Performance of FDG PET/CT in the Clinical Management of Breast Cancer[1]

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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 IIA and IIB and primary operable stage IIIA 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: $SUV = A_{mea}/(A_{inj}/W)$, where A_{mea} 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.

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Abbreviations:
NAC = neoadjuvant chemotherapy
SUV = standardized uptake value
SUV_{max} = maximum SUV

Conflicts of interest are listed at the end of this article.

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 [SUV_{max}], 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 progesterone 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 SUV_{max}, 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 SUV_{max}, 3.4) compared with the 107 patients with invasive ductal carcinoma (median SUV_{max}, 6.6). We further showed that seven patients with metaplastic breast cancer, a less common variety, had a very high FDG uptake (median SUV_{max}, 12.9) (23).

Figure 1

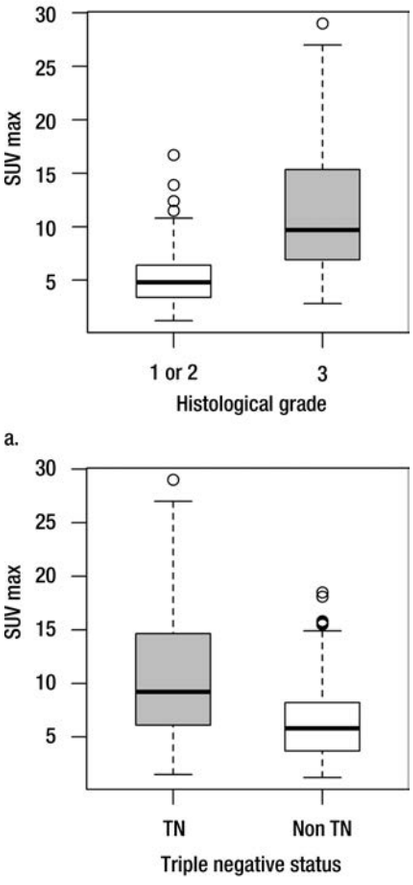


Figure 1: Graphs show results from prospective study evaluating SUV_{max} in the primary tumor of 132 women with large (>2-cm) or locally advanced breast carcinoma. **(a)** SUV_{max} according to histologic grade (52 grade 3 tumors vs 76 grade 1–2 tumors) and **(b)** SUV_{max} in 35 tumors with triple-negative *(TN)* status versus 96 tumors with no triple-negative *(Non TN)* phenotype. Central box = 25th to 75th percentiles, horizontal line = median. (Reprinted, with permission, from reference 23.)

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

FDG PET imaging has poor sensitivity for infracentimetric 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

unable to help define the nature (benign or malignant) of the mass.

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 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 ($P = .003$).

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.

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

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 66% (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.

Regional and Distant Staging in Large, Locally Advanced and Inflammatory Breast Cancer (Stages II–III)

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 extraaxillary nodal 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 IIIA, IIIB, and IIIC). 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

Table 1

TNM Staging System for Breast Cancer according to the *AJCC Cancer Staging Manual*

TNM Category	Clinical Data
Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	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
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
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 supraclavicular 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 supraclavicular lymph nodes
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Note.— Adapted and reprinted, with permission, from reference 36.

* A clinically detected lymph node is defined as one detected by using imaging studies (excluding lymphoscintigraphy) or by using clinical examination and having characteristics highly suggestive of malignancy, or a presumed pathologic macrometastasis on the basis of results of fine-needle aspiration biopsy with cytologic examination.

Table 2

TNM Stage Grouping for Breast Cancer according to the *AJCC Cancer Staging Manual*

Stage	T Category	N Category	M Category
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0	N1mi	M0
	T1*	N1mi	M0
IIA	T0	N1†	M0
	T1*	N1†	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

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.

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 (supraclavicular or internal mammary), may have important implications in surgical and radiation therapy. In a patient scheduled to undergo 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

Table 3

Studies Evaluating FDG PET/CT for Staging

Study/Year/Type	Setting	No. of Patients	PET/CT Imaging	Conventional Imaging, with Other Modalities Performed	Effect of PET/CT Results (%)*			
					Detection of Unknown Node Metastases†	Detection of Unsuspected Distant Metastases	Modification in Initial Staging	Modification in Treatment Plan
Groheux et al (40)/2008/P	Stage II–III breast cancer	39	WB PET performed approximately 60 min after FDG injection; low-dose nonenhanced CT	Mammography, with or without breast MR imaging; breast US; abdominal US, with or without abdominal CT; chest radiography or CT, bone scintigraphy	8	10	18	13
Heusner et al (27)/2008/R	T1–T3 noninflammatory breast cancer	40	WB PET performed approximately 60 min after FDG injection plus additional breast PET acquired 110 min after injection; contrast-enhanced CT	Breast MR imaging, axillary US, chest radiography, abdominal US, bone scintigraphy	7.5	7.5	NA	12.5
Fuster et al (39)/2008/P	Large (T category > 3 cm) noninflammatory breast cancer	60	WB PET performed approximately 60 min after FDG injection; nonenhanced CT	Breast MR imaging, chest contrast-enhanced CT, liver US, bone scintigraphy	5	8.5	42‡	6.5
Yang et al (38)/ 2008/R	Inflammatory breast cancer	24	WB PET performed approximately 60–90 min after FDG injection; nonenhanced CT	Mammography, breast US, and MR imaging	25§	38	NA	NA
Carkaci et al (37)/2009/R	Inflammatory breast cancer	41	WB PET performed approximately 60–90 min after FDG injection; nonenhanced CT	Mammography, breast US, or MR imaging; bone scintigraphy, chest radiography, chest and abdominal CT	15 for supraclavicular area; 22 for internal mammary basin§	17	NA	NA
Alberini et al (25)/2009/P	Inflammatory breast cancer	59	WB PET performed approximately 60 min after FDG injection; low-dose nonenhanced CT	Chest radiography, abdominal US, bone scintigraphy; if necessary, additional CT investigations were performed	56§	31§	NA	NA
Aukema et al (41)/2010/P	Stage II–III breast cancer	60	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	Mammography, breast US, breast MR imaging	17	NA	17	12
Segaert et al (42)/2010/R	Stage IIB–III breast cancer	70	WB PET performed 75 min after FDG injection; contrast-enhanced CT performed during breath hold at expiration tidal volume	Chest radiography, liver US, bone scintigraphy, breast and axillary US	13, internal mammary basin	10	NA	NA

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.

Figure 2

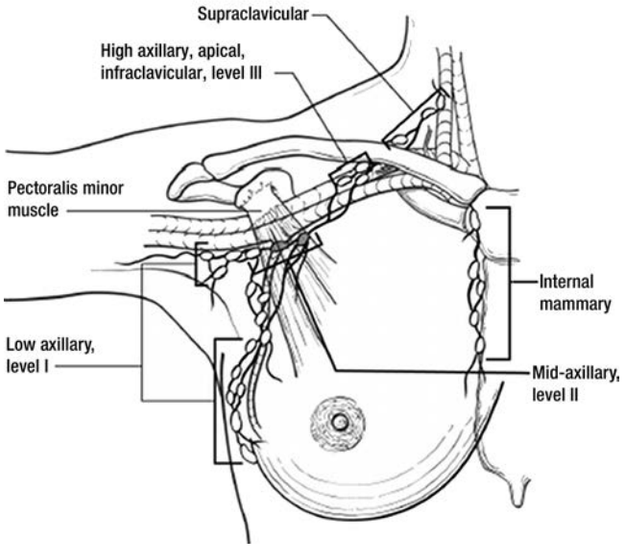


Figure 2: Schematic of breast and regional lymph nodes according to the *AJCC Cancer Staging Manual* (36). (Reprinted, with permission, from reference 36).

Figure 3

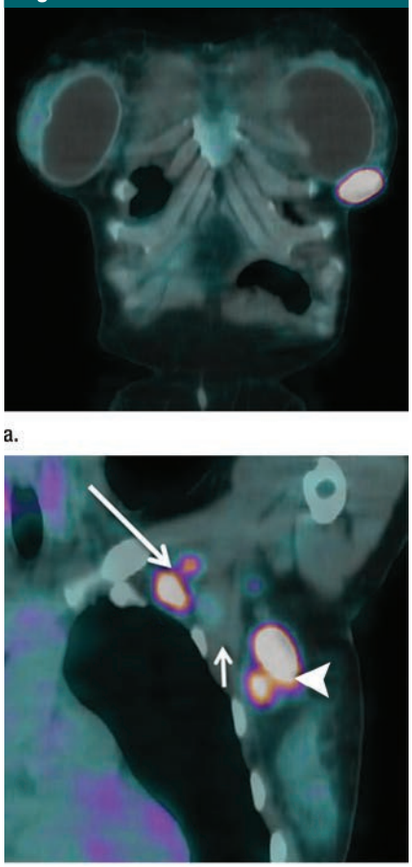


Figure 3: Invasive ductal carcinoma of left breast in a 61-year-old woman who had undergone aesthetic breast surgery, with bilateral breast prosthesis, 10 years earlier. Before PET/CT, the tumor was classified as a T2N2 lesion (primary tumor of 45 mm with ipsilateral matted level I axillary lymph node metastases). **(a)** Coronal PET/CT fusion image shows high FDG uptake in the primary tumor (SUV_{max}, 15.7). **(b)** Coronal PET/CT fusion image shows FDG uptake also in axilla, level I (arrowhead), as well as in infraclavicular nodes (axilla, level III [long arrow]), medial to the pectoralis minor muscle (short arrow). With PET/CT results, the clinical stage was T2N3a.

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 extraaxillary 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 extraaxillary lymph node involvement (12% of the total group) missed by using US (41).

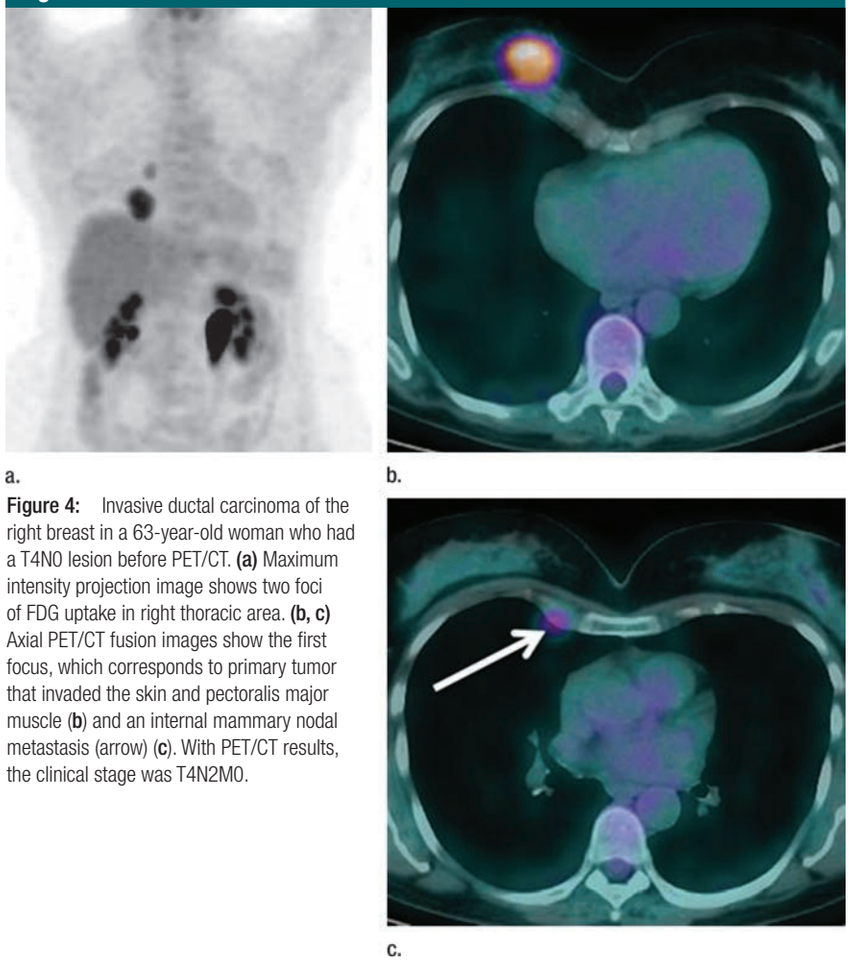
Detection of Distant Metastases

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 59 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

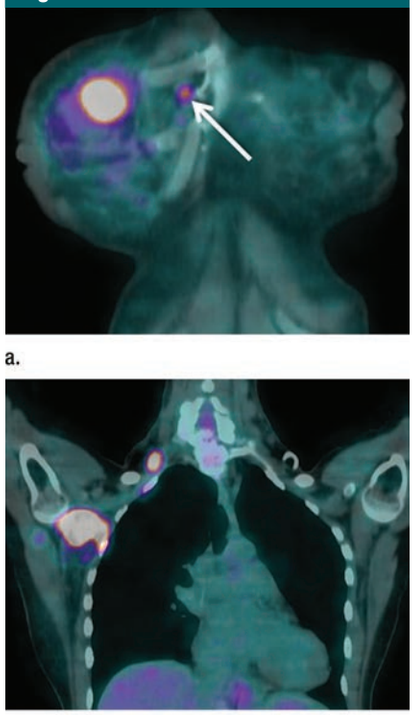
Figure 4



a. b. c.

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



a. b.

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 T4bN3cM0.

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 PET/CT was better than 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 6

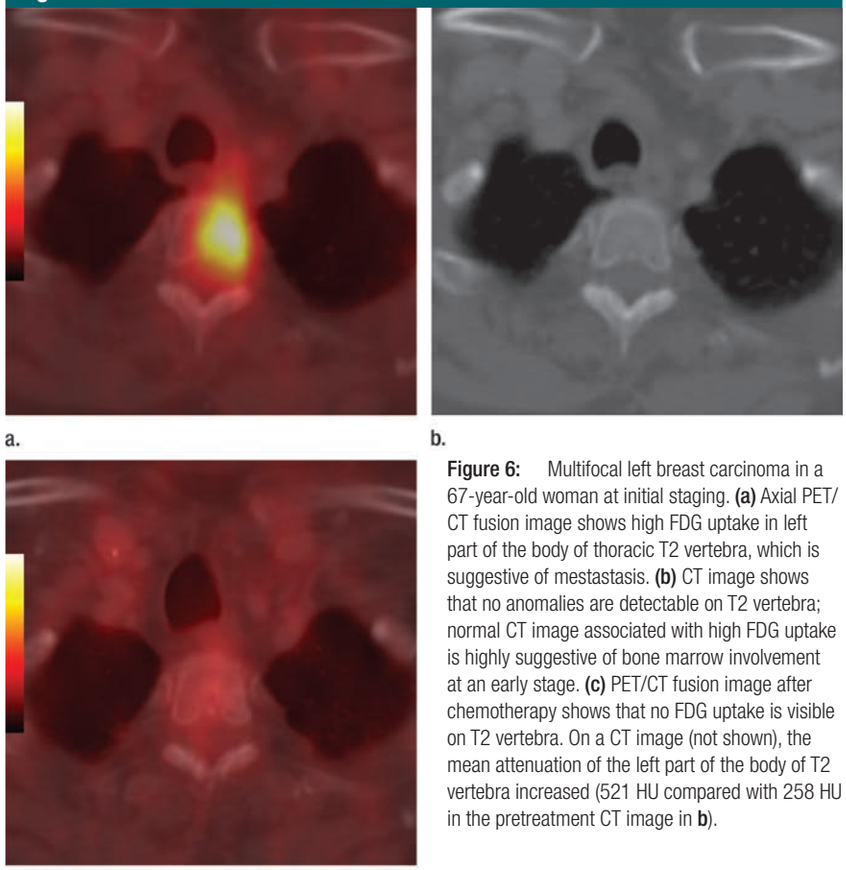


Figure 6: Multifocal left breast carcinoma in a 67-year-old woman at initial staging. **(a)** Axial PET/CT fusion image shows high FDG uptake in left part of the body of thoracic T2 vertebra, which is suggestive of mestastasis. **(b)** CT image shows that no anomalies are detectable on T2 vertebra; normal CT image associated with high FDG uptake is highly suggestive of bone marrow involvement at an early stage. **(c)** PET/CT fusion image after chemotherapy shows that no FDG uptake is visible on T2 vertebra. On a CT image (not shown), the mean attenuation of the left part of the body of T2 vertebra increased (521 HU compared with 258 HU in the pretreatment CT image in **b**).

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 lesionss), 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 (T3N1 lesions) (49). 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

Studies Evaluating FDG PET/CT for Restaging

Study/Year*	Inclusion Criteria	No. of Patients	PET/CT Timing and CT Type	Comparative Modality	PET/CT Results (%)					Best Imaging Modality	Remarks
					Sensitivity	Specificity	PPV	NPV	Accuracy		
Fueger et al (50)/2005	Elevated tumor marker; symptoms; equivocal or suspicious findings at other imaging studies	58	PET/CT, 60 min after FDG injection; NE CT	PET	94	84	NA	NA	90	PET/CT	PET was performed as part of PET/CT study; PET/CT marginally improved restaging accuracy compared with PET alone
Radan et al (51)/2006	Elevated serum tumor markers	46	PET/CT, 60 min after FDG injection; NE CT	CE CT	85	76	81	81	81	PET/CT	PET/CT performance was evaluated in 37 patients who underwent both CT and PET/CT
Haug et al (52)/2007	Elevated tumor markers but without proved metastases	34	PET/CT, 60 min after FDG injection; CE CT	CE CT and PET	96	89	96	89	NA	PET/CT	PET and CT were performed as part of PET/CT study; differences between PET/CT and CT ($P < .01$) and PET/CT and PET ($P < .01$) were significant
Veit-Haibach et al (53)/2007	Elevated tumor markers ($n = 15$); suspicious finding at examination with another imaging modality or suspicious physical examination results ($n = 29$)	44	PET/CT, 60 min after FDG injection; CE CT	CE CT and PET	NA	NA	NA	NA	91	PET/CT	PET and CE CT were performed as part of PET/CT study; PET/CT performance was better than PET or CT performance alone; differences were not significant
Schmidt et al (54)/2008	Clinical suspicion of recurrence ($n = 9$); conspicuous finding at examination with other imaging modality ($n = 14$); elevated tumor marker ($n = 10$)	33	PET/CT, 60 min after FDG injection; CE CT	WB MR imaging (1.5 T [$n = 23$], 3 T [$n = 10$])	91	90	NA	NA	91	PET/CT and MR imaging	PET/CT depicted more lymph node metastases than WB MR imaging; WB MR imaging was more precise in detection of distant metastases
Dirisamer et al (55)/2009	Elevated tumor marker ($n = 32$); clinical deterioration ($n = 16$) and/or suspicious findings at other imaging examination ($n = 48$)	52	PET, 50 min after FDG injection, with delayed scanning in case of suspected liver metastasis; CE CT	CE CT and PET	93	100	99	NA	98	PET/CT	PET and CE CT were performed as part of PET/CT study
Aukema et al (56)/2010	Patients with confirmed local-regional recurrence referred to visualize the extent of recurrence and exclude distant involvement	56	PET/CT, 60 min after FDG injection; low-dose NE CT	Chest MR imaging ($n = 21$); chest CT ($n = 20$), chest radiography ($n = 32$), liver US ($n = 30$), bone scintigraphy ($n = 35$)	97	92	94	96	95	PET/CT	PET/CT confirmed all local-regional recurrences and depicted additional findings in 12 patients

Table 4 (continues)

Table 4 (continued)

Studies Evaluating FDG PET/CT for Restaging

Study/Year*	Inclusion Criteria	No. of Patients	PET/CT Timing and CT Type	Comparative Modality	PET/CT Results (%)					Best Imaging Modality	Remarks
					Sensitivity	Specificity	PPV	NPV	Accuracy		
Grassetto et al (57)/2010	Increased marker levels with negative results of clinical examination and conventional imaging	89	PET/CT, 60 min after FDG injection; NE CT	Mammography, chest and abdominal CE CT, abdominal US, and bone scintigraphy	NA	NA	NA	NA	NA	PET/CT	Tumor deposits were detected in 40/89 (45%) patients
Evangelista et al (58)/2011	Suspicion at clinical examination or at examination with another imaging modality, such as chest or bone radiography or bone scanning	111	PET/CT, 60 min after FDG injection; low-dose NE CT	Diagnostic CT and CA 15-3	81	52	41	87	60	PET/CT	FDG PET/CT was more sensitive than CT and CA 15-3 in evaluation of disease relapse
Champion et al (59)/2011	Asymptomatic patients with increased CA 15-3 and/or CEA serum levels	228	PET/CT, 60 min after FDG injection; low-dose NE CT	Standard workup	94	85	97	74	92	PET/CT	Compared with conventional workup in 67 patients, PET/CT had higher sensitivity (94.5% vs 33%) and accuracy (94% vs 48%)

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.

* All studies were retrospective except that of Haug et al (52), where it was not specified, and of Schmidt et al (54), which was prospective.

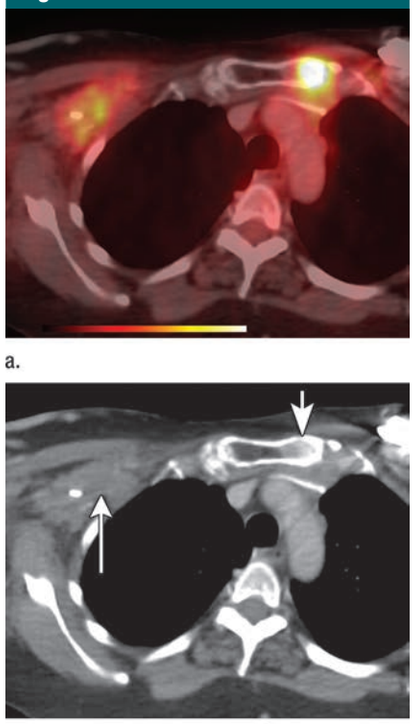
levels but negative conventional imaging (mammography, chest and abdomen contrast-enhanced CT, abdominal US, and bone scanning) results were examined with FDG PET/CT. Tumor deposits were detected in 40 of 89 patients, and 23 patients had a solitary small lesion treated by using radical therapy. In seven of these 23 patients, a complete disease remission lasting more than 1 year was observed.

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, et cetera.

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

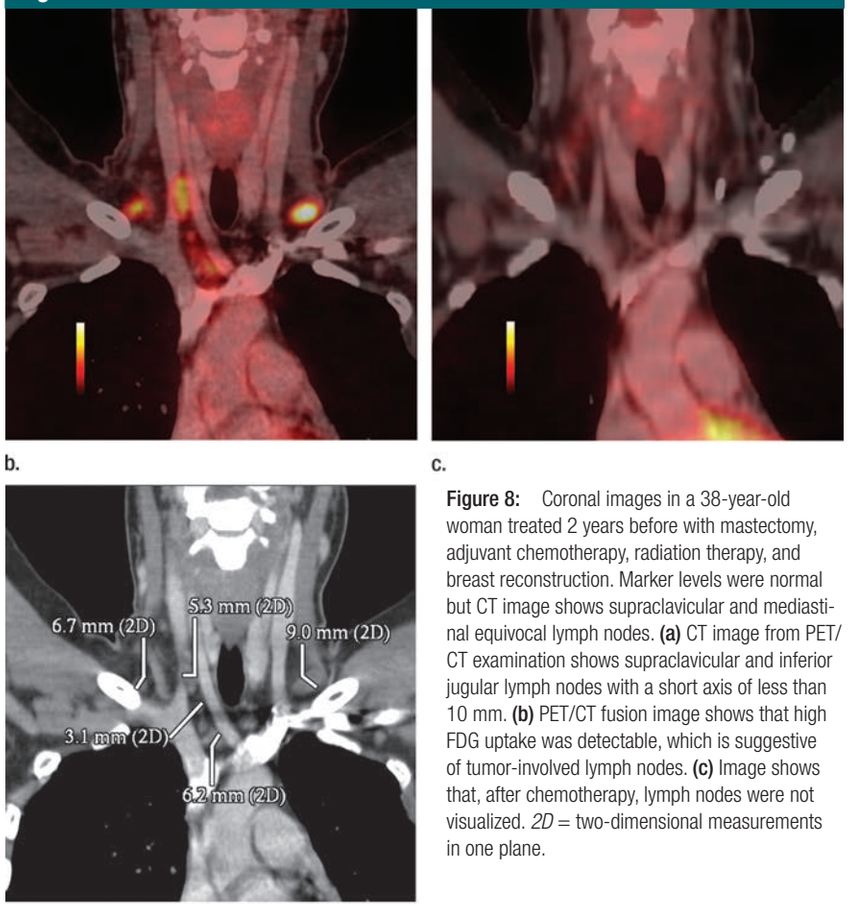


a.

b.

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



a. b. c.

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.

separated (61). Six studies performed with PET/CT were included (50–55). Hybrid PET/CT had significantly higher sensitivity compared with CT but the increase in specificity was not significant. PET/CT also had significantly higher sensitivity compared with PET, but the increase in specificity was not significant (61). There were no significant differences in the sensitivity or specificity of PET/CT when compared with MR 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).

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

Figure 9

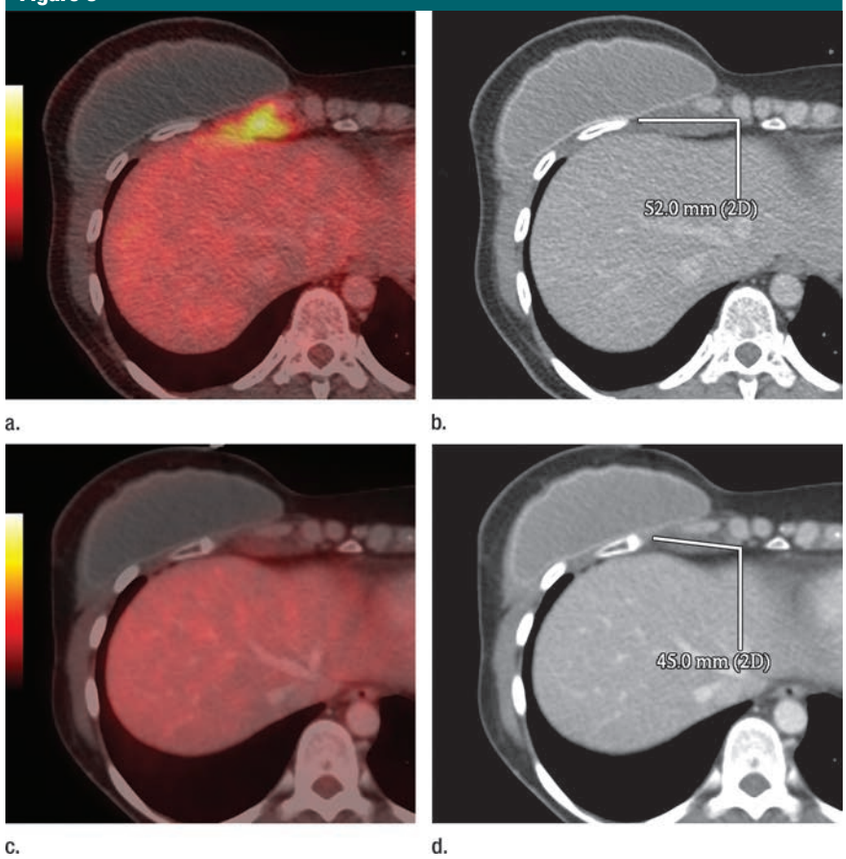


Figure 9: Same patient as in Figure 8. **(a)** Axial PET/CT fusion image shows high FDG uptake, which is suggestive of recurrence behind the breast prosthesis. **(b)** Axial CT image from PET/CT examination shows soft-tissue mass with a long axis of 52 mm. This recurrence behind the breast prosthesis was not reported before PET/CT. **(c)** Axial PET/CT fusion image shows that, after chemotherapy, FDG uptake no longer was visible behind the prosthesis. **(d)** Axial CT image shows persistent mass with long axis of 45 mm (−13% in comparison with 52 mm in the pretreatment image). *2D* = two-dimensional measurements in one plane.

Figure 10

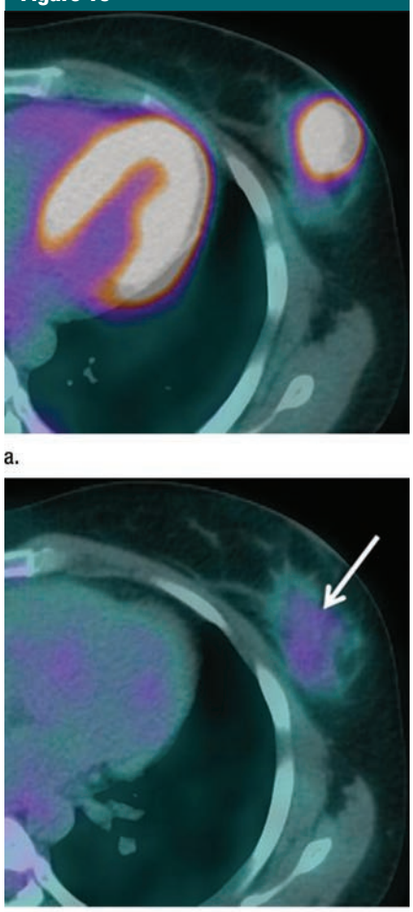


Figure 10: Early evaluation of NAC with FDG PET/CT (in the setting of a prospective study at Saint-Louis Hospital) in a 38-year-old woman with invasive ductal carcinoma of lower outer quadrant of the left breast. **(a)** Axial FDG PET/CT fusion image shows that, at baseline, SUV_{max} in the tumor was 13.6. **(b)** Axial image shows that, after two courses of primary chemotherapy, SUV_{max} was 2.3, corresponding to an 83% decrease (arrow). Mastectomy performed at completion of NAC (after eight courses) showed a pathologic complete response.

which a possible role for metabolic evaluation with FDG PET and PET/CT was examined, investigators demonstrated a correlation between early changes in the SUV_{max} 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

Studies Evaluating the Decrease of SUV_{max} during NAC for Breast Cancer with FDG PET (/CT)

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

Note.— LABC = locally advanced breast cancer, pCR = pathologic complete response.

change of treatment in case of ineffectiveness (66,68,74). However, performing response assessment as early as the first cycle might also be valuable (73).

Furthermore, the pretreatment tumor SUV index must be high to detect a meaningful reduction during treatment (70,73). This requirement limits the use of iterative PET in case of tumors 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 histopathologic 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, different risks of relapse, different treatment options, and different prognoses. We therefore suggest that the clinical aims of early FDG monitoring and the criteria used to assess effectiveness should be examined in specific subgroups (65,75). We recently reported results in the subset of patients with triple-negative tumors, showing that FDG PET/CT at two cycles can be efficient in discriminating 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 measurements of tumor lesions before and after treatment for response assessment and follow-up (77,78). However, several cycles of treatment are needed before a change in tumor size can be assessed with anatomic imaging. Moreover, modification in bone metastases, pleural effusion, and lymphangitis, which are common sites of breast cancer dissemination, 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 substantial modification of their size. Functional 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 additional and useful information to assess the evaluation of systemic chemotherapy. For example, the increase in attenuation in bone metastases (measured in Hounsfield units) and the decrease in SUV are altogether potential predictors 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 heterogeneous response (coexistence of responding and nonresponding lesions within the same patient) (83).

Specific PET criteria for determining the therapeutic response have already been proposed by various working 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 classified 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 longest 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 standardization 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 response. This phenomenon has been described 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 antagonist 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). However, these results have been reported in small numbers of patients, and furt work is therefore needed to better analyze 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 uptake is different from one study to another. 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 extraaxillary lymph nodes and distant metastases. PET/CT also brings valuable information in the staging of clinical stage IIB and primary operable stage IIIA breast carcinoma. 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.

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