-the-art positron emission tomography (PET)/computed tomography (CT) technology. The strengths and limitations of FDG PET/CT are examined in various clinical settings, and the following questions are answered: Is FDG PET/CT useful to differentiate malignant from benign breast lesions? Can FDG PET/CT replace sentinel node biopsy for axillary staging? What is the role of FDG PET/CT in initial staging of inflammatory or locally advanced breast cancer? What is the role of FDG PET/CT in initial staging of clinical stage II A and II B and primary operable stage III A breast cancer? How does FDG PET/CT compare with conventional techniques in the restaging of cancer in patients who are suspected of having disease recurrence? What is the role of FDG PET/CT in the assessment of early response to neoadjuvant therapy and of response to therapy for metastatic disease? Some recommendations for clinical practice are given.

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Positron emission tomography (PET) with fluorine 18 ($^{18}$F) fluorodeoxyglucose (FDG) has an important role in oncology. Its role in the management of breast cancer patients is evolving. These past years, combined PET and computed tomography (CT) (PET/CT) systems have replaced PET alone in most nuclear medicine departments. The CT portion of PET/CT provides the anatomic information useful for accurate interpretation of PET signal. It also provides a map used for attenuation correction of PET images. It also palliates the low sensitivity of PET for very small pulmonary nodules. It is now widely accepted that the performance of FDG PET/CT is better than the performance of FDG PET alone in oncology, although the added value might differ according to the clinical situation (1–3).

In this review, we examine the principles of this hybrid imaging approach, focusing on breast imaging. Then, we assess the advantages and limits of FDG PET/CT at diagnosis, initial staging, follow-up, and evaluation of response to therapy in breast cancer.

### Essentials
- Combined PET/CT is more sensitive and specific than either of its constituent imaging methods; it facilitates distinguishing normal physiologic uptake from pathologic FDG uptake, allows accurate localization of functional abnormalities, and reduces the incidence of false-positive and false-negative results of imaging studies.
- The factors that influence FDG uptake by breast tumors have an implication on how to interpret FDG PET/CT scans and who is the appropriate patient for imaging.
- FDG PET/CT is not part of current recommendations for initial staging in breast cancer patients; however, there is mounting evidence that, in high-risk patients, results of this examination may be used to modify staging and management in a substantial percentage of patients.
- On the basis of analysis of current literature, FDG PET/CT should be the first whole-body imaging modality used for restaging in breast cancer patients with known recurrence or those who are suspected of having recurrence.
- FDG PET/CT is emerging as a promising tool for early monitoring of the effectiveness of neoadjuvant chemotherapy; however, there are substantial disparities in regard to the way assessment of response is performed, with the need for standardization, and moreover, rules should be defined for each specific subtype of breast cancer (triple-negative breast cancer, HER2-overexpressing tumors, estrogen receptor–positive cancer).

### Principles of FDG PET/CT

Imaging usually starts 60 minutes after the intravenous injection of FDG. CT and PET data are acquired sequentially before being fused. The patient is instructed to avoid movement. Patients are imaged from the base of the skull to the midthigh, except for specific situations.

Imaging usually begins with the CT acquisition. Questions remain as to whether the CT part of PET/CT should be performed as contrast material–enhanced full-dose diagnostic CT or as nonenhanced, low-dose CT, with additional focused segmental examination in case of inconclusive findings. Some technical constraints imposed by the PET component, such as free breathing, might limit the full diagnostic power of CT when performed as part of PET/CT imaging.

$^{18}$F is a positron-emitting (β+) radionuclide. PET detects the dual-photons emitted in opposite directions following positron annihilation. The half-life of $^{18}$F is 110 minutes. Most malignant breast tumors overexpress glucose transporters (especially glucose transporter 1 and glucose transporter 3) and show increased hexokinase activity (4,5). After being phosphorylated by the hexokinase, FDG does not continue along the glycolysis pathway and remains trapped within cancer cells.

Modern whole-body PET systems typically have a reconstructed spatial resolution of 5–6 mm full width at half maximum, on the basis of phantom measurements. In clinical practice, however, reconstructed resolution is close to 10 mm. Small tumor foci and micrometastases cannot therefore be detected. However, detection depends not only on tumor size but also on the degree of FDG avidity, tumor-to-background ratio, effect of motion (respiration), et cetera. A smaller than 1 cm lesion can be detected when conditions are favorable.

Tumor FDG uptake can be expressed by using a so-called standardized uptake value (SUV). This index reflects the degree of FDG uptake within a volume of interest. It is calculated on the basis of the amount of activity injected and the patient’s body mass, as follows: SUV = $A_{\text{max}}$/(A_inj/W), where $A_{\text{max}}$ is the measured activity in the volume of interest in kilobecquerels per milliliter, A_inj is the injected activity in kilobecquerels, and W is the body weight of the patient in grams (6).

There are many other ways to measure FDG uptake, as well as other expressions for SUVs with calculations that are based on body surface area or lean body mass or with use of modifiers (eg, correction for blood glucose level). They are, however, less used in clinical practice.

The question remains open on whether 60 minutes after injection is the optimal timing for FDG PET/CT imaging. No optimal time has been defined in the literature. Uptake in breast tumors continues to increase beyond 60 minutes (6,7). Nevertheless, this time is widely used and has the advantage of simplicity.
What is most important within a given institution is to constantly adopt the same time delay after injection. The delay used at baseline imaging should be reproduced if the patient is referred for response evaluation. Some authors developed methods to make appropriate time corrections for tumor SUVs (6,7).

This pattern of dependence of SUV on the delay after injection has been well studied in untreated tumors (6,7), not for posttherapy measurement. Also, when clinicians perform SUV measurements for response evaluation, they should remember that there is a risk of underestimation of SUV values with PET instruments when the residual tumor is too small (partial volume effect). The time delay between the last chemotherapy use and FDG imaging might also influence response assessment.

FDG Uptake of Breast Cancer Depends on the Histologic and Biologic Characteristics of the Tumor

For a given tumor size, infiltrating ductal carcinoma has higher FDG uptake than infiltrating lobular carcinoma (4,8–12). The uptake in ductal carcinoma in situ is usually weak (8).

FDG uptake intensity correlates with breast cancer grade (8,13–16). There is also a correlation between the tumor proliferation index (Ki67 expression measured by using immunohistochemical analysis) and the intensity of FDG uptake (4,8,9,15).

There have been contradictory reports on steroid hormone receptor status and FDG uptake. Some studies showed no correlation between hormone receptor status and SUV values (9,10,13,15,17). However, recent series with a large number of patients showed higher SUV in estrogen receptor–negative tumors (8,14,18–20). Except for one study (21), most authors have found no correlation between FDG uptake and HER2/neu expression (8,9,14,15,18). Triple-negative breast tumors (negative for estrogen and progesterone receptors, and no HER2/neu overexpression) are currently a subject of major interest because of their aggressiveness, poor prognosis, and lack of targeted therapy.

In a study by Basu and colleagues (22), tumors with a triple-negative phenotype had a higher FDG uptake.

Breast cancers with a p53 mutation were repeatedly shown to be associated with poorer patient outcome. A positive correlation between FDG uptake intensity and p53 status has been found in three studies (8,11,14), but not in a fourth (9).

We prospectively studied the relationship between tumor characteristics and the SUV in 132 women with breast tumors greater than 20 mm (median, 51 mm; range, 21–140 mm) (23). It was clear that FDG uptake in the primary tumor correlated with several factors known to confer poorer prognosis. Thus, the uptake of FDG was, on average, twice as high for grade 3 tumors compared with grade 1 and 2 tumors (median maximum SUV [SUVmax], 9.7 vs 4.8; \( P < .0001 \)) (Fig 1a); it was also higher for breast cancer with a p53 mutation. Estrogen receptor–negative tumors were more FDG-avid than estrogen receptor–positive tumors. Similarly, FDG uptake was higher in progestrone receptor–negative tumors than in progesterone receptor–positive tumors. Breast cancers with a triple-negative phenotype had a significantly higher SUV than did others (median SUVmax, 9.2 vs 5.8; \( P = .0005 \)) (Fig 1b).

Considering histologic tumor type, we confirmed lower tumoral uptake in 15 patients with invasive lobular carcinoma (median SUVmax, 3.4) compared with the 107 patients with invasive ductal carcinoma (median SUVmax, 6.6). We further showed that seven patients with metaplastic breast cancer, a less common variety, had a very high FDG uptake (median SUVmax, 12.9) (23).

FDG PET/CT Has Little Role in Differentiating Benign from Malignant Breast Lesions

FDG PET imaging has poor sensitivity for infiltrative tumors (sensitivity of <50% in some studies) (13). This is explained by the limited spatial resolution of PET and, in some cases, by tumor characteristics (eg, low FDG avidity in grade 1 cancer and/or in lobular carcinoma) (12,13). Specificity can also be altered. Although rare, FDG uptake in some benign tumors, such as fibroadenomas, has been described (24). High uptake is possible in inflammatory granulomatous mastitis (25).

The CT part of PET/CT has no additional value in this setting: It can eventually allow detection of a breast mass, but CT (especially nonenhanced CT) is
To improve specificity, some authors would obtain a second series of PET images centered on the breast approximately 2 hours after FDG injection (dual-time imaging) (26,27). Indeed, FDG uptake seems to increase with time in the case of malignancy, while some inflammatory lesions show stable or decreasing uptake (26). However, dual-time imaging is time consuming, and its usefulness has not yet been demonstrated in large series.

FDG PET/CT is not a substitute for biopsy in the positive diagnosis of breast cancer. However, when an unexpected focus of FDG uptake is detected in the breast during an FDG examination performed for other reasons, it is necessary to explore it with conventional imaging and possible biopsy because of the high risk of malignancy (28). Among 4038 female patients undergoing FDG PET/CT for reasons other than breast cancer, unexpected FDG foci in the breast were identified in 33 patients (0.82%); 17 of these 33 foci proved to be malignant (28).

**Role of FDG PET/CT in Assessment of Multifocality and T Category of Breast Cancer**

In only a few studies, the role of PET/CT to assess the T category was analyzed. This was because of the limited spatial resolution of PET; FDG imaging has less sensitivity and less accuracy than magnetic resonance (MR) imaging in the determination of the delineation of the primary tumor and in screening for multifocality (27). Among 40 women undergoing PET/CT and MR imaging (27), MR imaging aided classification of the T category correctly in 77% of cases and PET/CT aided classification in only 54% of cases ($P = .001$). Therefore, with conventional instruments, PET/CT currently does not have a role in the assessment of the size of the primary tumor and presence of multifocal disease.

Performance might improve with the advent of higher-resolution PET systems dedicated to breast imaging called positron emission mammography (PEM) (28). In the recent study by Berg and colleagues (29), 388 women who were offered breast-conserving surgery underwent contrast-enhanced MR imaging and FDG positron emission mammography. Positron emission mammography and MR imaging had comparable breast-level sensitivity, although MR imaging had greater lesion-level sensitivity and more accurately depicted the need for mastectomy. Eighty-nine (23%) participants required more extensive surgery: Sixty-one (69%) of these women were identified with MR imaging, and 41 (46%) were identified with positron emission mammography ($P = .003$).

More studies are required to examine the potential role for positron emission mammography. Other work in progress concerns the development of PET/MR imaging hybrid systems. In the recent study by Berg and colleagues (29), 388 women who were offered breast-conserving surgery underwent contrast-enhanced MR imaging and FDG positron emission mammography. Positron emission mammography and MR imaging had comparable breast-level sensitivity, although MR imaging had greater lesion-level sensitivity and more accurately depicted the need for mastectomy. Eighty-nine (23%) participants required more extensive surgery: Sixty-one (69%) of these women were identified with MR imaging, and 41 (46%) were identified with positron emission mammography ($P = .003$).

PET/CT cannot be used as a substitute for sentinel node biopsy in patients with early-stage breast cancer (30). The spatial resolution of PET instruments precludes the detection of very small nodal metastases (31). In the American prospective multicenter study published in 2004, FDG PET (without the CT component) was performed in 360 women with newly diagnosed invasive breast cancer (31). For detecting axillary nodal metastasis, the mean sensitivity and specificity of PET were, respectively, 61% (range, 54%–67%) and 80% (range, 79%–81%) (31). In a study by Veronesi et al (32), in 236 patients with clinically negative findings for axillary involvement who underwent FDG PET prior to sentinel node biopsy, only 37% of patients with positive results of sentinel node biopsy had positive findings at PET. Overall accuracy and positive predictive value of FDG PET were, respectively, 70% and 88% (32). In a recent meta-analysis (33), researchers evaluated the diagnostic accuracy of PET (with or without CT). Across 19 studies of PET only ($n = 1729$), mean sensitivity was 60% (range, 50%–79%), and mean specificity was 93% (range, 89%–96%). Across seven studies of PET/CT ($n = 862$), mean sensitivity was 56% (range, 44%–67%) and mean specificity was 96% (range, 90%–99%) (33). Diagnostic performance of PET/CT does not seem to be superior to that of ultrasonography (US) (16) or MR imaging (34). PET/CT, therefore, cannot replace the sentinel node technique. Nevertheless, in a noninfectious setting, axillary node uptake is highly suggestive of malignancy, with a positive predictive value of more than 80% in most studies (32,35). Therefore, in the case of FDG uptake in the axilla, some authors recommend performing axillary clearance rather than sentinel node biopsy (32). Another possible option is to perform US-guided fine-needle aspiration biopsy of the suspicious axillary node. If the US-guided fine-needle aspiration biopsy results are positive, sentinel node biopsy can be bypassed.

**FDG PET/CT Comparison with Sentinel Node Biopsy for Axillary Staging**

When considering clinical disease stage at presentation (Tables 1, 2) (36), researchers in several studies (25,37,38) have shown a very high yield of FDG PET (with or without CT) in terms of a finding of extramammary involvement in patients who were not suspected of having it and of distant lesions in patients with inflammatory breast cancer. In one study (39), investigators reported on the usefulness of FDG PET (with or without CT) in patients with noninflammatory, but large (> 3 cm) breast cancer, and in three other studies (40–42), results pointed to a potential role in the workup in patients with stage II or III breast cancer. Unfortunately, the limited number of patients in each series would not allow measuring the yield separately in stage II and III and more precisely within specific substages (stages IIA and IIB and IIA, IIB, and IIC). Table 3 shows results of the main studies in which researchers evaluated the role of PET/CT at initial staging of breast cancer. Studies in which the researchers mixed patients referred for staging with others referred for restaging, as well as studies in which PET was performed without...
surgery, PET/CT results may indicate that the disease is not primarily treatable with surgery and requires preoperative chemotherapy. Correlative CT imaging is helpful to determine the precise location of lymph nodes with FDG uptake. Focus location in relation to the pectoralis minor muscle allows precise determination of the level of invasion in the axillary area (Figs 2, 3). The underlying CT image can also clearly pinpoint FDG uptake in the internal mammary chain or supraclavicular area (Figs 4, 5). Lymph node involvement in the axillary Berg level III area, in the supraclavicular area, or in the internal mammary basin (in association with axillary involvement) is classified as an N3 (stage IIIC) lesion according to the recently revised 7th edition of the AJCC Cancer Staging Manual (Tables 1, 2). Data from the national cancer database shows a poor survival rate (49% at 5 years) for the 6741 women with limited to Berg I and Berg II levels. The presence of FDG uptake, suggesting involvement at Berg level III (infraclavicular) or in extraaxillary local-regional nodes (supravacular or internal mammary), may have important implications in surgical and radiation therapy. In a patient scheduled to undergo the CT component, were excluded from this analysis.

Detection of Lymph Node Involvement Outside Berg I and Berg II Levels

PET/CT can be used to screen lymph nodes in the case of advanced tumor (Table 3). Axillary clearance is usually limited to Berg I and Berg II levels. The presence of FDG uptake, suggesting involvement at Berg level III (infraclavicular) or in extraaxillary local-regional nodes (supravacular or internal mammary), may have important implications in surgical and radiation therapy. In a patient scheduled to undergo

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### Table 1

<table>
<thead>
<tr>
<th>TNM Category</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)</td>
</tr>
<tr>
<td>T4a</td>
<td>Extension to the chest wall, not including only pectoralis muscle adherence/invasion</td>
</tr>
<tr>
<td>T4b</td>
<td>Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
</tbody>
</table>

#### Regional lymph nodes

| NX | Regional lymph nodes cannot be assessed (eg, previously removed) |
| N0 | No regional lymph node metastasis |
| N1 | Metastases to movable ipsilateral level I and II axillary lymph nodes |
| N2 | Metastases in ipsilateral level I and II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases* |
| N2a | Metastases in ipsilateral level I and II axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b | Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I and II axillary lymph node metastases* |
| N3 | Metastases in ipsilateral infraclavicular (level III axillary) lymph nodes with or without level I and II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph nodes with clinically evident level I and II axillary lymph node metastases; or metastases in ipsilateral supravacular lymph nodes with or without axillary or internal mammary lymph node involvement* |
| N3a | Metastases in ipsilateral infraclavicular lymph nodes |
| N3b | Metastases in ipsilateral internal mammary lymph nodes and axillary lymph nodes |
| N3c | Metastases in ipsilateral supravacular lymph nodes |

#### Distant metastasis

| M0 | No distant metastasis |
| M1 | Distant metastasis |

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### Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T0</td>
<td>N1mi</td>
<td>M0</td>
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<tr>
<td></td>
<td>T1*</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T0</td>
<td>N1</td>
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<td>T1*</td>
<td>N1</td>
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<tr>
<td>IB</td>
<td>T2</td>
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<td>M0</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
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<td>N2</td>
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<td>M0</td>
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<td></td>
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<td>M0</td>
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<tr>
<td>IIBC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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Note.— Adapted and reprinted, with permission, from reference 36. N1mi = nodal micrometastases. * T1 includes T1mi. † T0 and T1 tumors with nodal micrometastases only are excluded from stage IIA and are classified as stage IB.
<table>
<thead>
<tr>
<th>Study/Year/Type</th>
<th>Setting</th>
<th>No. of Patients</th>
<th>PET/CT Imaging</th>
<th>Conventional Imaging, with Other Modalities Performed</th>
<th>Effect of PET/CT Results (%)*</th>
<th>Detection of Unknown Node Metastases†</th>
<th>Detection of Unsuspected Distant Metastases</th>
<th>Modification in Initial Staging</th>
<th>Modification in Treatment Plan</th>
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<tbody>
<tr>
<td>Groheux et al (40)/2008/P</td>
<td>Stage II–III breast cancer</td>
<td>39</td>
<td>WB PET performed approximately 60 min after FDG injection; low-dose nonenhanced CT</td>
<td>Mammography, with or without breast MR imaging; breast US, abdominal US, with or without abdominal CT; chest radiography or CT, bone scintigraphy</td>
<td>8</td>
<td>10</td>
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<td>Heusner et al (27)/2008/R</td>
<td>T1–T3 noninflammatory breast cancer</td>
<td>40</td>
<td>WB PET performed approximately 60 min after FDG injection plus additional breast PET acquired 110 min after injection; contrast-enhanced CT</td>
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<td>Breast MR imaging, chest contrast-enhanced CT, liver US, bone scintigraphy</td>
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<td>8.5</td>
<td>42*</td>
<td>6.5</td>
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<tr>
<td>Yang et al (38)/2008/R</td>
<td>Inflammatory breast cancer</td>
<td>24</td>
<td>WB PET performed approximately 60–90 min after FDG injection; nonenhanced CT</td>
<td>Mammography, breast US, and MR imaging</td>
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<td>38</td>
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<td>Carkaci et al (37)/2009/R</td>
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<td>Mammography, breast US, or MR imaging; bone scintigraphy, chest radiography, chest and abdominal CT</td>
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<td>17</td>
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<td>Alberini et al (25)/2009/P</td>
<td>Inflammatory breast cancer</td>
<td>59</td>
<td>WB PET performed approximately 60 min after FDG injection; low-dose nonenhanced CT</td>
<td>Chest radiography, abdominal US, bone scintigraphy; if necessary, additional CT investigations were performed</td>
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<td>31*</td>
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<td>Aukema et al (41)/2010/P</td>
<td>Stage II–III breast cancer</td>
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<td>WB PET performed approximately 60 min after FDG injection plus additional PET of the thorax, including breasts and axillae, with the patient in prone position; low-dose nonenhanced CT</td>
<td>Mammography, breast US, breast MR imaging</td>
<td>17</td>
<td>NA</td>
<td>17</td>
<td>12</td>
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<td>70</td>
<td>WB PET performed 75 min after FDG injection; contrast-enhanced CT performed during breath hold at expiration tidal volume</td>
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<td>13, internal mammary basin</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Note.—NA = not available, P = prospective study, R = retrospective study, WB = whole body.

* Data are on a per-patient basis.
† Unknown node metastases refer to the metastases to the extraaxillary nodes.
‡ The high percentage of modification in this study can be explained by the detection of axillary infiltrated nodes (17%), and in 12% of patients who were suspected of having metastases at conventional imaging, downstaging occurred on the basis of the PET findings.
§ Some metastases were also detected by using conventional imaging.
stage IIIC disease among the 211,645 cases of breast carcinoma diagnosed in 2001–2002 (36). In our preliminary study (40) of 39 patients with stages II–III breast carcinoma, PET/CT revealed three cases of extranodal lymph node involvement that were missed by using the conventional workup. In all three cases, the extent of the surgical clearance and/or of the radiation therapy fields was modified according to the PET/CT information. In another study, also encompassing patients with stages II–III breast carcinoma, radiation therapy was altered in seven patients with extranodal lymph node involvement (12% of the total group) missed by using US (41).

Detection of Distant Metastases
Inflammatory breast cancer (T4d) is associated with a high rate of distant metastases, and PET/CT is useful for detecting occult metastases in these patients (25,37,38). In the study by Alberini and colleagues (25), PET/CT results suggested distant metastases in 18 of 39 patients with inflammatory breast cancer (31%), in only six of them, these metastases were recognized with a conventional workup. In patients who were not suspected of having distant metastases, distant metastases were also found in a nonnegligible percentage of patients with noninflammatory, but large (> 3 cm) breast cancer (39), as well as in two series of patients in whom PET/CT was used in the workup of patients with stage II or III breast cancer (40,42).

Hybrid PET/CT imaging leads not only to upstaging but also sometimes to downstaging of cancer (39,42). In the study by Fuster et al (39), additional PET findings led to downstaging of cancer in seven of 60 patients who were suspected of having metastatic disease suggested by using conventional imaging procedures: Seven lesions in bone scintigraphy images and no FDG uptake were finally confirmed to be benign. Concerning bone lesions, many teams have found that, while PET is more efficient than CT or bone scintigraphy for depicting lytic or mixed bone metastases and bone marrow lesions, PET can lack sensitivity for evidencing purely sclerotic bone metastases (43,44). For this reason, some teams advise clinicians to perform bone scanning, even in patients who have undergone FDG imaging. It is still unclear whether sclerotic bone metastases without FDG uptake are progressive (45). Moreover, while sclerotic metastases have no FDG uptake, they show
Radiology:
Volume 266: Number 2—February 2013
radiology.rsna.org
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osteocondensation on the CT images so that they can be detected by using the hybrid PET/CT procedure (42). In a retrospective study of 163 women, PET/CT and bone scintigraphy demonstrated a high degree of concordance, which suggested redundancy for detecting osseous metastases (46). Results of this study suggested that PET/CT was more accurate than scintigraphy to depict bone metastases (46). Consequently, the authors concluded that bone scanning may potentially be avoided in patients undergoing FDG PET/CT (46). Figure 6 shows a bone metastasis evidenced by using FDG PET/CT in the staging of a large breast carcinoma. Results from a prospective study (47) showed that the performance of diffusion-weighted MR imaging in the detection of bone metastases. However, more investigation on this topic is required.

In the staging of locally advanced breast cancer, PET/CT can also reveal distant lymph nodes and visceral metastases. In a group of 41 patients with inflammatory breast cancer, PET/CT revealed mediastinal lymph node metastases in 24% and liver metastases in 15% (37). In regard to the pulmonary parenchyma, PET efficiently depicts supracentimetric pulmonary nodules. However, because of the partial volume effect and respiratory movements, PET lacks sensitivity for smaller nodules. Careful scrutiny of the CT data obtained during the hybrid examination can reveal small nodules without FDG uptake. It should be noted that free-breathing CT is less efficient than standard diagnostic thoracic CT. Finally, the main limitation of PET/CT is its lack of sensitivity for brain metastases, because of physiologic FDG uptake in the brain.

In Which Patient Should FDG PET/CT Be Performed at Initial Staging?

The exact clinical stage at which PET/CT could be performed with a favorable balanced cost-effectiveness is uncertain. In most studies, patients with stage II and stage III carcinoma were mixed (Table 3). We recently reported

Figure 4: Invasive ductal carcinoma of the right breast in a 63-year-old woman who had a T4N0 lesion before PET/CT. (a) Maximum intensity projection image shows two foci of FDG uptake in right thoracic area. (b, c) Axial PET/CT fusion images show the first focus, which corresponds to primary tumor that invaded the skin and pectoralis major muscle (b) and an internal mammary nodal metastasis (arrow) (c). With PET/CT results, the clinical stage was T4N2M0.

Figure 5: Invasive ductal carcinoma of right breast in a 54-year-old woman at initial staging. (a, b) Coronal PET/CT fusion images show (a) uptake in primary tumor and internal mammary basin (arrow) and (b) in axillary and supraclavicular lymph nodes. After PET/CT, the clinical stage was T4N3cM0.
results from a prospective evaluation of the yield from FDG PET/CT in specific subsets of patients with stage IIA, IIB, and IIIA breast cancer (48). Of the 131 examined patients, 36 had clinical stage IIA cancer (34 with T2N0 lesions, two with T1N1 lesions), 48 had stage IIB cancer (20 with T3N0 lesions, 28 with T2N1 lesions), and 47 had stage IIIA cancer (29 with T3N1 lesions, nine with T2N2 lesions, nine with T3N2 lesions). FDG PET/CT results helped clinicians modify staging for 5.6% of patients with stage IIA cancer, for 14.6% of patients with stage IIB cancer, and for 27.6% of patients with stage IIIA cancer. Within stage IIIA, the yield for primary operable stage IIIA cancer (T3N1 lesions) was similar to that of stage IIB cancer, while it was very high for patients with N2 disease. We suggested that the use of FDG PET/CT at initial staging of breast cancer patients might be appropriate starting with clinical stage IIB and primary operable stage IIIA (48). Similar findings on a potential role of FDG PET/CT in stage IIB and primary operable stage IIIA cancers were also reported by Segaert and colleagues (42). These results, if confirmed by findings in other series, might call for reevaluation of the National Comprehensive Cancer Network guidelines. These studies should also include an evaluation of the cost-effectiveness. At the time of writing this review, the National Comprehensive Cancer Network guidelines recommend FDG PET or FDG PET/CT in patients with inflammatory breast cancer (49). They recommend against its use in stage IIB and primary operable stage IIIA breast carcinoma (48). FDG PET/CT is only advised in situations where results of standard staging studies are equivocal (49).

**Performance of PET/CT in Restaging of Breast Carcinoma**

A patient may be suspected of having a breast cancer recurrence because of a clinical symptom, a radiologic finding, or an increase in a biological marker (cancer antigen 15-3 and/or carcinoembryonic antigen). In all these different settings, PET/CT seems to perform better than conventional imaging (whole-body CT and bone scanning for distant recurrences, US and mammography for local recurrences) and better than PET alone (50–59). Table 4 shows results of the main studies in which researchers evaluated the role of PET/CT. We excluded studies in which staging and restaging populations were mixed. However, even the listed studies have some limitations. Most of them were retrospective. PET/CT was sometimes compared with its own CT component without intravenous contrast material enhancement (Table 4); such CT scanning is obviously not state of the art.

The sensitivity of FDG PET/CT ranged between 85% and 97%; the specificity, between 52% and 100%; and the accuracy, between 60% and 98% (Table 4). The accuracy was particularly high (98%) in the study by Dirisamer and colleagues (55). In this work, the CT component was performed with a diagnostic multidetector CT scanner, and 100 mL of contrast medium was routinely injected (55).

Restaging by using PET/CT imaging results leads to a change in management in a substantial percentage of patients (51,56,57). FDG PET/CT has an important role in the setting of asymptomatic patients with rising tumor marker levels and negative conventional imaging results; this hybrid imaging allows detection of early recurrence, before conventional methods. The effect on a patient’s outcome can be substantial. In the study by Grassetto and colleagues (57), 89 patients with breast cancer who had posttherapy rising tumor marker
### Table 4

<table>
<thead>
<tr>
<th>Study/Year*</th>
<th>Inclusion Criteria</th>
<th>No. of Patients</th>
<th>PET/CT Timing and CT Type</th>
<th>Comparative Modality</th>
<th>PET/CT Results (%)</th>
<th>Best Imaging Modality</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fueger et al (50)/2005</td>
<td>Elevated tumor marker; symptoms; equivocal or suspicious findings at other imaging studies</td>
<td>58</td>
<td>PET/CT, 60 min after FDG injection; NE CT</td>
<td>PET</td>
<td>94</td>
<td>84</td>
<td>NA</td>
</tr>
<tr>
<td>Radan et al (51)/2006</td>
<td>Elevated serum tumor markers</td>
<td>46</td>
<td>PET/CT, 60 min after FDG injection; NE CT</td>
<td>CE CT</td>
<td>85</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Haug et al (52)/2007</td>
<td>Elevated tumor markers but without proved metastases</td>
<td>34</td>
<td>PET/CT, 60 min after FDG injection; CE CT</td>
<td>CE CT and PET</td>
<td>96</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>Veit-Haibach et al (53)/2007</td>
<td>Elevated tumor markers (n = 15); suspicious finding at examination with another imaging modality or suspicious physical examination results (n = 29)</td>
<td>44</td>
<td>PET/CT, 60 min after FDG injection; CE CT</td>
<td>CE CT and PET</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Schmidt et al (54)/2008</td>
<td>Clinical suspicion of recurrence (n = 9); conspicuous finding at examination with other imaging modality (n = 14); elevated tumor marker (n = 10)</td>
<td>33</td>
<td>PET/CT, 60 min after FDG injection; CE CT</td>
<td>WB MR imaging (1.5 T [n = 23], 3 T [n = 10])</td>
<td>91</td>
<td>90</td>
<td>NA</td>
</tr>
<tr>
<td>Dirisamer et al (55)/2009</td>
<td>Elevated tumor marker (n = 32); clinical deterioration (n = 16) and/or suspicious findings at other imaging examination (n = 48)</td>
<td>52</td>
<td>PET, 50 min after FDG injection, with delayed scanning in case of suspected liver metastasis; CE CT</td>
<td>CE CT and PET</td>
<td>93</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Aukema et al (56)/2010</td>
<td>Patients with confirmed local-regional recurrence referred to visualize the extent of recurrence and exclude distant involvement</td>
<td>56</td>
<td>PET/CT, 60 min after FDG injection; low-dose NE CT</td>
<td>Chest MR imaging (n = 21); chest CT (n = 20), chest radiography (n = 32), liver US (n = 30), bone scintigraphy (n = 35)</td>
<td>97</td>
<td>92</td>
<td>94</td>
</tr>
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</table>

*Table 4 (continues)*
<table>
<thead>
<tr>
<th>Study/Year</th>
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<th>PET/CT Results (%)</th>
<th>Best Imaging</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grassetto et al (57)/2010</td>
<td>Increased marker levels with negative results of clinical examination and conventional imaging</td>
<td>89</td>
<td>PET/CT, 60 min after FDG injection; NE CT</td>
<td>Mammography, chest and abdominal CE CT, abdominal US, and bone scintigraphy</td>
<td>PET/CT was more sensitive than CT in evaluation of disease relapse</td>
<td>PET/CT</td>
<td>Tumor deposits were detected in 40/89 (45%) patients</td>
</tr>
<tr>
<td>Evangelista et al (58)/2011</td>
<td>Suspicion at clinical examination or at examination with another imaging modality, such as chest or bone radiography or bone scanning</td>
<td>111</td>
<td>PET/CT, 60 min after FDG injection; low-dose NE CT</td>
<td>Diagnostic CT and CA 15-3</td>
<td>PET/CT was more sensitive than CT and CA 15-3 in evaluation of disease relapse</td>
<td>PET/CT</td>
<td>Compared with conventional workup in 67 patients, PET/CT had higher sensitivity (94.5% vs. 3.3%) and accuracy (94% vs. 49%)</td>
</tr>
<tr>
<td>Champion et al (59)/2011</td>
<td>Asymptomatic patients with increased CA 15-3 and/or CEA serum levels</td>
<td>228</td>
<td>PET/CT, 60 min after FDG injection; low-dose NE CT</td>
<td>Standard workup</td>
<td>PET/CT</td>
<td>Compared with conventional workup in 67 patients, PET/CT had higher sensitivity (94.5% vs. 3.3%) and accuracy (94% vs. 49%)</td>
<td></td>
</tr>
</tbody>
</table>

Note.—CA 15-3 = carcinoma antigen 15-3, CE = contrast enhanced, CEA = carcinoembryonic antigen, NPV = negative predictive value, NA = not available, NE = nonenhanced, PPV = positive predictive value, WB = whole body.

PET/CT is efficient for detecting a distant metastasis and to demonstrate local-regional relapses, especially in the chest wall, the axilla, and the extraaxillary lymph node basins (Fig 7). Investigators in several studies have showed that PET/CT is more efficient than CT or MR imaging for depicting nodal recurrences (54–56). In the study by Schmidt et al (54), PET/CT was more sensitive than whole-body MR imaging to detect lymph node involvement (n = 21 vs n = 16); however, whole-body MR imaging was slightly more sensitive (n = 154 vs n = 147) in the detection of distant metastases. Recent data point to improved sensitivity of whole-body MR imaging when a diffusion-weighted sequence was added. Improvements are also expected with FDG PET/CT through the use of contrast enhancement for the CT part, respiratory gating, etcetera.

When a recurrence is depicted or a patient is suspected of having a recurrence by using conventional imaging, PET/CT is useful to determine whether this recurrence is isolated or not, and such a determination may have a potential effect on the patient’s treatment. In a study of 56 patients who were clinically eligible for curative surgery of a local recurrence, PET/CT depicted additional lesions not visible at conventional imaging in 25 (45%) patients (56).

Two meta-analyses have been recently published encompassing PET/CT studies (60,61). In the first meta-analysis, MR imaging and PET (with or without CT) were more efficient than US or CT to detect recurrent breast cancer (61). No difference was found between MR imaging and PET; unfortunately, PET and PET/CT were not separated in this analysis. In the second meta-analysis, PET and PET/CT modalities were
Figure 7: Paresis of the right upper limb (the arm [shoulder to elbow], the forearm [elbow to wrist], and the hand) in a 50-year-old woman with a history of cancer in the right breast. (a) Axial PET/CT fusion image shows two FDG foci. One was observed in the right axilla near surgical staples. This uptake invaded the pectoralis minor muscle and brachial plexus. The second focus over the left part of the sternum is suggestive of metastasis to the bone. (b) Axial CT image shows a heterogeneous mass in the axilla, invading the pectoralis minor muscle (long arrow). Scrutiny at the sternum shows a high-attenuation area corresponding to an osteoblastic metastasis (short arrow).

Figure 8: Coronal images in a 38-year-old woman treated 2 years before with mastectomy, adjuvant chemotherapy, radiation therapy, and breast reconstruction. Marker levels were normal but CT image shows supraclavicular and mediastinal equivocal lymph nodes. (a) CT image from PET/CT examination shows supraclavicular and inferior jugular lymph nodes with a short axis of less than 10 mm. (b) PET/CT fusion image shows that high FDG uptake was detectable, which is suggestive of tumor-involved lymph nodes. (c) Image shows that, after chemotherapy, lymph nodes were not visualized. 2D = two-dimensional measurements in one plane.

In conclusion, FDG PET/CT is useful for detecting recurrence and for restaging in breast cancer patients (Figs 7–9).

Performance of PET/CT for Treatment Response Assessment

Early Evaluation of Neoadjuvant Chemotherapy with PET with or without CT

Neoadjuvant chemotherapy (NAC) is the first treatment in nonoperable locally advanced and inflammatory breast cancer. NAC is also commonly used in case of operable but large tumor to increase the chances of performing breast-conserving surgery (62). Although an overall survival benefit for NAC compared with adjuvant chemotherapy in operable breast cancer has not been clearly proved, it is generally accepted that absence of residual cancer cells in the primary tumor following NAC is strongly associated with improved disease-free survival and overall survival (63). Pathologic complete response after completion of NAC occurs in 13%–26% of patients (62,64).

NAC is an excellent setting to document response of the tumor to the administered chemotherapy regimen which is not possible in the adjuvant setting. Early prediction during NAC of what would be the final pathologic response might offer an early opportunity to change strategy in case of ineffectiveness. Stopping ineffective chemotherapy could avoid unwarranted side effects. In several studies (65–74) in imaging, but only the study by Schmidt et al (54) was included.

In conclusion, FDG PET/CT is useful for detecting recurrence and for restaging in breast cancer patients (Figs 7–9).
which a possible role for metabolic evaluation with FDG PET and PET/CT was examined, investigators demonstrated a correlation between early changes in the SUVmax value (after one or two courses of chemotherapy) and the final pathologic response at completion of chemotherapy (Fig 10). Among these studies, only a few were performed with a PET/CT system (68,71,72,74) (Table 5). In this setting, the CT part of the hybrid system is not decisive and the performance of the hybrid PET/CT system was no better than the performance of PET alone.

In every study, an optimal threshold value of decrease in SUV (ΔSUV) has been proposed for discriminating metabolic responders (diminution of SUV superior to the threshold value) from nonresponders. The cutoff chosen is supposed to help best prediction of the final pathologic response. Unfortunately, the specific threshold value proposed varies dramatically across studies (Table 5). Several factors can explain differences in the cutoff value (65).

First, the definition of what is a good histopathologic responder varies. For example, Rousseau et al (68) define a tumor regression superior to 50% as a good response while Schwarz-Dose and colleagues (73) consider no residual invasive tumor or only a few scattered foci of microscopic residual tumor as indicators of a satisfactory pathologic response.

Second, the optimal timing for the interim PET remains unclear. For several teams, performing PET after the second course of NAC is a good compromise to evidence effects of chemotherapy and to still allow an early...
### Table 5

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Imaging Performed</th>
<th>No. of Patients</th>
<th>No. of Patients Not Included because of Low Initial FDG Uptake</th>
<th>Tumor Characteristics</th>
<th>No. of Cycles of NAC</th>
<th>Timing of PET Evaluation</th>
<th>Definition of Pathologic Responders</th>
<th>Auxiliary Status Taken into Account</th>
<th>Optimal PET</th>
<th>Optimal SUV Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schelling et al (66)/2000</td>
<td>PET</td>
<td>22</td>
<td>0</td>
<td>Large (&gt; 3 cm) and LABC</td>
<td>2–4</td>
<td>After 1 and 2 cycles</td>
<td>pCR or residual microscopic foci</td>
<td>No</td>
<td>PET after 2 courses</td>
<td>55%</td>
</tr>
<tr>
<td>Smith et al (67)/2000</td>
<td>PET</td>
<td>30</td>
<td>0</td>
<td>Large (&gt; 3 cm) and LABC (T3, T4, or Tx, N2)</td>
<td>8</td>
<td>After 1 and 4 cycles and before surgery</td>
<td>Partial response and complete response</td>
<td>Yes</td>
<td>Not stated</td>
<td>SUV threshold not stated</td>
</tr>
<tr>
<td>Rousseau et al (68)/2006</td>
<td>PET/CT</td>
<td>64</td>
<td>0</td>
<td>Stages IIA–IIIB; IIA–IIB</td>
<td>4–6</td>
<td>After 1, 2, and 3 cycles and before surgery</td>
<td>Therapeutic effect &gt; 50%</td>
<td>No</td>
<td>PET after 2 courses</td>
<td>40%</td>
</tr>
<tr>
<td>Berriolo-Riedinger et al (69)/2007</td>
<td>PET</td>
<td>47</td>
<td>0</td>
<td>Large and LABC</td>
<td>4–6</td>
<td>After 1 cycle</td>
<td>Total or near total therapeutic effect</td>
<td>Yes</td>
<td>-</td>
<td>60%</td>
</tr>
<tr>
<td>McDermott et al (70)/2007</td>
<td>PET</td>
<td>96</td>
<td>24</td>
<td>Large and LABC (T3–T4 N0 or Tx N2)</td>
<td>6 or 8</td>
<td>After 1 cycle, at midpoint, at end point</td>
<td>pCR or malignant cells &lt; 25% of the tumor area</td>
<td>No</td>
<td>Between the end of the 1st cycle and the midpoint</td>
<td>24% after 1 cycle; 58% at midpoint and 64% at end of NAC</td>
</tr>
<tr>
<td>Duch et al (71)/2009</td>
<td>PET/CT</td>
<td>50</td>
<td>0</td>
<td>Stages IIB; IIA–IIB</td>
<td>4</td>
<td>After 2 cycles</td>
<td>pCR or malignant cells &lt; 25% of the tumor area</td>
<td>No</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td>Kumar et al (72)/2009</td>
<td>PET/CT</td>
<td>23</td>
<td>0</td>
<td>Stages IIB, IIA, IIB</td>
<td>6</td>
<td>After 2 cycles</td>
<td>pCR or malignant cells &lt; 25% of the tumor area</td>
<td>No</td>
<td>-</td>
<td>Just 50% of decrease was used</td>
</tr>
<tr>
<td>Schwarz-Dose et al (73)/2009</td>
<td>PET</td>
<td>104</td>
<td>24</td>
<td>Large and LABC (T2–T4, N0–N2)</td>
<td>4–6</td>
<td>After 1 and 2 cycles</td>
<td>pCR or residual microscopic foci</td>
<td>No</td>
<td>PET after 1 and 2 courses perform equally</td>
<td>45% after 1 course and 55% after 2 courses</td>
</tr>
<tr>
<td>Martoni et al (74)/2010</td>
<td>PET/CT</td>
<td>34</td>
<td>0</td>
<td>Large and LABC (T2–T4, N0–N3)</td>
<td>6–8</td>
<td>After 2 and 4 cycles and before surgery</td>
<td>pCR or malignant cells &lt; 10% of the tumor area</td>
<td>Yes</td>
<td>PET after 2 courses</td>
<td>50%</td>
</tr>
</tbody>
</table>

Note — LABC = locally advanced breast cancer; pCR = pathologic complete response.
change of treatment in case of ineffec-
tiveness (66,68,74). However, perform-
ing response assessment as early as the
first cycle might also be valuable (73).

Furthermore, the pretreatment tu-
mor SUV index must be high to detect
a meaningful reduction during treat-
ment (70,73). This requirement limits
the use of iterative PET in case of tu-
mors with a low SUV. It is important to
note that low tumor metabolic activity
at pretreatment could be an indicator
of chemotherapeutic resistance (73). In
the study by Schwarz-Dose et al (73),
none of the 23 patients with initial SUV
less than three achieved a complete his-
topathologic response. On the other hand,
breast cancer comprises different groups of tumors
(estrogen receptor–positive tumors,
tumors with HER2 overexpression,
triple-negative tumors) with different
response rates to chemotherapy, differ-
ent risks of relapse, different treatment
options, and different prognoses. We
therefore suggest that the clinical aims of
early FDG monitoring and the crite-
ria used to assess effectiveness should
be examined in specific subgroups
(65,75). We recently reported results
in the subset of patients with triple-neg-
ative tumors, showing that FDG PET/CT
at two cycles can be efficient in dis-
criminating patients who are unlikely
to achieve a complete pathologic response
with the prescribed NAC regimen and
have a high risk of early relapse (75).

In total, encouraging data plea for a
role of FDG PET (with or without CT)
in the early evaluation of the response
to NAC. However, more studies are
necessary to better define criteria of
evaluation. Moreover, the place of PET
in comparison with MR imaging, which
is also useful in the early evaluation
of NAC, remains to be better determined
(76).

Evaluation of Response of Metastatic
Disease with FDG PET/CT
Anatomic imaging, predominantly CT,
is currently used to obtain measure-
ments of tumor lesions before and after
treatment for response assessment and
follow-up (77,78). However, several cy-
cles of treatment are needed before a
change in tumor size can be assessed
with anatomic imaging. Moreover,
modification in bone metastases, pleu-
ral effusion, and lymphangitis, which
are common sites of breast cancer dis-
semination, are difficult to assess.

Changes in metabolic activity generally
occur earlier than changes in
tumor size (Fig 9). This is particularly
the case for targeted therapies, because
these treatments can render tumors
metabolically inactive without substan-
tial modification of their size. Func-
tional imaging techniques such as PET
can be used earlier than morphologic
imaging methods to evaluate treatment
response. Only a few studies reported
on the clinical use of sequential FDG
PET (with or without CT) in patients
with metastatic breast disease. In most
of them, PET is performed without
CT (79–81). Studies with PET/CT are
clearly needed. There is some evidence
that hybrid FDG PET/CT (when both
CT information and tumor metabolic
activity are considered) provides addi-
tional and useful information to assess
the evaluation of systemic chemothe-
rapy. For example, the increase in atten-
duation in bone metastases (measured
in Hounsfield units) and the decrease
in SUV are altogether potential predic-
tors of response duration (82) (Fig 6).
Another important finding is that PET/
CT allows evaluation of response in
many different metastases. Therefore,
PET/CT is helpful to evidence a het-
erogeneous response (coexistence of
responding and nonresponding lesions
within the same patient) (83).

Specific PET criteria for determin-
ing the therapeutic response have al-
ready been proposed by various work-
ing groups (84,85). For example, the
experts of the European Organization
for Research and Treatment of Cancer
consider that reduction of more than
25% in the SUV within the tumor after
several cycles of chemotherapy is clas-
sified as a partial metabolic response
and an increase of at least 25% in the
SUV, visible increase in the extent of
FDG tumor uptake (20% in the lon-
gest dimension), or the appearance of
new FDG uptake is progressive disease
(84). However, recommendations of the
European Organization for Research
and Treatment of Cancer group are not
widely used in clinical practice. Newer
evaluation criteria taking into account
not only the PET but also the CT part of
the hybrid imaging are needed.

Thus, PET/CT is a promising method
for early assessment of chemotherapy
in patients with metastatic disease, but
more data are needed and standardiza-
tion in criteria evaluation is necessary.

Assessment of Response to Hormonal
Therapy: The Paradoxical Metabolic Flare
A paradoxical increase in FDG uptake
during the 1st days after initiation of
hormone therapy was observed in
patients with a good therapeutic re-
ponse. This phenomenon has been de-
scribed with the term metabolic flare
(86). This effect typically occurs during
the 10 days after initiation of hormone
therapy (86). An explanation for this
phenomenon is that endocrine therapy
has initial agonist effects before antag-
onist effects dominate. Therefore, an
increase in SUV in tumors during PET
performed early after the initiation of
hormone therapy is predictive of a good
therapeutic response (87–89). How-
ever, these results have been reported
in small numbers of patients, and furt
ework is therefore needed to better ana-
lyze this phenomenon.

Prognostic Value of FDG PET (/CT)
In the study by Inoue et al (90), FDG
PET was performed preoperatively in
81 women with breast cancer. Patients
were dichotomized according to the
SUV max into high- and low-SUV groups
by using a cutoff value of an SUV max
of 4.0 (90). The high-SUV group (n = 40)
showed a significantly (P = .011) poorer
prognosis than the low-SUV group (n = 41)
(5-year disease-free survival rates,
75.0% vs 95.1%). Researchers in other
studies have also suggested that the
SUV in the primary tumor could be
predictive of outcome (20,25,91,92).
Unfortunately, the FDG uptake cutoff
used to discriminate high from low up-
take is different from one study to an-
other. These findings are nevertheless
in agreement with data showing higher
SUV uptake in tumors of high histologic grade (grade 3) or in triple-negative tumors (Fig 1).

FDG response of metastatic disease also has prognostic value. In a group of 47 patients, Cachin et al (93) showed that overall survival was significantly better for patients with negative findings on a PET scan after chemotherapy, in comparison with persistent FDG uptake (24 months vs 10 months, P < .001).

Conclusion

FDG PET/CT is very useful for restaging of cancer in patients with documented breast cancer recurrence or in those who are suspected of having breast cancer recurrence and is more efficient than PET alone and conventional imaging methods. FDG PET/CT is also efficient to perform the staging of locally advanced and inflammatory breast cancer. It allows detection of extranodal lymph nodes and distant metastases. PET/CT also brings valuable information in the staging of clinical stage IIB and primary operable stage IIIA breast carcinomas. In contrast, the spatial resolution of PET (approximately 5–6 mm) is not sufficient to allow the detection of early axillary node involvement and micrometastases. PET/CT cannot replace staging by using the sentinel node procedure. Also, PET is not recommended for the initial assessment of stage I breast cancer. The metabolic information provided by using PET has been shown to be valuable for the early assessment of response to chemotherapy (at the neoadjuvant and metastasis settings), but this indication remains to be validated.

Disclosures of Conflicts of Interest: D.G. No relevant conflicts of interest to disclose. E.H. No relevant conflicts of interest to disclose.

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Radiology: Volume 266: Number 2—February 2013  •  radiology.rsna.org 405


