Currently, the clinical role of positron emission tomography (PET) and PET/computed tomography (CT) in patients with breast cancer is to provide additional information in select scenarios in which results of conventional imaging are indeterminate or of limited utility. There is currently no clinical role for fluorodeoxyglucose (FDG) PET in detection of breast cancer or evaluation of axillary lymph nodes, but these are areas of active research. FDG PET is complementary to conventional staging procedures and should not be a replacement for either bone scintigraphy or diagnostic CT. FDG PET and PET/CT have been shown to be particularly useful in the restaging of breast cancer, in evaluation of response to therapy, and as a problem-solving method when results of conventional imaging are equivocal. In these situations, FDG PET often demonstrates locoregional or unsuspected distant disease that affects management. PET has demonstrated a particular capability for evaluation of chemotherapy response in both patients with locally advanced breast carcinoma and those with metastatic disease.
Introduction

Positron emission tomography (PET) and combined PET/computed tomography (CT) are increasingly used for oncologic imaging. Fluorodeoxyglucose (FDG) PET demonstrates abnormal metabolic features associated with malignancy that often precede morphologic findings demonstrated with anatomic imaging. Combined PET/CT systems are increasingly available and currently account for almost all of the new whole-body PET installations. In these systems, the CT and PET images are fused and provide combined anatomic and physiologic imaging. Typically, the CT portion is used to provide attenuation correction as well as anatomic correlation for the PET imaging component. This modality allows more precise anatomic localization of PET abnormalities and in general has been shown to improve diagnostic accuracy compared with FDG PET alone (1).

FDG PET and to a lesser degree FDG PET/CT have been evaluated for primary breast cancer detection and diagnosis, staging of locoregional and distant sites, and monitoring the response to therapy. As far as PET/CT and breast cancer, there have been several reports demonstrating increased diagnostic confidence as well as diagnostic accuracy with PET/CT compared to PET alone (2,3). The clinical significance of this improvement has not yet been fully established, but it is likely that combined PET/CT will become increasingly common as these devices become more widely available.

Currently, however, PET/CT is not a replacement for contrast material–enhanced diagnostic CT for routine staging of patients with breast cancer. In fact, the majority of clinical staging guidelines and the imaging literature do not support the routine use of FDG PET or FDG PET/CT in patients with stage I and early stage II breast cancer. However, maximizing the clinical potential of PET/CT is an active area of ongoing research. Although PET imaging is possible with a large number of positron-emitting isotopes, in clinical practice almost all PET imaging for cancer is performed with FDG (Figs 1, 2). This review emphasizes the current and future clinical applications of PET and PET/CT in patients with breast carcinoma.

Breast Cancer Detection with FDG PET

FDG PET has high sensitivity and specificity for detection of malignant lesions in general, but breast cancer detection requires the ability to demonstrate nonpalpable, small (<1.0 cm) invasive and in situ malignancies. These requirements are beyond the capability of current whole-body FDG PET, and thus FDG PET is not used for primary breast cancer detection. In one study, Kumar et al (4) reviewed 85 breast cancers and demonstrated that both tumor size less than 10 mm and low tumor grade were significant predictors of a false-negative FDG PET result, substantiating observations made by multiple other investigators.

Samson et al (5) performed a meta-analysis on 13 published articles evaluating whole-body FDG PET and breast cancer detection. On the basis of this analysis, FDG PET was 88% sensitive and
80% specific for breast cancer with false-negative results in 12% of cancer cases. Not only did the authors conclude that whole-body FDG PET should not be used to evaluate breast lesions, they also pointed out that most studies evaluating FDG PET of breast cancer were unevenly weighted toward large palpable primary lesions and typically omitted nonpalpable imaging-detected cancers, which are the critical segment of the biopsy population. Currently, there is widespread agreement that whole-body FDG PET does not have a clinical role in detecting primary breast cancer, nor is it an alternative to histologic sampling to establish or exclude primary breast cancer because of the well-documented inability of FDG PET to consistently demonstrate small and low-grade lesions.

Detection with Dedicated Positron Emission Mammography

More recently, dedicated breast positron emission mammography (PEM) units have been developed to overcome the limitations of whole-body PET and to provide a positron-emitting imaging platform capable of detection and depiction of primary breast carcinoma (Fig 3). In general, these systems consist of two planar detectors placed opposite a gently compressed breast. The advantages of such dedicated systems include improved geometric sensitivity, higher spatial resolution, shorter imaging time, and reduced attenuation compared with whole-body PET systems. They also have a small physical footprint, which makes their use in a breast imaging facility feasible and allows correlation of the results with those of conventional breast imaging as well as PEM-guided biopsy. Although preliminary data demonstrate that these systems are capable of imaging smaller primary breast carcinomas than whole-body systems, their clinical utility has not been adequately demonstrated (Table 1) (6–10). Certain limitations such as imaging posterior lesions, variable

Table 1
Summary of the Results of Published FDG PEM Studies

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Average Lesion Size (cm)*</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murthy et al 2000</td>
<td>18</td>
<td>NA</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>Levine et al 2003</td>
<td>14</td>
<td>2.0 (1.0–5.5)</td>
<td>86</td>
<td>91</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>Rosen et al 2005</td>
<td>23</td>
<td>2.1 (0.4–4.6)</td>
<td>86</td>
<td>33†</td>
<td>90</td>
<td>25†</td>
</tr>
<tr>
<td>Tafra et al 2005</td>
<td>44 + 10</td>
<td>2.2‡ (0.1–10.0)</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
<td>45</td>
</tr>
<tr>
<td>Berg et al 2006</td>
<td>92</td>
<td>2.1‡ (0.3–10.0)</td>
<td>90</td>
<td>86</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Rosen et al 2006</td>
<td>50</td>
<td>1.4 (0.8–4.0)</td>
<td>87</td>
<td>70</td>
<td>71</td>
<td>86</td>
</tr>
</tbody>
</table>

Note.—NA = not available, NPV = negative predictive value, PPV = positive predictive value.

*Numbers in parentheses are ranges.
†Only two of 23 were true negative, according to Breast Imaging Reporting and Data System criterion 5 only.
‡Median size, invasive lesions only.
FDG uptake in small tumors, and false-positive findings from prior biopsy have been reported, and biopsy capability needs to be further addressed (8,10–12). Potential roles advocated for these systems include detection, problem solving, local staging, local recurrence, and assessing or predicting response of the primary tumor to chemotherapy. Dedicated breast PEM and PET are a promising technology to help overcome the limitations of whole-body imaging and may eventually provide a positron emission imaging platform capable of reliably imaging primary breast carcinoma.

### Table 2
Results of Early Studies of FDG PET in Axillary Nodal Staging versus Results of a Multicenter Trial

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utech et al 1996</td>
<td>124</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Avril et al 1996</td>
<td>51</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td>Adler et al 1997</td>
<td>52</td>
<td>95</td>
<td>66</td>
</tr>
<tr>
<td>Smith et al 1998</td>
<td>50</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>Crippa et al 1998</td>
<td>68</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>Wahl et al 2004</td>
<td>308</td>
<td>61</td>
<td>80</td>
</tr>
</tbody>
</table>

Note.—Results of the early studies suggested high sensitivity and high specificity for nodal disease; these were not found in the 2004 multicenter trial, which evaluated 360 women with newly diagnosed breast carcinoma (axillae were assessed in only 308 patients). In the later trial, almost 50% of the women had small T1 breast cancers, whereas the earlier trials were biased toward larger primary lesions.

### Table 3
Results of Studies of FDG PET in Staging Axillary Nodal Disease

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Hoeven et al 2002</td>
<td>80</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>Kelleman et al 2003</td>
<td>15</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>Barranger et al 2003</td>
<td>32</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Wahl et al 2004</td>
<td>308</td>
<td>61</td>
<td>80</td>
</tr>
<tr>
<td>Zornoza et al 2004</td>
<td>200</td>
<td>84</td>
<td>98</td>
</tr>
<tr>
<td>Fehr et al 2004</td>
<td>30</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>Lovrics et al 2004</td>
<td>98</td>
<td>40</td>
<td>97</td>
</tr>
<tr>
<td>Kumar et al 2006</td>
<td>80</td>
<td>44</td>
<td>95</td>
</tr>
<tr>
<td>Gil-Rendo et al 2006</td>
<td>275</td>
<td>84</td>
<td>98</td>
</tr>
<tr>
<td>Chung et al 2006</td>
<td>54</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

Note.—Recent studies demonstrate a consistently high specificity for axillary nodal metastases but lower sensitivity compared with that of sentinel lymph node biopsy. FDG PET is not sufficient for exclusion of axillary metastases, which requires histologic evaluation.

### Locoregional Staging with FDG PET

#### Routine Axillary Staging

Early studies demonstrating abnormal FDG PET uptake in metastatic axillary lymph nodes of breast cancer patients (Table 2) (13,14) prompted a prospective multicenter trial to evaluate the ability to stage the axilla with FDG PET before surgery (15). FDG PET was performed in 360 patients with newly diagnosed breast carcinoma, and the results were interpreted by one of four experienced readers. The PET results were compared with those of pathologic analysis of axillary nodes. Overall, FDG PET was 61% sensi-
tive and 80% specific for axillary metastases, with a positive predictive value of 62% and a negative predictive value of 79%. Receiver operating characteristic curve analysis demonstrated that FDG PET had high specificity for nodal disease when a threshold standardized uptake value (SUV) of 1.8 was used; however, this increased specificity reduced sensitivity for nodal disease to 32%. On the basis of the results of their analysis, the authors concluded that “FDG-PET is not routinely recommended for axillary staging” in women with breast cancer.

Further studies comparing FDG PET to sentinel lymph node biopsy support sentinel lymph node biopsy for early-stage disease and confirm the relatively low sensitivity of FDG PET for axillary nodal metastases in early-stage breast cancer (Table 3) (15–22). The moderate sensitivity of FDG PET for axillary metastases, particularly small and isolated lesions, is not sufficient to preclude tissue sampling, usually performed with sentinel lymph node mapping and biopsy, which is highly sensitive for axillary metastases. There is currently no clinical role for routine FDG PET axillary staging in women with newly diagnosed early-stage breast cancer.

**Axillary Nodal Disease in Patients at High Risk**

It is interesting that studies have repeatedly demonstrated a high specificity for axillary nodal metastases, particularly in patients at high risk for nodal disease (Fig 4). Although FDG PET is clearly not a substitute for histologic sampling, there may be a clinical role for preoperative FDG PET in certain patient populations, such as those with LABC, advanced axillary disease, plexopathy, and symptomatic metastases. In patients with symptomatic advanced disease, FDG PET can help accurately determine the extent of disease and distinguish radiation plexopathy from recurrence (23–25).

In these populations, there is a high likelihood of axillary metastases; if this is confirmed with preoperative FDG PET, directed ultrasonography (US) to survey the high-risk axillae followed by US-guided tissue sampling of any abnormal-appearing nodes can establish the presence of axillary metastases. Then, patients may proceed directly to axillary dissection rather than sentinel lymph node biopsy. This approach could avoid sentinel lymph node biopsy in patients with a very high likelihood of axillary metastases and has been supported by several studies (18–22) (Table 3).

**Internal Mammary Nodal Status**

FDG PET can be helpful in assessing breast cancer spread to regional nodal sites outside the axilla, particularly the internal mammary (IM) chain. These nodal basins are not routinely sampled given their relative inaccessibility and their uncertain clinical significance and treatment. However, FDG uptake in IM nodes has
been anecdotally reported in some studies (Table 4) (18,22,26,27). Our experience in patients with LABC demonstrated FDG uptake in IM nodes in up to 25% of patients and that such uptake is predictive of both the likelihood and pattern of treatment failure, consistent with IM nodal disease involvement and progression (Fig 5).

### Systemic Staging with FDG PET

Systemic staging is not routinely performed in patients with early-stage breast cancer owing to the low likelihood of distant metastases. In fact, current National Comprehensive Cancer Network practice guidelines recommend routine chest imaging (chest radiography) only for patients with clinical stage I breast cancer. In patients with node-positive stage II and stage III disease, imaging typically consists of bone scanning and contrast-enhanced chest or abdominal CT. FDG PET is recommended as an option for patients with either recurrent or stage IV disease and in this setting has been shown to be both sensitive and specific (Table 5) for metastases (23, 28–32). Moon et al (30) evaluated FDG PET performed in 57 patients suspected to have recurrent or metastatic breast cancer and demonstrated that FDG PET was 93% sensitive and 79% specific in this setting.

![FDG PET image of a patient with LABC displaying uptake in an IM node.](image)

Moreover, FDG PET can be particularly helpful by identifying occult sites of malignant involvement and thus affecting therapeutic options.
In patients suspected to have recurrent or metastatic breast carcinoma, FDG PET and FDG PET/CT can be instrumental by demonstrating otherwise occult disease, particularly in the locoregional and mediastinal nodal basins (Fig 6). These are common sites of metastatic involvement and are not optimally evaluated with conventional imaging alone. FDG PET and FDG PET/CT can improve staging and alter therapeutic options in patients suspected to have breast cancer recurrence and distant metastatic disease, primarily by demonstrating local or distant nodal involvement occult at other imaging studies.

Eubank et al (23) demonstrated that FDG PET changes or affects treatment in up to 44% of patients suspected to have locoregional recurrence. In this setting, FDG PET changed therapy by demonstrating more widespread disease than demonstrated with other imaging studies (Fig 7). Accurate staging is particularly important in these patients because their treatment options may include surgery, radiation, chemotherapy, and hormonal therapy, depending on the distribution and burden of disease. Although FDG PET also demonstrates more lesions than conventional imaging in patients with known metastatic disease, there was less impact on clinical management in this setting.
FDG PET and PET/CT of Skeletal Metastases

Skeletal metastases are the most common site of distant disease in breast cancer, accounting for 90% of all metastatic lesions as well as representing the most common site of initial metastatic involvement. The role of FDG PET and PET/CT for detection and evaluation of skeletal metastases remains unanswered. Breast cancer is one of several malignancies that can result in bone metastases that are either osteolytic or osteoblastic. Although most lesions are mixed, with some combination of lytic and blastic components, some lesions are purely lytic or blastic, and these lesions can pose difficulties for imaging.

It appears that FDG PET is complementary to bone scintigraphy, which remains the standard imaging procedure for surveying the skeleton for metastatic involvement. Several studies have shown that FDG PET is superior to bone scintigraphy in detecting lytic and intramedullary metastases. However, FDG PET frequently fails to demonstrate blastic lesions, which are readily detected with bone scintigraphy (2,30,33–37).

In clinical practice, the combination of bone scintigraphy and CT remains the standard imaging combination for staging breast cancer, when staging is clinically indicated, and FDG PET is most helpful in clarifying difficult or equivocal cases. The use of FDG PET/CT as a single staging examination is the subject of ongoing studies and has yet to be determined (Fig 8). In the future, other PET agents such as fluorine-18 fluoride PET may offer improved bone metastasis detection compared to FDG and bone scintigraphy (34).

Staging with FDG PET and PET/CT: When Does It Help?

Although FDG PET and PET/CT are not currently recommended for routine staging of breast cancer, there are several scenarios where FDG PET is often helpful. FDG PET may be particularly helpful in restaging cases of locally recurrent disease if aggressive local therapy is being considered, since it may reveal unsuspected mediastinal or distant metastatic disease, the presence of which would change clinical management (24) (Fig 7). The sensitivity of FDG PET is superior to that of CT in detecting nodal disease of the IM and mediastinal nodal basins, which are common sites of involvement in patients with advanced or recurrent disease (24,26). The additional information provided by PET aids clinical decision making in this complex group of patients.

The improved sensitivity and accuracy of FDG PET compared with those of CT in restaging cases of advanced breast cancer was important in obtaining approval for medical insurance reimbursement for FDG PET from the Centers for Medicare and Medicaid Services for this scenario.
Eubank et al (23) demonstrated that FDG PET alters therapy options in up to 44% of patients with suspected locoregional recurrence, by demonstrating more widespread disease than CT and avoiding local surgical procedures for patients with metastatic disease. Combined PET/CT will likely add even more clinically important information in this setting, since initial reports have demonstrated that FDG PET/CT adds incremental diagnostic confidence to PET results in more than 50% of patients and that integrated PET/CT allows more accurate restaging of breast cancer than PET alone.

FDG PET and FDG PET/CT may be useful for evaluating asymptomatic treated breast cancer patients with rising levels of tumor markers without clinical symptoms. In this clinical scenario, FDG PET allows more accurate diagnosis of metastatic disease compared with conventional imaging. In a recent study, FDG PET/CT was 90% sensitive for diagnosing recurrent tumor in patients with elevated levels of tumor markers, and affected clinical management in 51% of the patients (38). In this study, FDG PET/CT demonstrated improved sensitivity, specificity, accuracy, and predictive value compared with CT alone.

Monitoring Response to Therapy with FDG PET and PET/CT

Neoadjuvant Systemic Therapy in LABC

Neoadjuvant (preoperative) systemic chemotherapy has become standard treatment for patients with LABC—which is defined as primary breast cancer exceeding 5 cm, fixed axillary lymph nodes, or skin or chest wall invasion—but neoadjuvant systemic therapy (NST) is increasingly used in patients with nonmetastatic operable breast cancer. Although NST has not been shown to improve survival compared to similar adjuvant therapy, it does improve surgical options and provides prognostic information. Studies have demonstrated that the extent of residual breast and axillary disease after treatment is prognostic for both disease-free survival and overall survival (39–43). Patients demonstrating complete pathologic response, defined as no residual invasive tumor at histopathologic analysis, have improved long-term outcome compared to patients without complete pathologic response (39,40,43). One of the primary aims of NST is therefore to assess the response of the primary tumor to the treatment regimen.

Serial FDG PET imaging has been widely studied as a method for assessing tumor response to NST, by using comparison to histopathologic assessment of response from the postsurgery specimen as the standard of reference (44–56). In these studies, FDG PET was performed before therapy and then at two or more time points (early [after a single cycle of therapy], mid-therapy, and after therapy) during the course of NST (Fig 9). The pretherapy scan serves as
the baseline to assess future changes in the level of FDG uptake (Fig 10) but is also important in defining the extent of disease that may affect postsurgical treatment, such as radiation therapy, by demonstrating occult nodal or distant metastatic disease.

The majority of studies evaluating FDG PET to assess response to NST have measured change in FDG uptake at midtherapy compared to baseline as a measure of response. The results of these studies are summarized in Table 6. Wahl et al (56) were among the first to show that serial FDG PET imaging allows differentiation of responders versus nonresponders, by measuring changes in tumor FDG SUVs with treatment. They showed significant quantitative differences in the FDG uptake measured before and after 2 months of therapy for responders versus nonresponders.

Almost all of the subsequent studies have substantiated these findings by demonstrating that decline in primary tumor FDG uptake by approximately 50% or more is predictive of a good response to NST, while more modest decline in FDG uptake is characteristic of nonresponders (47) (Fig 11). The prognostic significance of the degree of FDG decline has not yet been established, but Mankoff and colleagues (47–50,57) have shown that a 50% or greater decline is associated with improved survival.

Table 6

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Therapy*</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahl et al 1993</td>
<td>11</td>
<td>AC</td>
<td>Response = 48% decrease in SUV, NR = 19% decrease in SUV for all patients</td>
</tr>
<tr>
<td>Bassa et al 1996</td>
<td>15</td>
<td>FAC</td>
<td>51% decrease in SUV for all patients</td>
</tr>
<tr>
<td>Schelling et al 2000</td>
<td>24</td>
<td>EC or ET</td>
<td>mCR = 46% decrease in SUV, no mCR = 8% decrease in SUV</td>
</tr>
<tr>
<td>Smith et al 2000</td>
<td>30</td>
<td>CVAP</td>
<td>mCR = 86% decrease in SUV, no mCR = 40% decrease in SUV</td>
</tr>
<tr>
<td>Mankoff et al 2003</td>
<td>35</td>
<td>FAC or AC (weekly)</td>
<td>mCR = 65% decrease in MRFDG, PR = 49% decrease in MRFDG, NR = 40% decrease in MRFDG</td>
</tr>
</tbody>
</table>

*AC = doxorubicin and cyclophosphamide; CVAP = cyclophosphamide, vincristine, doxorubicin, and prednisolone; EC = epirubicin and cyclophosphamide; ET = epirubicin and paclitaxel; FAC = fluorouracil, doxorubicin, and cyclophosphamide.
†mCR = macroscopic complete response, MRFDG = metabolic rate of FDG, NR = no response, PR = partial response.
have demonstrated a trend toward improved disease-free survival for patients who had lower midtherapy FDG uptake. The possibility that FDG PET could serve as a quantitative surrogate marker for treatment efficacy is an important focus of ongoing research (57).

Studies evaluating change in FDG uptake early in the course of therapy suggest that early assessment of response is possible and predictive of subsequent pathologic response (Table 7). Three studies that measured FDG uptake after the first cycle of therapy all demonstrated that early FDG PET results were predictive of final response (53, 54, 56). In two of these studies, the data suggest that early FDG PET imaging may demonstrate greater separation between responders and nonresponders than midtherapy imaging.

Rousseau et al (52) recently reported on the efficacy of FDG PET for evaluating early response to NST in 64 patients with stage II and III breast cancer who underwent PET after the first, second, third, and sixth courses of chemotherapy. Using a 60% decrease in baseline SUV as their threshold for response, they found that FDG PET was 61% sensitive and 96% specific after a single cycle, and this increased to 89% sensitive and 95% specific after two cycles of therapy. The negative predictive value of FDG PET rose from 68% after a single cycle to 85% after a second cycle. Of interest is that FDG PET performed after the third cycle was less sensitive and specific and had lower negative predictive value than imaging performed after the second cycle. This

---

Table 7

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Therapy*</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahl et al 1993</td>
<td>11</td>
<td>AC</td>
<td>Response = 22% decrease in SUV, NR = no change</td>
</tr>
<tr>
<td>Schelling et al 2000</td>
<td>24</td>
<td>EC or ET</td>
<td>mCR = 54% decrease in SUV, no mCR = 19% decrease in SUV</td>
</tr>
<tr>
<td>Smith et al 2000</td>
<td>30</td>
<td>CVAP</td>
<td>mCR = 77% decrease in SUV, no mCR = 1% increase in SUV</td>
</tr>
</tbody>
</table>

*AC = doxorubicin and cyclophosphamide; CVAP = cyclophosphamide, vincristine, doxorubicin, and prednisolone; EC = epirubicin and cyclophosphamide; ET = epirubicin and paclitaxel.

†mCR = macroscopic complete response; NR = no response.
study suggests that early response to NST is accurately predicted with FDG PET but may be best assessed after two courses of chemotherapy. These findings suggest that FDG PET may serve as an early predictor of chemotherapy response, which is clinically relevant given the increasing number of new medical therapies available for breast cancer.

Studies performed after the completion of chemotherapy (Table 8) have shown that while residual FDG uptake is predictive of residual disease, the absence of FDG uptake is not a reliable indicator of complete pathologic response (44–47). This is especially true for axillary nodal disease, since the sensitivity for residual microscopic disease is low. In patients with gross residual disease, posttherapy FDG PET has been shown to be complementary to magnetic resonance (MR) imaging in helping define the extent of residual disease (58).

In summary, multiple studies have evaluated serial FDG PET imaging performed at different time points after initiation of neoadjuvant therapy and have demonstrated the following: (a) A serial decrease in tumor FDG uptake, measured as SUV or the metabolic rate of FDG, is an indicator of response. (b) FDG PET performed early or at midtherapy is predictive of complete microscopic response and may serve as a surrogate marker for response. (c) Changes in FDG metabolism often precede morphologic changes in tumor and therefore PET can demonstrate response sooner than conventional imaging techniques. (d) FDG PET is likely to be most helpful as an early marker for resistance to therapy. FDG PET imaging performed after completion of therapy allows confirmation of gross residual disease but does not allow exclusion of residual microscopic malignancy.

### Evaluating Treatment of Recurrent or Metastatic Disease with FDG PET

Metastatic breast cancer is often responsive to systemic therapy, and although cure is rarely achieved, with appropriate therapy, patients often have prolonged survival and preserved quality of life. FDG PET can be particularly useful in this setting to evaluate the response of metastatic breast cancer to systemic therapy, since conventional imaging is often challenging in this setting.

Studies have shown that, as in presurgical therapy of LABC, serial FDG PET is accurate in depicting response to treatment. Gennari and colleagues (59) demonstrated that a decline in FDG uptake of 50% or greater indicated a good response to treatment in the metastatic disease setting. They also showed that response might be visible as early as after a single cycle of chemotherapy. Their results were confirmed in a recent study by Dose Schwarz et al (60). A recent study by Cachin et al (61) demonstrated that changes in FDG uptake were prognostic. Absence of FDG uptake after therapy predicted better survival compared to that of patients with residual FDG-positive disease in a series of patients with metastatic breast cancer.

Bone metastases have presented a particularly vexing problem for measuring response. While bone scanning, MR imaging, and CT are effective in detecting bone metastases, it can be difficult to discern changes in response to therapy with these modalities. The bone scan can even worsen or “flare” in response to successful therapy (62). Recent studies have suggested that serial FDG PET can be helpful in measuring bone metastasis response and that changes in FDG uptake correlate with clinical response and changes in breast cancer tumor markers (63). Recent data show that these changes are predictive of time to progression and the likelihood of a skeletal event (64). Further study is needed to evaluate the utility and accuracy of PET in this role. The combination of FDG and fluoride PET, to measure

### Table 8
Results of Studies of Posttherapy Response Evaluation with FDG PET

<table>
<thead>
<tr>
<th>Authors and Year of Study</th>
<th>No. of Patients</th>
<th>Therapy*</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassa et al 1996</td>
<td>11</td>
<td>FAC</td>
<td>In the primary tumor, sensitivity = 75%; in the axilla, sensitivity = 42% and specificity = 100%</td>
</tr>
<tr>
<td>Burcombe et al 2002</td>
<td>9</td>
<td>FEC</td>
<td>In the primary tumor, sensitivity = 0% (0 of 9 patients); in the axilla, sensitivity = 0% (0 of 3 patients)</td>
</tr>
<tr>
<td>Kim et al 2002</td>
<td>50</td>
<td>AT or XT</td>
<td>In the primary tumor, sensitivity = 86% and specificity = 83%</td>
</tr>
</tbody>
</table>

*AT = doxorubicin and docetaxel; FAC = fluorouracil, doxorubicin, and cyclophosphamide; FEC = fluorouracil, etoposide, and cisplatin; XT = capecitabine and docetaxel.
both sclerotic and lytic lesion response, may be helpful in this application (Fig 12).

**Conclusions**

FDG PET and PET/CT have been shown to be most helpful in staging recurrent or metastatic breast cancer and in evaluating the response of locally advanced and metastatic breast cancer to treatment. These are the only current clinical indications for FDG PET/CT in breast cancer and the only ones routinely reimbursed by the Centers for Medicare and Medicaid Services. Emerging data support the use of FDG PET/CT in advanced axillary disease and evaluation of regional nodal spread in LABC. Currently, only FDG and occasionally fluoride PET are used in clinical practice. It is likely that future studies will benefit from tracers other than FDG, for example 18F fluorestradiol to image estrogen receptor expression, to image a much wider range of tumor biologic features (65,66).

**References**

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