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# Evolving Role of Positron Emission Tomography in Breast Cancer Imaging

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**$^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for detection, staging, and response monitoring in breast cancer patients. Although studies have proven its accuracy in detection of the primary tumor and axillary staging, its most important current clinical application is in detection and defining the extent of recurrent or metastatic breast cancer and for monitoring response to therapy. PET is complementary to conventional methods of staging in that it provides better sensitivity in detecting nodal and lytic bone metastases; however, it should not be considered a substitute for conventional staging studies, including computed tomography and bone scintigraphy. FDG uptake in the primary tumor carries prognostic information, but the underlying biochemical mechanisms responsible for enhanced glucose metabolism have not been completely elucidated. Future work using other PET tracers besides FDG will undoubtedly help our understanding of tumor biology and help tailor therapy to individual patient by improving our ability to quantify the therapeutic target, identify drug resistance factors, and measure and predict early response.**

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Breast cancer is the most common nonskin cancer and the second-leading cause of cancer death in women.[1] Despite advances in the adjuvant treatment of early stage disease, many women will have breast cancer relapse that often is not amenable to complete surgical excision. There are 40,000 women per year dying of breast cancer in the United States, and most breast cancer victims die of progressive metastatic disease.[1] The ability to define the extent of disease, to monitor response, and to predict tumor behavior in patients with breast cancer are therefore important public health problems in which positron emission tomography (PET) imaging may play a significant role.

The recognition that breast cancer is a systemic disease, even in its early stages, led to the current approach to treatment that combines local measures such as surgery and radiotherapy with systemic treatment.[2] Defining the extent of disease is key to choosing appropriate treatment and to tailoring local treatment options to the patient and her disease. This is an important role for PET, especially in patients with more advanced or recurrent disease. An equally important clinical need is monitoring systemic therapy to assess the success or failure of a particular form of systemic treatment. Many solid tumors respond poorly to systemic therapy; however, breast cancer is one of the more chemotherapy-sensitive solid tumors.[2] Women with locally advanced or metastatic breast cancer can have prolonged remissions.[3-5] Those that have failed first-line chemotherapy still have a number of reasonable choices for second-line therapy with substantial response rates.[2] In addition, there are a number of other systemic options besides cytotoxic chemotherapy, including hormonal and other biologically targeted therapies.[6,7] However, the ability to predict and evaluate systemic therapy response in these patients is limited. Because we currently rely on changes in tumor size to assess response, it takes several weeks to months to evaluate efficacy.[8,9] For therapies that are potentially cytostatic, such as hormonal therapy, it can be impossible to discern tumor response from slow disease progression when relying on anatomically-based measures of response. This is an area where biochemical imaging using PET offers significant advantages and where PET is likely to play a clinically important role. In this review, we highlight current and future applications of PET to breast cancer, focusing on those applications of greatest current and future clinical relevance.

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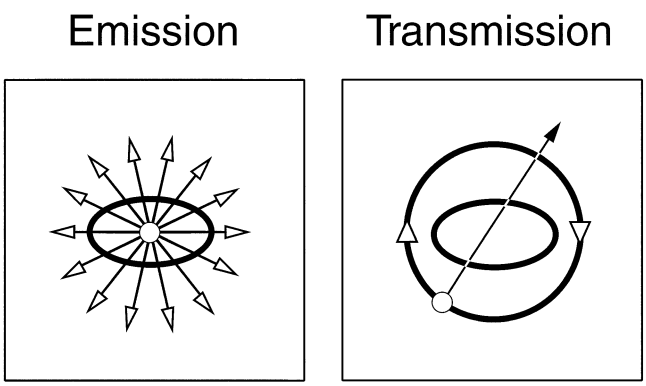


**Figure 1** Illustration of scanning modes for PET. Emission scanning (left) captures annihilation photons from positron-emitting tracers in the patient. Transmission scanning (right) uses a source external to the patient to measure photon attenuation.

## PET Principles and Instrumentation

Positron-electron annihilation after positron emission leads to 2 opposing 511 kev photons. PET tomographs are designed to detect "coincident" photon pairs along all possible projection lines through the body to reconstruct quantitative maps of tracer concentration. Tomographs primarily collect annihilation photon counts from the patient (emission scans); however, they also use transmission or attenuation scanning to correct for the body's absorption of photon pairs (Fig. 1). Commercially available dedicated PET tomographs achieve high sensitivity to annihilation photon pairs using a ring of detectors, either blocks of small crystals or large continuous crystals, surrounding the patient. The practical spatial resolution using current instrumentation is 5 to 10 mm.[10,11] High-quality imaging of the torso can be achieved in 45 to 60 minutes.

The positron-emitter most commonly used in routine clinical applications is F-18 (in the form of $^{18}$F-fluorodeoxyglucose [FDG]). With a nearly 2-hour half-life, FDG can be produced in regional tracer production facilities and shipped to facilities that are within a 1- to 2-hour flight of the production facility. The biochemical behavior of FDG is illustrated in Fig. 2. FDG is transported into cells and phosphorylated in parallel to glucose; however, unlike glucose, it is not a substrate for enzymatic reactions beyond phosphorylation. Furthermore, it is not readily dephosphorylated in most tissues, including tumors, and the phosphorylated compound cannot cross cell membranes. Therefore, phosphorylated FDG is "metabolically trapped" in the cell as FDG-6P.

The rate of FDG uptake and trapping is a quantitative indicator of glucose metabolism. Static measures of FDG uptake normalized to the injected dose, frequently referred to as the standard uptake value (SUV), provide an approximate indicator that correlates with FDG metabolism:[12] SUV = A/(ID/BW), where A is the tissue tracer content ($\mu$Ci/g), ID is injected dose (mCi), and BW is patient weight (kg). Although less precise than kinetic determinations, SUV is conveniently implemented in a routine clinical setting.

The studies of Warburg in the 1930s[13] established that glucose metabolism is elevated in tumors in comparison with normal tissues. The observation that FDG accumulates in most untreated tumors led to the concept that increased FDG uptake reflects increased glucose metabolism in tumors. Although this is undoubtedly an important cause of uptake in tumors, some recent work[14] has suggested that the handling of FDG relative to glucose is different in tumors versus normal tissue in a way that may increase the prominence of FDG uptake in tumors. Ongoing studies seek to elucidate the nature of FDG uptake in tumors and will provide further insights into the biologic significance of increased FDG uptake in tumors.

## Detection of Primary Breast Cancer

Most of the larger prospective studies using FDG-PET on patients with unconfirmed, suspicious breast abnormalities by clinical or mammographic examinations have shown some of the limitations of FDG-PET in detecting (1) smaller (<1 cm) tumors, (2) more well-differentiated histologic subtypes of tumors (tubular carcinoma and in situ carcinoma), and (3) lobular carcinomas. The overall sensitivities and specificities in these studies ranged from 80% to 100% and 75% to 100%, respectively.[15-20] In the largest of these series,[18] the sensitivity for detecting tumors less than 1 cm using sensitive imaging reading criteria was 57% (13/22), compared with 91% (155/170) for tumors larger than 1 cm. The sensitivity for detecting carcinoma in situ was even lower at 25% (3/12), and there was a significantly higher false-negative rate with infiltrating lobular carcinoma (65% [15/23]) than infiltrating ductal carcinoma (24% [23/97]). The specificity of FDG-PET in differentiating benign from malignant lesions was near 90% in most of these studies with inflammatory conditions accounting for most of the false positive results. Using SUV threshold values of 2.0 to 2.5,[15,17] discrimination of benign from malignant lesions can be obtained with about 90% accuracy.

The ultimate role of FDG-PET in imaging primary breast lesions is not clear. It is not suited for screening purposes of primary breast cancer because of its high expense and modest whole-body radiation exposure. For diagnostic purposes in

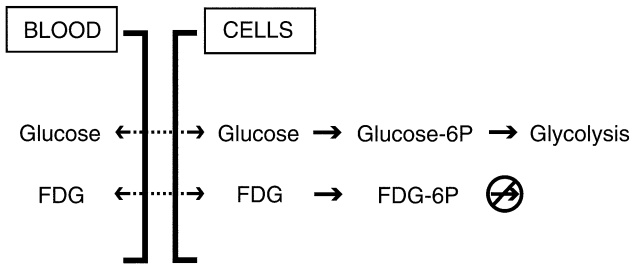


**Figure 2** Diagram of FDG metabolism in comparison to glucose. FDG phosphorylated by hexokinase is "metabolically trapped" and therefore has increased uptake and retention in metabolically active tissue.

general screening, its accuracy does not appear comparable with the standard practice of mammography supplemented by ultrasonography and histologic analysis of specimen obtained from image-directed core needle biopsy.[21] FDG-PET may be helpful because of its high positive predictive value, in selected patients; however, its role in primary tumor detection, especially given evolving alternative imaging methods such as magnetic resonance (MR),[22] remains to be determined.

Recent technologic advances may improve primary breast tumor detection by PET. One prominent approach has been termed positron emission mammography (PEM).[23-26] In PEM, 2 planar detectors are integrated into a conventional mammographic system that enables coregistration of mammographic and emission FDG images of the breast. Although these dedicated breast-imaging systems have the potential capability to detect smaller and less FDG-avid breast tumors than conventional whole-body PET, their role in breast cancer screening or as a diagnostic adjunct to mammography is uncertain. It is likely that certain early breast tumors, with less biologically aggressive features, are less glycolytic than more advanced breast cancer and will evade detection due to insufficient FDG uptake, not simply because of instrumentation limitations.[27] As our knowledge of early breast cancer biology and experience with alternative PET tracers grows, dedicated breast imaging devices may become clinically more important. For now, FDG-PET, even with dedicated imaging devices, is likely to have a relatively small, niche role in primary breast cancer detection.

## Prognostic Value of FDG Uptake in Primary Tumor

Studies have shown that the level of FDG uptake in primary breast tumors carries clinical and biological information.[28-33] The reason for variable FDG uptake among primary breast tumors is unknown. FDG uptake reflects the culmination of complex and incompletely understood biologic characteristics that affect glycolysis in a specific tumor. Most studies suggest that higher FDG uptake is correlated with more clinically aggressive behavior. This information may help to noninvasively (1) stratify patients according to risk for recurrence or treatment failure and (2) target the aggressiveness of therapy for an individual patient to the aggressiveness of her tumor.

Findings from the largest studies that correlate FDG uptake with histologic and immunohistochemical characteristics in postoperative specimens have not been consistent.[29-31,32] Characteristics that show strong positive correlates with FDG SUV in most of these studies include histologic type (higher uptake in ductal versus lobular),[28,30,31,33] tumor histologic grade,[15,28,29] and indices of cellular proliferation (higher uptake with higher levels of proliferation).[30,31,33] Weaker correlation has been reported with microvessel density, a surrogate of angiogenesis[29,31] and tumor cell density.[30,31] Established breast cancer prognostic factors that generally do not correlate with primary tumor FDG uptake are steroid receptor status,[30,33-35] axillary node status,[28,30,33] and tumor size.[30,33,35] Our experience with patients with locally advanced breast cancer (LABC), where the effect of tumor size on FDG uptake is not a factor, shows correlation of FDG uptake with histologic grade and weak correlation with proliferative index. Interestingly, there was an inverse correlation between age and FDG uptake, suggesting a more aggressive phenotype with younger women.[32] In general, correlative studies have suggested that FDG-PET provides information on tumor behavior that is fairly independent of established breast cancer markers and prognostic factors and may therefore contribute additional information that can be used to infer tumor behavior and help tailor therapy.

We postulate an intriguing, but untested, hypothesis that FDG uptake may be a marker of tumor cell resistance to apoptosis, the process that underlies tumor response to therapy.[36] Circumstantial data supporting this hypothesis include the fact that FDG uptake is predictive of response and outcome for tumors treated with a variety of different treatments.[29,32] Several biologic investigators of tumor glucose metabolism have suggested that enhanced glycolysis is part of a coordinated tumor response to avoid apoptosis triggered by environmental stress factors.[37,38] More recent in vitro data suggest that intermediates in the glycolytic pathway are key in initiating apoptosis and that alterations limit apoptosis.[39] Some gene products whose overexpression is associated with resistance to apoptosis, for example, the PI3K/Akt pathway, also are associated with high glycolytic rates.[40] Thus, through a variety of mechanisms, high FDG uptake may be associated with resistance to apoptosis. We continue to investigate this intriguing hypothesis in ongoing studies in our laboratory.

A few studies have evaluated the correlation of FDG uptake in the primary tumor by quantitative methods and patient outcome.[29,32,41] In one study,[29] 70 primary breast cancers were categorized into either low or high FDG uptake and patients were clinically followed for 5 years. The group with high FDG uptake had a significantly worse relapse-free and overall survival compared with the low FDG uptake group. Inoue and coworkers[41] showed that the combination of high pretherapy SUV (>4.0) in the primary tumor and PET-positive axilla was a highly significant and independent prognostic factor of disease-free survival in multivariate analysis. Similarly, our study of patients with LABC showed that high tumor metabolic rate relative to blood flow predicted poorer survival.[32] Larger studies with multivariate analysis and clinical follow-up of at least 5 years will be needed to establish the prognostic value of FDG uptake. Additional insights into tumor biology brought on by the development of newer PET tracers such as $^{11}$C-thymidine (marker for cellular proliferation)[42] and $^{18}$F-fluoromisonidazole (marker for tumor hypoxia)[43] will further refine in vivo characterization of individual tumors.

## Axillary Node Staging

Because axillary node metastasis is the most important prognostic factor in early stage breast cancer patients and the extent of axillary disease influences the choice of therapeutic

**Table 1** Largest Prospective Series Comparing Axillary Nodal Staging Using FDG-PET With Pathologic Results of Axillary Lymph Node Dissection in Patients With Breast Cancer

| Series | Number of Patients | Sensitivity | Specificity |
|---|---|---|---|
| Adler, 1997[44] | 52 | 95 (19/20) | 66 (21/32) |
| Utech, 1996[45] | 122 | 100 (44/44) | 75 (60/80) |
| Avril overall, 1996[46] | 51 | 79 (19/24) | 96 (26/27) |
| T1 tumors | 18 | 33 (2/6) | 100 (12/12) |
| >T1 tumors | 23 | 94 (17/18) | 100 (5/5) |
| Crippa, 1998[28] | 72 | 85 (23/27) | 91 (41/45) |
| Smith, 1998[47] | 50 | 90 (19/21) | 97 (28/29) |
| Greco, 2001[48] | 167 | 94 (68/72) | 86 (82/95) |
| Schirrmeister, 2001[89] | 113 | 79 (27/34) | 92 (73/79) |
| Wahl, 2004[49] | 308 | 61 | 80 |
| Lovrics, 2004[50] | 90 | 40 | 97 |

Numbers in parentheses are patient numbers used to derive sensitivity and specificity values.

regimen for individual patients, a number of studies have evaluated the use of FDG-PET for axillary node staging. The larger series using FDG-PET for axillary staging in breast cancer patients showed a sensitivity in 57% to 100% and specificity in 66 to 100% ranges,[19,35,44-50] shown in the Table 1. Results from these studies, plotted in a receiver-operating curve (Fig. 3), emphasize the trade-off between sensitivity and specificity in the interpretation of FDG-PET findings. In 2 series that included a substantial proportion of patients with smaller primary tumors,[49,50] FDG PET consistently underestimated the number of tumor-involved nodes compared

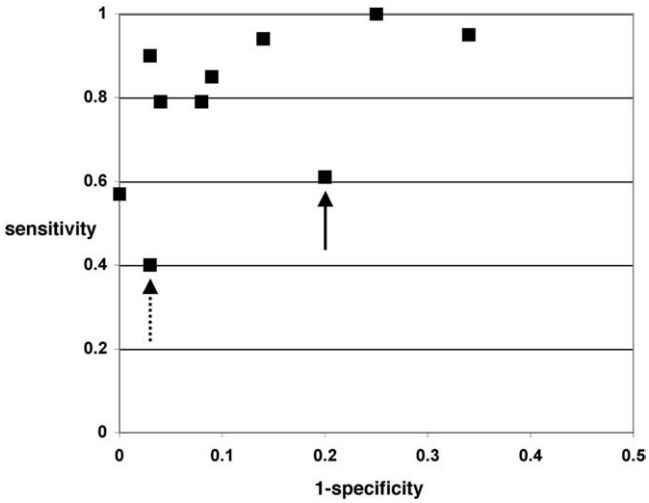


**Figure 3** Receiver operating curve (ROC) scatterplot for prospective studies (see Table 1) evaluating FDG-PET in axillary nodal staging in breast cancer patients. Data points show trade-off between sensitivity and specificity in the interpretation of FDG-PET findings. The data points marked by arrows represents the results from more recent studies that included a greater proportion of T1 tumors (solid arrow; study by Wahl and coworkers[49] and dashed arrow; study by Lovrics and coworkers[50]); performance of FDG-PET in accurately staging the axilla was considerably worse in these 2 studies.

**Table 2** Largest Series Comparing Axillary Nodal Staging Using FDG-PET With Pathologic Results of Sentinel Node Lymph Node Biopsy in Breast Cancer

| Series | N | Sensitivity | Specificity |
|---|---|---|---|
| Yang, 2001[57] | 18 | 50% | 100% |
| Kelemen, 2002[58] | 15 | 20% | 90% |
| Guller, 2002[56] | 31 | 43% | 94% |
| Van der Hoeven, 2002[55] | 70 | 25% | 97% |
| Fehr, 2004[59] | 24 | 20% | 93% |
| Lovrics, 2004[50] | 72 | 27% | 96% |

with pathologic evaluation from conventional axillary dissection. Both of these studies showed that the sensitivity of FDG-PET in detecting axillary metastases is significantly less when only one node is positive versus several positive nodes and when the primary tumor has infiltrating lobular versus ductal histology. These more recent studies underscore the limitation of PET's ability to detect small-volume axillary disease in early-stage breast cancer.

The results of these studies suggest that FDG-PET should not replace axillary node sampling for routine staging of the axilla because even microscopic nodal involvement may be important for prognosis and treatment planning.[51,52] In addition, PET cannot accurately quantify the number of involved nodes or the presence of extranodal extension, other important prognostic factors, because of limited spatial resolution. Sentinel lymph node (SLN) mapping is now a validated, minimally invasive technique that includes histologic analysis of the primary draining nodes in the axilla identified at surgery after perilesional injection of [$^{99m}$Tc]-sulfur colloid and/or blue dye.[53] This technique enables detection of microscopic nodal involvement, using more sensitive immunohistochemical staining of the nodal specimen, and identification of patients with early-stage disease who do not require full axillary dissection. Recent studies comparing preoperative FDG-PET with pathologic results from SLN biopsy in patients with early-stage breast cancer show sensitivity in range of 20% to 50%[50,54-60] (Table 2) with false-negative FDG-PET results occurring predominantly in small-sized (10 mm or less) metastatic sentinel nodes.[54]

Although recent data do not support the routine use of FDG-PET for axillary staging of early breast cancer, FDG-PET may be complementary to SLN mapping and other standard axillary procedures in patients with more advanced tumors and/or equivocally palpable axillary nodes A potential algorithm for using FDG-PET in this fashion is shown in Fig. 4. One concern in more advanced disease, especially with palpable axillary nodes, is that a SLN "packed" with a large volume of disease may not be visualized at mapping because lymph flow is diverted around it, resulting in a potential false negative examination.[61] A clearly positive FDG-PET in selected patients with a high risk of nodal metastases carries high positive predictive value and may identify patients with evidence of nodal metastases. This could indicate the need for standard axillary nodal dissection or other diagnostic and therapeutic approaches, rather than SLN biopsy. This algorithm for evaluating patients at high risk for axillary metas-

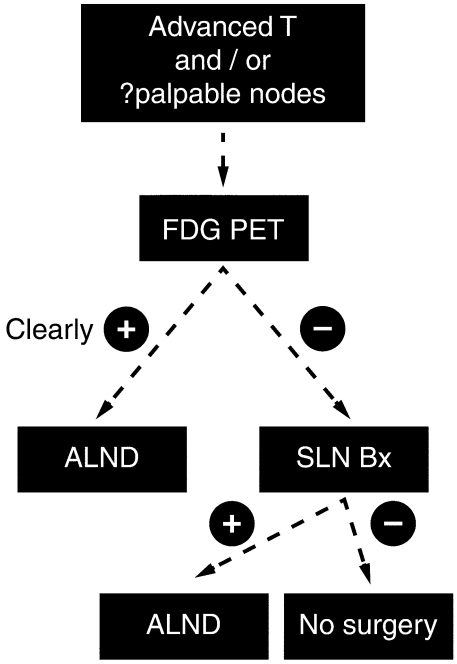


**Figure 4** Potential algorithm for workup of patients with advanced primary tumor (T) and/or equivocally palpable axillary nodes. Using this scheme, patients who have clearly positive findings in the axilla by FDG PET would forgo sentinel lymph node mapping and biopsy (SLN Bx) and undergo complete axillary node dissection (ALND).

tases may be practical and cost-effective, as suggested by other investigators.[19,62]

## Detection of Locoregional and Distant Recurrences

FDG-PET can contribute in significant ways to the clinical management of patients with suspected locoregional or distant recurrences. Because it provides functional information, FDG-PET often is complementary to conventional staging methods such as physical examination, cross-sectional imaging (CT or MR) and bone scintigraphy, which rely more on changes in morphology to detect disease recurrence. This is particularly true in the evaluation of anatomic regions that have been previously treated by surgery or radiation[63] where the discrimination between posttreatment scar and recurrent tumor can be problematic. Because of its high sensitivity in the detection of metabolically active tissue, FDG-PET can help define the extent of disease when conventional imaging (CI) is equivocal or negative and recurrence is suspected. Earlier recognition of recurrent disease will hopefully provide more effective treatment options and improve survival in this group of patients.

The most common sites of locoregional recurrence among patients treated with mastectomy, axillary node dissection and radiation therapy are the chest wall and supraclavicular nodes.[64] A particularly vexing clinical problem occurs in the patient with symptoms of brachial plexopathy since either tumor recurrence or treatment-induced scarring can be responsible for the symptoms. Hathaway and coworkers[65] showed the value of combining the functional information of FDG-PET and the anatomic information from dedicated MR imaging to decide whether patients would benefit from further surgery (Fig. 5). Other studies[66] have confirmed these early findings.

Lymphatic spread of tumor to the internal mammary (IM) nodes occurs in up to 25% of patients at the time of initial diagnosis and possibly more commonly in recurrent cancer.[67,68] Metastases to IM and axillary nodes are usually synchronous and prognosis is significantly worse when IM nodes are involved.[68] However, IM nodes are not routinely sampled or evaluated in any systematic fashion in current practice because (1) compared with axillary nodes, they are not as accessible and (2) in older studies, radiotherapy of IM nodal disease failed to show improvements in survival and

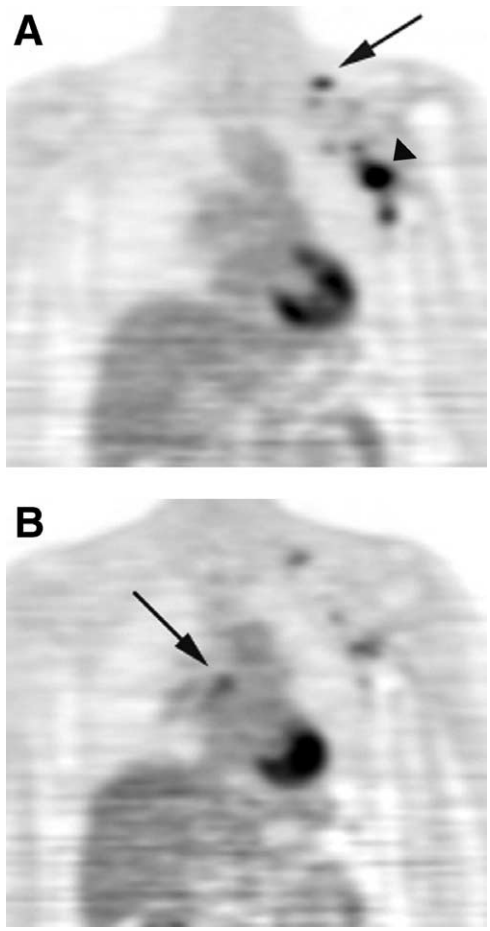


**Figure 5** A 57-year-old woman with second left axillary recurrence 6 years after modified radical mastectomy. She was being considered for aggressive local therapy (surgery and radiation). Conventional imaging was negative for distant metastases. Coronal FDG PET image (A) shows uptake in the left axilla consistent with disease recurrence (solid arrow; SUV = 14.7), but also uptake in the left supraclavicular region (open arrow; SUV = 4.4). A more posterior coronal image (B) shows uptake in the right hilum (SUV = 5.9). Patient was treated with systemic chemotherapy rather than local therapy due to the widespread foci of suspected disease; follow-up imaging confirmed disease at PET-positive sites.

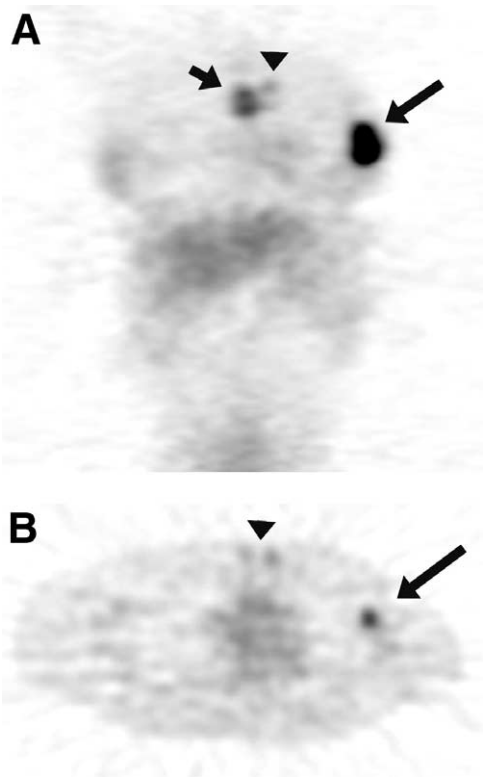


**Figure 6** A 47-year-old woman with newly diagnosed LABC (infiltrating ductal). Anterior coronal image from baseline FDG scan (A) shows hypermetabolic primary tumor in the left breast (long arrow; SUV = 7.7), uptake in the left IM region (arrowhead), and adjacent uptake in the sternum (short arrow; SUV = 3.2) consistent with direct spread to the sternum from IM nodal disease. Axial image (B) shows uptake in the lower left axilla (arrow; SUV = 2.9) and IM regions bilaterally (arrowhead).

remains controversial in current practice.[69] FDG uptake in the IM nodal chain has been anecdotally reported in some of the studies that have focused on detection of primary tumor or axillary staging.[19,48] In one study of 85 patients who underwent FDG-PET before axillary node dissection, 12 (14%) had uptake in the IM region but there was no histologic confirmation of these nodes.[19] Our experience with imaging patients with LABC shows that the prevalence of IM FDG uptake can be as high as 25% (Fig. 6) and that the presence of IM FDG uptake predicts treatment failure patterns of disease consistent with IM nodal involvement and progression[70] (Fig. 7). A preliminary study by Bernstein and coworkers[71] showed the feasibility of detecting IM nodal metastases in early-stage patients using FDG PET and an ongoing study will investigate the utility of FDG-PET in this role.

Neoplastic spread to mediastinal nodes is also common in patients with advanced disease and as a site of recurrence in patients who have undergone axillary node dissection and radiation. As with IM nodes, mediastinal nodes are rarely sampled in breast cancer patients. CT, the conventional method of staging these nodes, relies on size criteria to determine the presence or absence of disease; this method has been proven significantly less accurate than FDG-PET in patients with nonsmall cell lung cancer, for which histologic analysis is used as the gold standard.[72,73] In our retrospective series of 73 patients with recurrent or metastatic breast cancer who underwent both FDG-PET and chest CT,[74] FDG uptake in mediastinal or IM nodes was 2 times more prevalent than suspiciously enlarged nodes by CT, suggesting that PET is a much more sensitive technique at detecting nodal disease. In the subset of patients with confirmation, the sensitivity of FDG-PET was significantly higher (85%) than CT (50%) with nearly the same level of specificity (90% for PET and 83% for CT). Ten of 33 (30%) patients suspected of having only locoregional recurrence by CI and clinical examination had mediastinal or IM FDG uptake; risk factors associated with mediastinal or IM FDG uptake in these patients were recurrent chest wall invasion and 3 or more positive axillary nodes.

Whole-body surveys have shown that FDG-PET can accurately detect sites of distant disease with sensitivity and specificity ranges of 80% to 97% and 75% to 94%, respectively, on a per patient basis.[75-84] Several investigations have shown the added benefit of FDG-PET to CI in patients with elevated tumor marker serum levels and negative or equivocal CI.[77,82,84] In a retrospective study of 39 patients comprised mainly of asymptomatic patients with rise in tumor markers,[77] FDG-PET detected recurrences in 31/33 (94% sensitivity) patients whereas CI was positive in only 6/33 (18% sensitivity) patients. In a retrospective study of 61 patients,[85] FDG-PET was significantly more accurate at predicting disease-free survival after treatment than CI. The difference in outcome was significantly worse when results (positive versus negative) of FDG-PET were compared with CI. This difference was due largely to higher sensitivity of FDG-PET in detecting nodal and skeletal recurrences than CI. These studies indicate a significant improvement in sensitivity in detecting recurrences, especially in locoregional and distant nodal regions, compared with CI.

The skeleton is the most common site of distant metastasis in breast cancer. Bone scintigraphy is considered the most sensitive method of detecting and determining the extent of skeletal metastases. However, purely lytic lesions or metastases confined to the marrow cavity may be difficult to detect on bone scan because of a lack of sufficient osteoblastic response.[86] In a study of 23 breast cancer patients with known skeletal metastases who underwent both bone scintigraphy and FDG-PET, Cook and coworkers[87] showed that FDG-PET detected more lesions than bone scintigraphy except in a subgroup of patients with osteoblastic metastases. Moreover, the level of FDG uptake in lytic lesions was significantly greater compared with osteoblastic lesions and the prognosis of patients with lytic-predominant disease was significantly worse. These data clearly show a complementary nature of bone scintigraphy and FDG PET in the evaluation of skeletal metastases in breast cancer patients. These results also suggest that FDG-PET and bone scan should not be considered substitutes for each other for bone metastasis staging in breast cancer. In our center, bone scintigraphy remains one of the routine studies in breast cancer metastatic staging, with FDG-PET to help clarify staging in the case of difficult or equivocal conventional staging. Evolving data suggest that

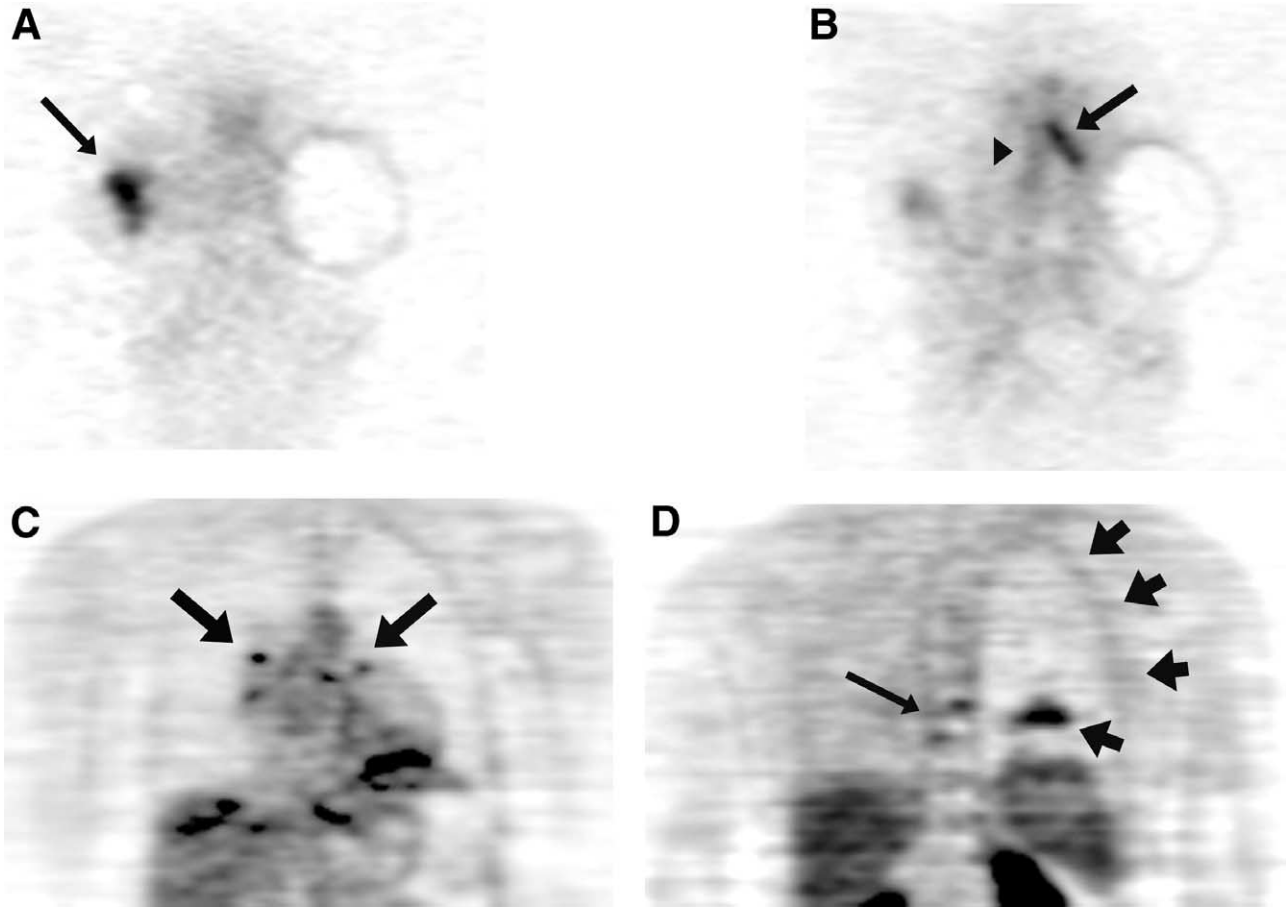


**Figure 7** A 38-year-old woman, treated previously with left mastectomy and saline implant reconstruction for invasive lobular carcinoma, developed recurrence in the right breast that had the same histologic features as the original tumor. Coronal images (anterior to posterior; A to D) from FDG PET performed to determine the extent of disease shows recurrence in the right breast (arrow in A), uptake in the sternum (arrowhead in B) and adjacent left costal margin (arrow in B) consistent with direct spread form IM nodal disease. Uptake in mediastinal nodes (arrows in C) and pleura (short arrows in D) was consistent with further intrathoracic spread of disease. Bone metastases to the lower thoracic spine (long arrow in D) are also present.

$^{18}$F-fluoride PET may provide similar and likely improved bone metastasis detection in breast cancer and other tumors compared with bone scintigraphy[88,89] and may play a role in breast cancer bone metastasis staging in the future.

Unlike patients with some other advanced-stage malignancy, patients with advanced breast cancer can benefit from a variety of therapies including surgery, radiation, chemotherapy and hormonal therapy. Choosing the most appropriate therapy depends primarily on accurately defining the extent of disease. In a prospective study of 50 women undergoing staging studies for suspected recurrent breast cancer,[90] FDG-PET had a significant impact on defining the extent of disease by changing the clinical stage in 36% of patients and on management by inducing changes in therapy in 58% of the patients. In our retrospective study of 125 patients with advanced breast cancer undergoing conventional imaging and FDG-PET for staging,[91] the extent of disease was changed in 67% (increased in 43% and decreased in 24%) of patients and the therapeutic plan was altered in 32% of patients based on FDG-PET findings. Among different referral categories, FDG-PET altered therapy most frequently in patients suspected of locoregional recurrence, under consideration for aggressive local therapy (44%) (Fig. 8), and patients with known metastases being evaluated for response to therapy (33%). In our study, these 2 subgroups of patients with advanced disease were most likely to benefit from staging with FDG-PET. The need for a more sensitive staging tool in patients with first-episode locoregional recurrence was recently corroborated by van Oost and coworkers;[92] their study of 175 patients showed that 16% had distant metastases at the time of locoregional recurrence and 24% developed distant metastases within 18 months of confirmation of recurrence. They estimated that FDG-PET would upstage, and likely change the therapeutic plan, in up to 29% of patients with negative conventional staging studies. These results indicate that FDG-PET should not be used as the sole restaging tool in patients with recurrent or metastatic disease but to answer specific questions that will likely impact their management. Future prospective trials using oncologist-directed questionnaires will help to further define the role and provide

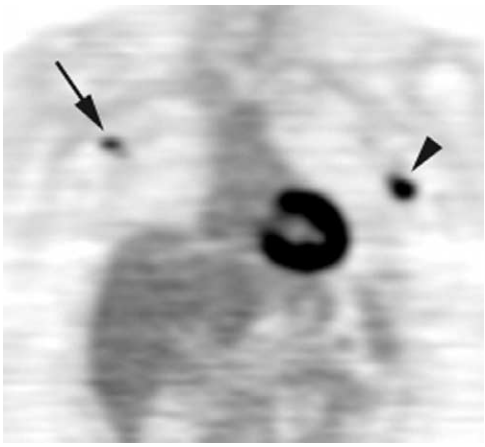

**Figure 8** A 54-year-old woman with left axillary recurrence (biopsy-proven) 17 years after initial diagnosis of malignancy in the contralateral breast. A new primary cancer in the left breast was not detected by mammography or sestamibi scan and there was no evidence of distant metastases on CI (chest CT and bone scan). FDG-PET, performed to exclude distant metastases, shows uptake in the right axilla (arrow; SUV = 6.8) in addition to the left axilla (arrowhead; SUV = 7.4). Management plan was altered from left modified radical mastectomy and axillary lymph node dissection to systemic chemotherapy after malignancy was confirmed in right axilla by biopsy.

data for the cost-benefit analysis of FDG-PET in staging patients with advanced breast cancer.

## Evaluation of Therapy Response

Neoadjuvant chemotherapy has been used in patients with LABC to (1) improve primary tumor resectability, including the use of breast-conserving surgery and (2) assess in vivo response (chemosensitivity) to selected chemotherapeutic agents. Response (complete pathologic resolution) to therapy provides favorable prognostic information whereas nonresponse dictates a change in therapeutic regimen.[4] Early assessment of response would greatly benefit management of patients receiving neoadjuvant therapy by assuring continuance of effective therapy in those who respond and instituting alternative therapy in those who do not. Conventional methods of assessing response to therapy, such as physical examination, mammography, or ultrasound, depend on morphologic or physical characteristics of tumors and are often inaccurate or slow to detect change in the malignant portion of breast masses.[93] There have been several good initial studies showing the utility of metabolic imaging with FDG-PET in the evaluation of treatment response, specifically its ability to discriminate responders from nonresponders more accurately and earlier than CI.[94-98] Significant drops in tumor SUV occur by the end of the first cycle of chemotherapy and as early as 8 days posttreatment in responders with no change or slight increase in nonresponders.[94] Two separate investigations[97,98] have evaluated FDG-PET in predicting complete macroscopic pathologic (pCR-macro) response to therapy, defined as the absence of gross viable tumor in the surgical specimen posttherapy, after a single cycle of chemotherapy. These exciting results suggest a possible role for PET in the early evaluation of response to therapy.

FDG uptake by tumor reflects one aspect of its physiology, namely glucose metabolism. Other PET tracers are becoming recognized as probes to additional important biologic and physiologic tumor properties that may be responsible for clinical prognosis and/or type of response to therapeutic agents. For example, dynamic imaging with $^{15}$O-water can estimate regional blood flow within a tumor; low tumor perfusion may be one factor responsible for poor response to intravenous chemotherapy.[99] In our experience with evaluating treatment response and predicting outcome in patients with LABC, the simultaneous measurement of the pretherapy metabolic rate of FDG (MRFDG), and blood flow predicted complete pathologic response and disease-free survival.[32] We found a correlation between MRFDG and degree of response; tumors with high rates of glucose metabolism pretherapy tended to have poor responses. In addition, a low metabolism-to-blood flow ratio (MRFDG/flow) was an independent predictor of complete pathologic response to treatment. Preliminary survival analysis also showed that low MRFDG/flow predicts disease-free survival. Further analysis of glucose use and blood flow measurements using PET at baseline and after 2 months of neoadjuvant chemotherapy in 35 patients with LABC showed a statistically significant association between the change in tumor blood flow in clinical and pathologic responders versus nonresponders; blood flow declined on average 32% in responders and increased on average 48% in nonresponders.[100] The posttherapy blood flow measurement was the only statistically significant variable associated with improved disease-free survival in this study. Using PET in this way may help to identify the physiologic manifestations of drug resistance and elucidate biologic mechanisms associated with resistance, helping to individualize and maximize the effectiveness of systemic therapy.

There is preliminary evidence that using FDG-PET to monitor response to treatment in sites of disease other than the primary tumor may be helpful.[98,101] Smith and coworkers[98] showed by quantitative methods that a significant reduction in axillary nodal FDG uptake after neoadjuvant chemotherapy can predict complete microscopic pathologic response in a small group of patients. Axillary nodal response to therapy may be an even more important marker for prognosis since nodal disease is thought to reflect the presence of occult disseminated disease; however, larger studies are needed to confirm this relationship. In a study of 9 patients with breast cancer metastases (liver, lung, and soft tissues), Gennari and coworkers[101] showed an average decrease in lesion SUV of 72% after the planned course of chemotherapy among patients who showed clinical response to treatment compared with no change in lesion SUV from baseline in nonresponders. The responders also showed an appreciable drop in lesion FDG uptake after the first course of chemotherapy. These small preliminary studies show the potential value of FDG-PET in evaluating response of patients with advanced breast cancer to systemic therapy. As more effective first and second line therapies are developed for this patient

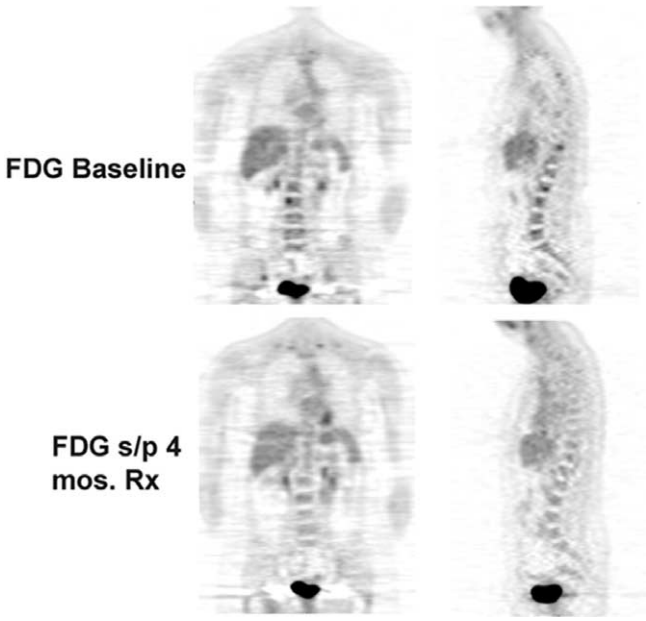


**Figure 9** A 47-year-old woman developed bone-dominant metastases nine years after treatment for ER positive invasive lobular carcinoma of the left breast. Baseline FDG-PET (top row) shows multiple foci of uptake in the thoracic and lumbar spine and right ilium. After 4 months of aromatase inhibitor therapy, a follow-up PET scan (bottom row) shows resolution all FDG-avid foci; patient had also clinically improved (less pain) during this interval.

group, monitoring early response to therapy with imaging tools such as FDG-PET will play an increasingly important role in management.

Another application of potential clinical importance is in monitoring the response of bone metastases to treatment. Evaluating response to treatment in patients with bone-dominant metastases using CI, including bone scintigraphy and MR, can be problematic. These methods detect reactive changes in bone adjacent to tumor that may not be a true representation of pathologic response.[86,102,103] In a retrospective study, we evaluated the response of skeletal metastases to therapy using serial FDG-PET[104] and found a strong correlation between the quantitative change in FDG SUV and overall clinical assessment of response (combination of CI, tumor markers and clinical examination) and change in tumor marker, CA 27.29 (Fig. 9). These preliminary results show the potential efficacy of FDG-PET to quantitatively assess treatment of skeletal metastases to therapy.

A novel application of FDG PET is predicting the response to antiestrogen therapy in patients with advanced estrogen receptor (ER) positive breast cancer by taking advantage of the flare phenomenon associated with the institution of therapy. Mortimer and coworkers[105] reported a series of 40 patients who underwent FDG PET for the evaluation of response to tamoxifen 7 to 10 days after institution of therapy. FDG uptake predicted a subsequent response to therapy consistent with a "metabolic flare." These data show a clear in vivo correlation between early posttreatment ER agonist effect and increase in glucose utilization by tumor cells. This is a good example of how PET can be used to characterize tumors in vivo, evaluate response to treatment, and provide important prognostic information.

## Beyond FDG: Future Applications of PET to Breast Cancer

Although FDG continues to play an increasingly important role in diagnosis and management for a variety of cancers, including breast cancer, it is likely that other radiopharmaceuticals will also play a role in the management of breast cancer in the near future. Energy metabolism is associated with tumor growth, but also with a variety of other biological processes, including inflammation and tissue repair in response to damage. As breast cancer therapy continues to evolve to more targeted treatment, individualized to a particular patient and her tumor's biologic characteristics, more specific PET radiopharmaceuticals will help guide treatment selection. PET can help at each stage of treatment selection by (1) quantifying the therapeutic target, (2) identifying resistance factors, and (3) measuring early response to therapy. These applications are reviewed below, with specific examples of the use of PET for each task.

### Quantifying the Therapeutic Target

The trend toward more specific therapy requires the ability to measure the level of target expression in the breast tumor. Current examples of specific targets (and examples of treatments directed at them) include the ER (tamoxifen and letrozole), HER2 (trastuzumab [Herceptin]), EGFR (gefitinib [Iressa]), and angiogenesis factors (bevacizumab [Avastin]).[106] In current practice, target expression is measured by in vitro assay of biopsy material. This is appropriate for early-stage disease, in which all disease sites can be sampled, but is inadequate for more advanced disease, where target expression can be heterogeneous. Assay of a sample from a needle biopsy of a particular portion of one or more disease sites may not be representative of the disease burden as a whole. Measuring the target expression at each site of disease is a task for which PET is ideally suited. PET imaging can determine whether or not the target is expressed at all disease sites, and importantly, it can quantify the level of target expression at each site.

Current examples of the PET imaging to measure target expression include ER imaging;[42,107] HER2 imaging;[108] imaging angiogenesis both nonspecifically by measuring blood flow[32,109-111] or by measuring specific components expressed in neovessels;[112,113] and measuring novel targets such as matrix metalloproteins[114] and vasoactive intestinal peptide.[115] In the future, it also may be possible to measure target expression in conjunction with gene therapy using a transgene imaging reporter.[116]

The majority of breast cancers express ER. ER expression is an indicator of prognosis and predicts the likelihood of responding to antiestrogen therapy.[117,118] Assessment of ER expression in primary breast cancer by in vitro assay of biopsy material, most typically by immunohistochemistry, is

part of the standard care of breast cancer patients and weighs heavily in the choice of therapy.[118] However, in vitro measurements of ER do not discriminate between functional and nonfunctional receptors and provide only an estimate of hormone sensitivity.[119] Furthermore, ER expression can be heterogenous in large or metastatic breast cancers, and biopsy can be misleading due to sampling error. Heterogeneity of ER expression has been shown by in vitro assay between lesions in patients with multiple metastases.[120] A variety of agents has been tested for PET ER imaging,[107] and new compounds continue to be evaluated.[121] The close analog of estradiol, the labeled estrogen, 16 $\alpha$-[F-18]- fluoroestradiol-17$\beta$ (FES),[122] has shown the most promise in quantifying the functional ER status of breast cancer, either in the primary tumor or in metastatic lesions. Studies have shown that the quantitative level of FES uptake in primary tumors correlates with the level of ER expression measured by in vitro assay by radioliagand binding[123] and in preliminary data by immunohistochemistry.[124] FES PET provides sufficient image quality to image metastatic lesions with high sensitivity in patients with ER positive tumors[125] at an acceptable radiation dose to the patient.[126]

An important use of FES-PET will be to image and characterize the entire volume of disease in an individual patient, especially in patients with recurrent or metastatic breast cancer, where tissue sampling at all sites is not feasible. Studies using FES-PET have shown heterogeneous FES uptake within the same tumor and between metastatic lesions, both qualitatively and quantitatively.[34,127] This type of comprehensive evaluation of functional ER status of the entire disease burden in patients will likely give important information about prognosis and help guide treatment selection.

PET-ER imaging can be used, in analogy to assay of ER in biopsy specimens, to predict the likelihood of response to hormonal therapy and thereby guide appropriate selection of patients for this type of treatment. Paralleling results showing that the level of ER expression predicts response to hormonal therapy,[128] studies by Mortimer, Dehdashti and colleagues[105,129] have shown that a higher level of FES uptake in advanced tumors predicts a greater chance of response to tamoxifen. Preliminary results in our center show similar results for patients with recurrent or metastatic breast treated with a variety of hormonal agents[130] (Fig. 10). Serial FES-PET can also assess the functional response to hormonal therapy, or ER blockade in the case of tamoxifen, in the primary tumor or metastasis.[125] High degrees of ER blockade in the primary tumor (about 50% decrease in SUV from baseline) also portend a good response to therapy.[105] These exciting preliminary results show the potential of PET ER imaging to help guide appropriate, individualized breast cancer treatment and point the way for future studies and clinical use.

Other tracers for ER imaging may also play a role in breast cancer. Labeled analogs of commonly used hormonal agents such as tamoxifen and fulvestrant have been developed[131,132] and may indicate the likelihood of response to specific agents. Conjugated estrogens have also been tested as a way to explore estrogen metabolism at the tumor site.[133] In developing and testing these new agents, preclinical studies using appropriate animal models and animal imaging will be an important part of translating new compounds into clinical studies.[134]

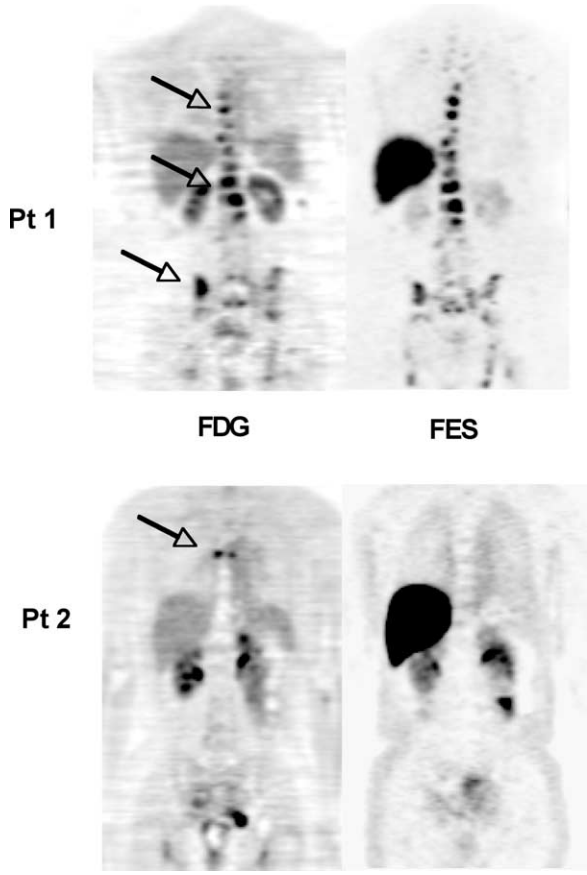


**Figure 10** FES-PET imaging predicts response to hormonal therapy. FDG (left) and FES (right) coronal PET images through the spine and pelvis are shown for 2 patients with breast cancer bone metastases from ER+ primary tumors. Both were treated with aromatase inhibitors, and FDG and FES-PET studies were obtained close to the start of treatment. Patient 1 (top row) had extensive bony disease involving the T-spine, L-spine, and pelvis, seen clearly on FDG-PET (arrows) and showing high uptake of FES. This patient had an excellent response to therapy, as indicated by improved symptoms and improvements on imaging studies, including FDG-PET. Patient 2 (bottom row) had relatively small-volume T-spine disease seen on FDG-PET (arrow), but not on FES. The patient subsequently had disease progression documented by multiple modalities.

## Identifying Resistance Factors

Even when a breast tumor expresses appropriate levels of the target, targeted therapy may fail if the tumor also has characteristics that will render it resistant to the chosen treatment. Examples include the expression of HER2 as a resistance factor for hormone therapy[135]; the expression of P-glycoprotein (P-gp) as a resistance factor for doxorubicin, taxanes, and other chemotherapy agents that are P-gp substrates[136]; altered DNA repair mechanisms[137]; and tumor hypoxia as a broad resistance factor for radiotherapy and cytotoxic chemotherapy.[138,139] Preliminary studies of PET agents targeted to each of these areas have been undertaken largely in animal

models with some early human studies.[108,140-143] The ability to measure both the therapeutic target and specific resistance factors underlies the emerging role of PET in early drug testing.[144]

Tumor hypoxia imaging with PET has received considerable attention and has undergone preliminary human testing for a number of tumors, including breast cancer. Tumor hypoxia has been established as a resistance factor for radiotherapy, and evolving evidence indicates it promotes tumor aggressiveness and resistance to a variety of systemic treatment modalities.[138,139] Although severe hypoxia is rare in smaller breast tumors, data from oxygen electrodes suggests that up to 30% of larger or more advanced breast cancers exhibit severe hypoxia in part of the cancer.[145] Imaging is ideally suited to determine the extent and heterogeneity of tumor hypoxia. Although hypoxia likely contributes to increased rates of glycolysis, supported by in vitro studies of FDG uptake,[146] a recent study in patients with a variety of tumor types, including breast cancer, showed that hypoxia could not be simply predicted by FDG uptake.[147] Several PET agents specifically designed to image tumor hypoxia have been tested for hypoxia imaging.[140] Of these, $^{18}$F-fluoromisonidazole has the largest current body of preclinical validation studies and clinical experience.[140,148] A preliminary study at our center that included large primary and metastatic breast cancers showed that approximately 1/3 of tumors had one or more areas of severe hypoxia by $^{18}$F-fluoromisonidazole PET[147] (Fig. 11). Other PET hypoxia tracers have also been studied in patients.[149] PET imaging holds great promise for identifying the subset of breast cancers with significant hypoxia, where alternate therapeutic strategies that can overcome the resistance associated with hypoxia will likely be needed.

Another area of active investigation in patients has been characterization of drug efflux proteins, in particular P-gp. P-gp is a membrane transport protein for which a number of xenobiotics are substrates.[136] P-gp may mediate resistance in breast cancer and other tumors by enhanced efflux of a number of chemotherapeutic agents, including agents like doxorubicin and taxol, which are important in breast cancer treatment. Based on observations by Pinwica-Worms and others,[150] Ciarmello observed that enhanced washout of the single-photon emission computed tomography agent, $^{99}$Tc-m-sestamibi (MIBI) predicted resistance to epirubicin-based therapy.[142] However, interpretation of MIBI images is confounded by blood flow, which is an important factor in MIBI's uptake and washout.[151] Alternate PET radiotracers, such as $^{11}$C-verapamil, have been developed as agents for imaging P-gp transport.[141] Early studies of this radiopharmaceutical applied to drug transport are ongoing in our center.[152]

## Measuring Early Response

As the choice of breast cancer treatments expands, there will be an increasing need to measure the efficacy of treatments early in the course of treatment. With many potentially effective treatments to choose from, it will be important to identify ineffective treatments early after initiation. This poses several challenges. A decrease in tumor size, the current standard in therapeutic monitoring, is a late event in response to treatment; it is therefore desirable to measure response well before any significant changes in tumor size would be expected. Additionally, some new therapies may be cytostatic instead of cytoreductive, in which case successful treatment may not lead to a decrease in tumor size at all. Studies of FDG-PET after a single dose of chemotherapy have supported the ability of in vivo biochemical imaging to measure early response.[97,98] However, it is likely that other imaging agents that more directly measure cell growth and death will be even more effective at measuring early response.

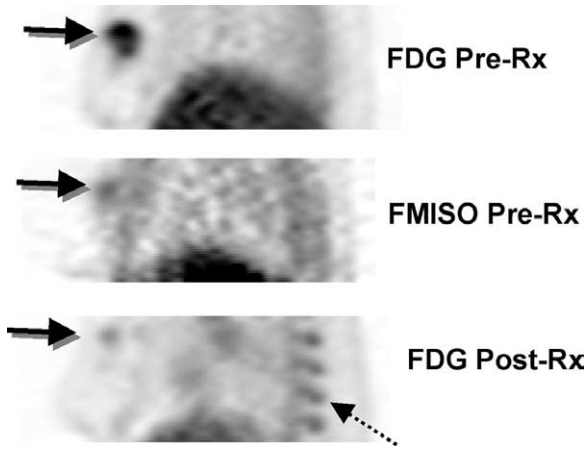


**Figure 11** Breast tumor hypoxia as a predictor of drug resistance. A patient with a large, locally advanced right breast tumor underwent FDG and FMISO-PET pretherapy (top and middle) and after approximately 10 weeks of chemotherapy (bottom). Images are thick sagittal images, similar to MLO mammography views. The pretherapy FDG study showed uniformly high FDG uptake throughout the tumor. FMISO-PET showed uptake suggestive of tumor hypoxia, but only close to the center of the tumor (arrow). Posttherapy images show a dramatic reduction in the extent and intensity of FDG uptake with residual activity in the part of the tumor that had FMISO uptake pretherapy, suggesting that the hypoxic core of the tumor was more resistant than the rest of the tumor. Residual viable tumor was found at surgery. Marrow uptake of FDG also was seen posttherapy (dashed arrow) because of granulocyte colony-stimulating factor administered for marrow support as part of the treatment.

Decreased tumor proliferation is an early event in response to successful treatment.[153] This underlies the use of labeled thymidine and analogs to image cellular proliferation and early response to treatment.[42] Thymidine is incorporated into DNA, but not RNA; therefore, thymidine uptake and retention in the tumor serves as a specific marker of cell growth.[154,155] Recent studies using $^{11}$C-thymidine and PET show promise in assessing response,[42,156] especially early response. Because of the short half-life of $^{11}$C (approximately 20 minutes) and the extensive metabolism of thymidine, $^{11}$C-thymidine is not practical for routine clinical use outside of academic centers. This spurred the development of $^{18}$F-labeled, nonmetabolized thymidine analogs to image tumor proliferation. The most promising thus far is $^{18}$F-fluoro-L-

thymidine (FLT).[157,158] Studies in several tumor types have shown that FLT uptake correlates with in vitro measures of proliferation performed on biopsy specimens.[159] FLT has been preliminarily tested in breast cancer patients.[160] Several laboratories have ongoing studies using FLT PET to measure response in several different tumor types, including breast cancer.[161]

A novel use of proliferation imaging to detect treatment effect has been described by Wells and colleagues.[162] In this elegant study, Wells showed that inhibition of the de novo thymidine synthesis pathway by an investigational thymidylate synthase inhibitor transiently increased thymidine flux through the salvage pathway, quantified by $^{11}$C-thymidine PET. This approach demonstrated the ability of PET to measure an in vivo drug defect and may be of clinical importance in breast cancer with the increasing use of capecitabine, a thymidylate synthase inhibitor, as second and third line therapy.[163]

Besides an early decline in cell growth, effective treatments often lead to an early increase in cell death, typically by apoptosis.[36] The SPECT agent $^{99m}$Tc-annexin V has shown promise as a way to image apoptosis in vivo.[164] Annexin tracers labeled for use in PET offer better image quality and quantification, and are under development in many centers.[165,166] The ability to image both changes in cell proliferation and cell death in response to treatment will be an effective means of characterizing how tumors respond to targeted therapy.

## Summary

PET with FDG is currently most useful as a staging tool in breast cancer, especially in patients with recurrent or metastatic disease. It also can be used to measure response to therapy, possibly earlier than conventional methods. Future applications of PET will likely involve other tracers in addition to FDG, to better characterize tumor biology and more effectively measure response to therapy. This potential refinement in tumor characterization will help predict clinical behavior and tailor therapy to tumor biology and thereby individualize treatment.

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