Current and Future Uses of Positron Emission Tomography in Breast Cancer Imaging

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Positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) has been used for the 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 that are 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, improve our ability to measure and predict response and help tailor therapy to individual patients.

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, often 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 where 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 which 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.

DETECTION OF PRIMARY BREAST CANCER

The earliest studies of positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) in breast cancer imaging centered on the feasibility of detecting the primary tumor.[10-12] Patients imaged in these early studies generally had confirmed, locally advanced breast cancer (LABC) or metastatic disease. In some individual cases from these early series,[10-12] focal FDG uptake was demonstrated in some primary tumors that could not be detected by mammography due to dense fibroglandular tissue. Because of the selection bias of patients with advanced disease, the sensitivity of FDG-PET was near perfect and specificity could not be determined. Only one false-negative case, a 1-cm tubular carcinoma, was encountered early in these studies.[11]

A host of larger prospective studies using FDG-PET on patients with unconfirmed, suspicious breast abnormalities by clinical or mammographic examinations followed.[14-19] Although there was less selection bias with respect to tumor size, the ratio of malignant lesions

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to benign lesions (average about 3.5) and the size of the lesions in these studies was much higher than the general population undergoing breast biopsy. Despite the evolution of more dedicated and sophisticated PET imaging devices, follow-up studies with less selection bias 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. In the largest of these series,[17] 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 standard uptake value (SUV) threshold values of 2-2.5,[14,16] discrimination of benign from malignant lesions can be obtained with approximately 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 due to its high expense and modest whole-body radiation exposure. For diagnostic purposes in 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.[20] FDG-PET may be helpful, due to 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),[21] remains to be determined.

Recent technologic advances may improve primary breast tumor detection by PET. Recent work includes the development of dedicated breast imaging devices, which can be tailored specifically to the task of breast radiotracer imaging. One prominent approach has been termed positron emission mammography.[22-24] In positron emission mammography, two planar detectors are integrated into a conventional mammographic system which enables coregistration of mammographic and emission FDG images of the breast. The in-plane spatial resolution achieved in early studies was 2.8-mm full width at half maximum, about half that of current whole-body PET instruments, using a lower dose of radiotracer and decreased acquisition time. Further improvements in spatial resolution are likely. 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 due to intrumentation limitations.[25] 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.[26-31] 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.[27-29,31] Characteristics that show strong positive correlates with FDG SUV in most of these studies include histologic type (higher uptake in ductal versus lobular),[26,28,29,31] tumor histologic grade,[14,26,27] and indices of cellular proliferation (higher uptake with higher levels of proliferation).[28,29,31] Weaker correlation has been reported with microvessel density, a surrogate of angiogenesis[27,29] and tumor cell density.[28,29] Established breast cancer prognostic factors that generally do not correlate with primary tumor FDG uptake are steroid receptor status,[28,31-33] axillary node status[26,28,31] and tumor size.[28,31,33] Our experience with patients with 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.[30] 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.[34] 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.[27,30] 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.[35,36] More recent in vitro data suggest that intermediates in the glycolytic pathway are key in initiating apoptosis and that alterations limit apoptosis.[37] Some gene products whose overexpression is associated with resistance to apoptosis, for example the PI3K/Akt pathway, are also associated with high glycolytic rates.[38] 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.[27,30] In one study,[27] 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. Similarly, our study of patients with LABC showed that high tumor metabolic rate relative to blood flow predicted poorer survival.[30] 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 [C-11]-thymidine (marker for cellular proliferation)[39] and [F-18]-fluoromisonidazole (marker for tumor hypoxia)[40] will further refine in vivo characterization of individual tumors.

Table 1. Largest Prospective Series of Axillary Nodal Staging with Positron Emission Tomography Using ^{18}F-fluorodeoxyglucose in Breast Cancer

Series	Number of Patients	Sensitivity	Specificity
Tse[13]	10	57 (4/7)	100 (3/3)
Adler 1997[14]	52	95 (19/20)	66 (21/32)
Utech[42]	122	100 (44/44)	75 (60/80)
Avril[43] overall	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[26]	72	85 (23/27)	91 (41/45)
Smith[44]	50	90 (19/21)	97 (28/29)
Greco[45]	167	94 (68/72)	86 (82/95)
Schirrmeister[84]	113	79 (27/34)	92 (73/79)
Wahl[46]	308	61	80

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

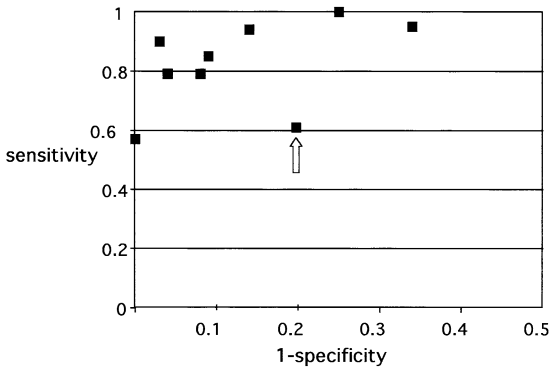

Fig 1. Receiver operating curve (ROC) scatterplot for prospective studies (see Table 1) evaluating positron emission tomography using F-fluorodeoxyglucose (FDG-PET) in axillary nodal staging in breast cancer patients. Data points show trade-off between sensitivity and specificity in the interpretation of FDG-PET findings. The data point marked by arrow represents the results from large multicenter prospective trial of 308 women with newly diagnosed invasive breast cancer who underwent presurgical FDG-PET (Wahl and coworkers[31]).

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 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,[13,18,33,41-46] shown in Table 1. Results from these studies, plotted in a receiver operating curve (Fig 1), emphasize the trade-off between sensitivity and specificity in the interpretation of FDG-PET findings. For example, two large studies[41,42] showed near perfect sensitivity of detecting axillary metastasis but had lower specificity values than the other studies. However, in both of these studies, there was a preponderance of patients with primary tumors measuring $>$ 1 cm. This introduces a selection bias toward patients with relatively large-volume axillary disease since size of the primary tumor correlates with the burden of axillary disease.[47] In a series that included a larger proportion of patients with smaller primary tumors,[43] the sensitivity of detecting axillary disease in patients with T1 tumors (33%) was significantly less than for patients with tumors larger than 2 cm (94%) with the same specificity (100%) for both subgroups. The number of tumor-involved nodes at dissection also influenced the sensitivity of PET, which was 25% when only one node was

involved and 100% when more than five nodes were involved. Crippa and coworkers[33] demonstrated a difference in the sensitivity of FDG-PET for detecting axillary disease according to clinical stage: 70% for clinical stage N0 and 100% for stage N2. Analysis of data from a prospective multi-center study of axillary nodal staging with FDG-PET compared with pathologic results in 308 women with newly diagnosed invasive breast cancer, presented by Wahl and coworkers,[46] showed a mean sensitivity and specificity of 61% and 80%, respectively, when at least one foci of abnormal axillary uptake was detected. These more recent studies indicate the potential limitation of the ability of PET 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 since even microscopic nodal involvement may be important for prognosis and treatment planning.[48] In addition, PET cannot accurately quantify the number of involved nodes or the presence of extranodal extention, other important prognostic factors, due to 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.[49] This technique enables detection of microscopic nodal involvement 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] with false-negative FDG-PET occurring predominantly in small-sized (10 mm or less) metastatic sentinel nodes.[50] An example of false-negative FDG-PET results for axillary staging is shown in Fig 2. 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 3. 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.[55] 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 metastases may be practical and cost-effective, as suggested by other investigators.[18,56]

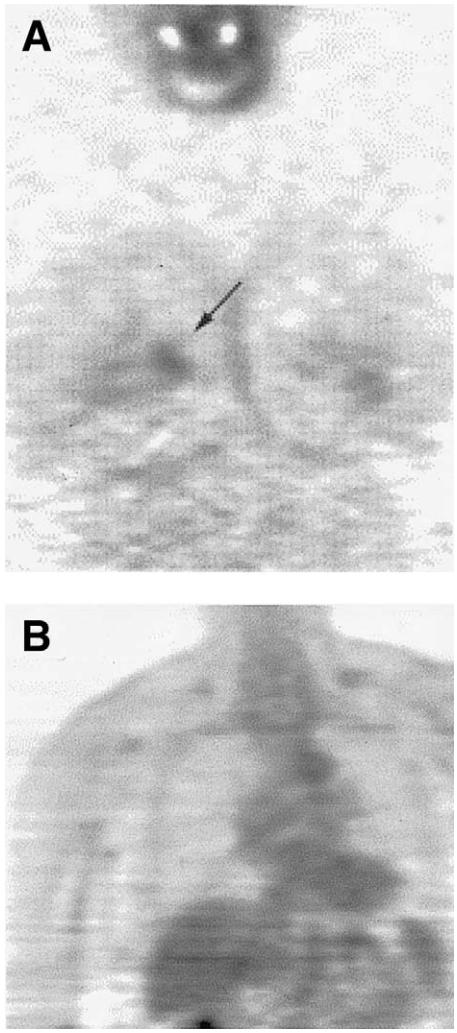

Fig 2. A 64-year-old woman with newly diagnosed pleomorphic lobular carcinoma in the upper inner quadrant of the right breast. An anterior coronal preoperative positron emission tomography using F-fluorodeoxyglucose image (A) shows a small focus of uptake in the medial right breast (arrow) with a maximum standard uptake value (SUV) of 2.4, corresponding to the patient's primary tumor. A more posterior coronal image (B), at the level of the axilla, shows no focal uptake. The patient underwent lumpectomy and sentinel node biopsy, which revealed a 5-cm infiltrating lobular carcinoma and two of three sentinel nodes positive on hematoxylin and eosin-stained sections. A completion axillary lymph node dissection was performed and 19 nodes were negative for carcinoma.

DETECTION OF LOCOREGIONAL AND DISTANT RECURRENCES

FDG-PET can contribute in significant ways to the clinical management of patients with suspected locore-

gional or distant recurrences. Since it provides functional information, FDG-PET is often complementary to conventional staging methods such as physical examination, cross-sectional imaging (CT or MR) and bone scintigraphy that 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[57] where the discrimination between posttreatment scar and recurrent tumor can be problematic. Due to 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.[58] 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[59] 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 4). Other studies[60] have confirmed these early findings.

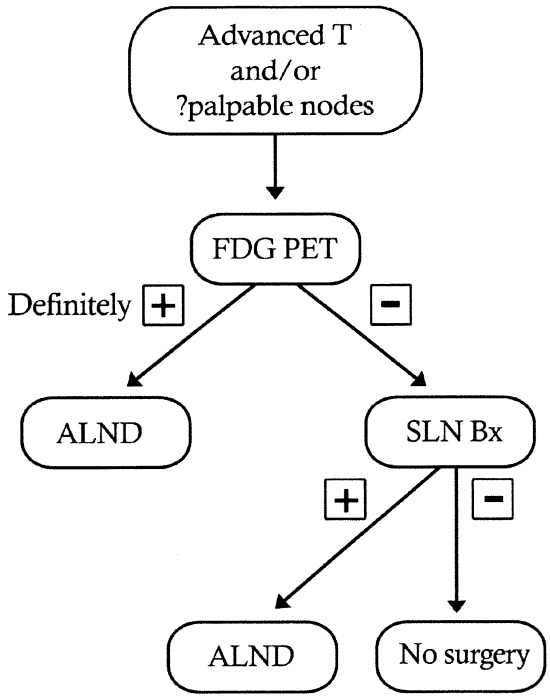

Fig 3. Potential algorithm for workup of patients with advanced primary tumor (T) and/or equivocally palpable axillary nodes. Using this scheme, patients who have clearly positive findings in the axilla by FDG-PET would forgo sentinel lymph node mapping and biopsy (SLN Bx) and undergo complete axillary node dissection (ALND).

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.[61,62] Metastases to IM and axillary nodes are usually synchronous and prognosis is significantly worse when IM nodes are involved.[62] 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 remains controversial in current practice.[63] 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.[18,45] 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.[18] Our experience with imaging patients with LABC shows that the prevalence of IM-FDG uptake can be as high as 25% (Fig 5) and that the presence of IM-FDG uptake predicts treatment failure patterns of disease consistent with IM nodal involvement and progression (Fig 6).[64] A preliminary study by Bernstein and coworkers[65] 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 lung cancer where histologic analysis is used as the gold standard.[66,67] In our retrospective series of 73 patients with recurrent or metastatic breast cancer who underwent both FDG-PET and chest CT,[68] FDG uptake in mediastinal or IM nodes was two 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

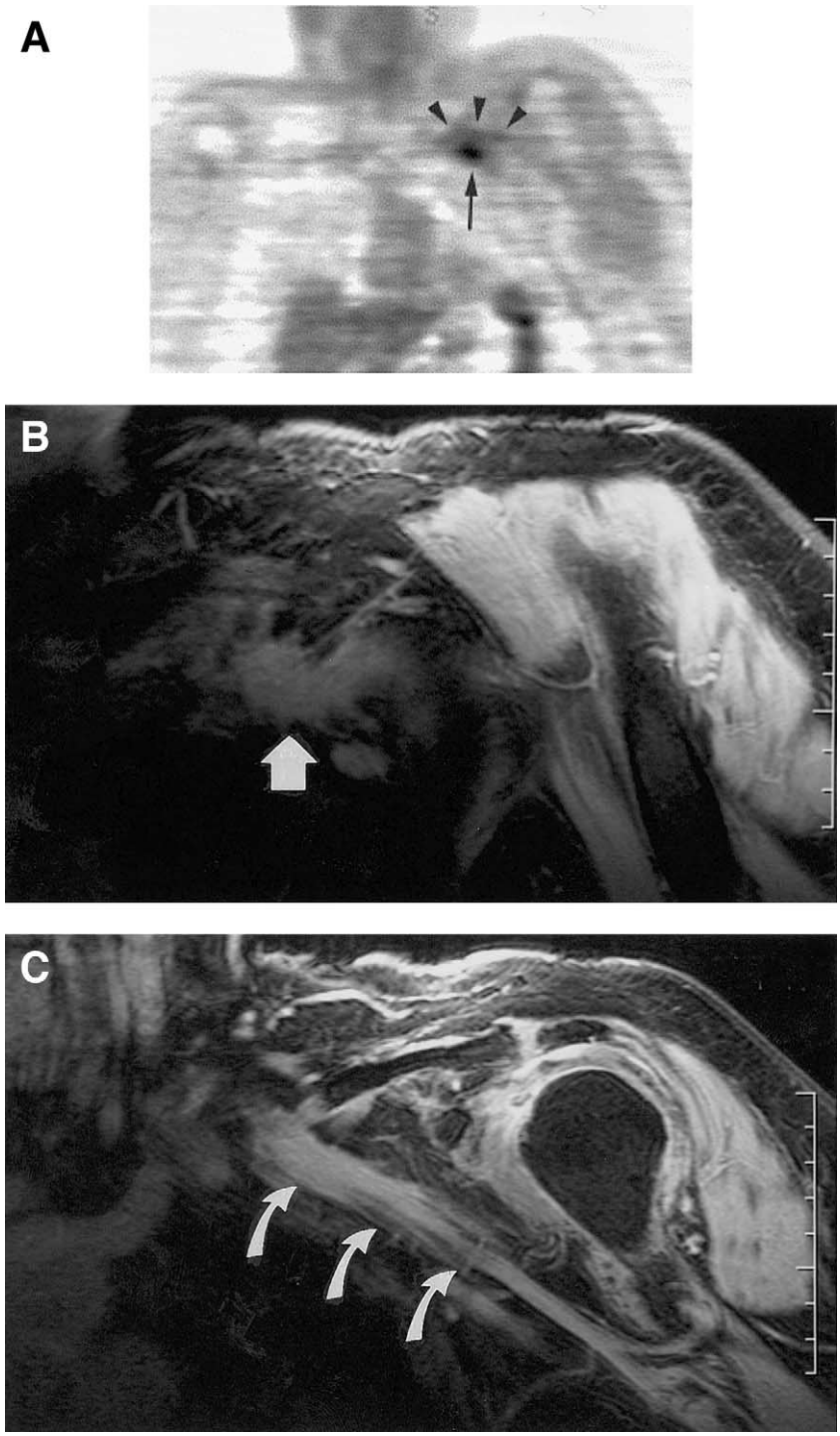

Fig 4. A-56 year-old woman developed progressive left arm pain and paralysis 2 years after left mastectomy and axillary lymph node dissection for infiltrating ductal carcinoma. She also received adjuvant chemotherapy and radiotherapy to the chest wall, axilla, and supraclavicular regions. Positron emission tomography using F-fluorodeoxyglucose (FDG-PET) and magnetic resonance of the brachial plexus were performed to determine the resectability of potential disease. Coronal FDG-PET image (A) shows a swollen left arm with an intense focus of FDG uptake consistent with axillary recurrence (arrow, maximum standard uptake value of 6.9) and linear uptake in the region of the left brachial plexus (arrowheads). Coronal image from fat-suppressed T1-weighted gadolinium-enhanced fast gradient-echo magnetic resonance examination (B) shows a spiculated soft tissue mass (arrow) in the superior left axilla consistent with axillary recurrence. A more posterior coronal image from the same magnetic resonance examination (C) shows enhancing soft tissue encasing all three cords of the distal left brachial plexus (arrows). FDG-PET and bone scan also showed multiple skeletal foci of uptake consistent with bone metastases (not shown). She was treated with systemic chemotherapy for palliation rather than aggressive surgery because of her widespread disease.

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.[69-78] We recently published a series of cases showing common patterns of spread of disease in patients with recurrent or metastatic breast cancer using FDG-PET.[79] An example of intrathoracic recurrence is shown in Fig 7. Moon and coworkers[69] reported an overall lesion-by-lesion sensitivity of 85% (35/41) and specificity of 79% (31/39). In a retrospective study of 61 patients[80] FDG-PET was significantly more accurate at predicting disease-free

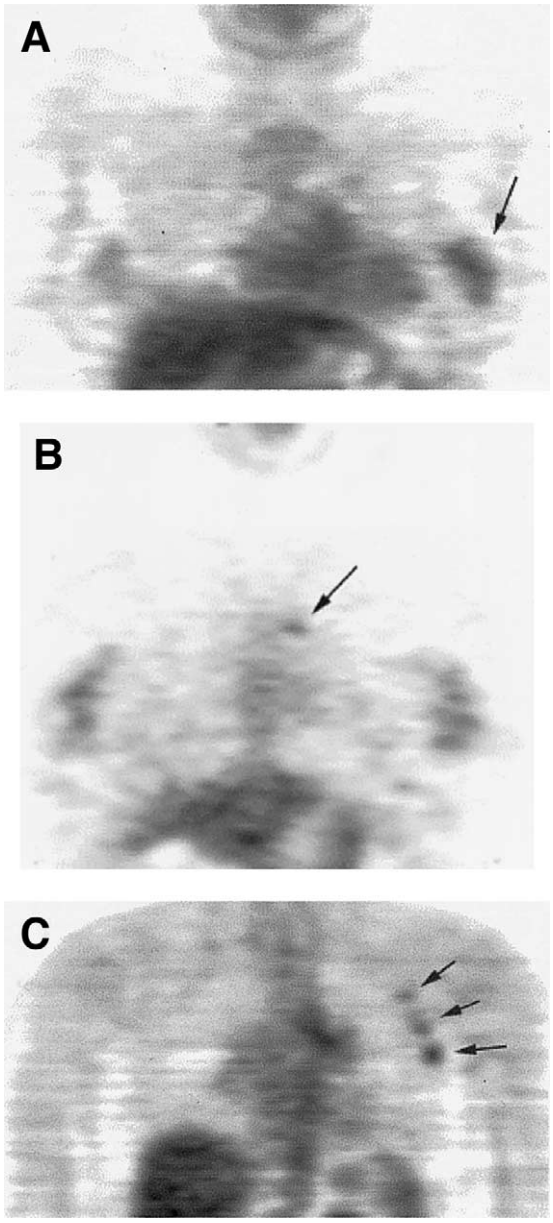

Fig 5. A 57-year-old woman with locally advanced infiltrating ductal carcinoma of the left breast underwent positron emission tomography using F-fluorodeoxyglucose to better define the extent of disease before neoadjuvant chemotherapy. Anterior coronal image from pretherapy positron emission tomography using F-fluorodeoxyglucose (A) shows a hypermetabolic focus in the left breast (arrow, maximum standard uptake value [SUV] of 2.5) consistent with patient's primary tumor. A more posterior coronal image (B) shows focal uptake to the left of midline in the anterior chest (arrow, maximum SUV of 2.5) consistent with left internal mammary node metastasis. Even more posterior coronal image (C) shows several hypermetabolic foci in the axilla (arrows, maximum SUV of 4.9) consistent with axillary node metastases.

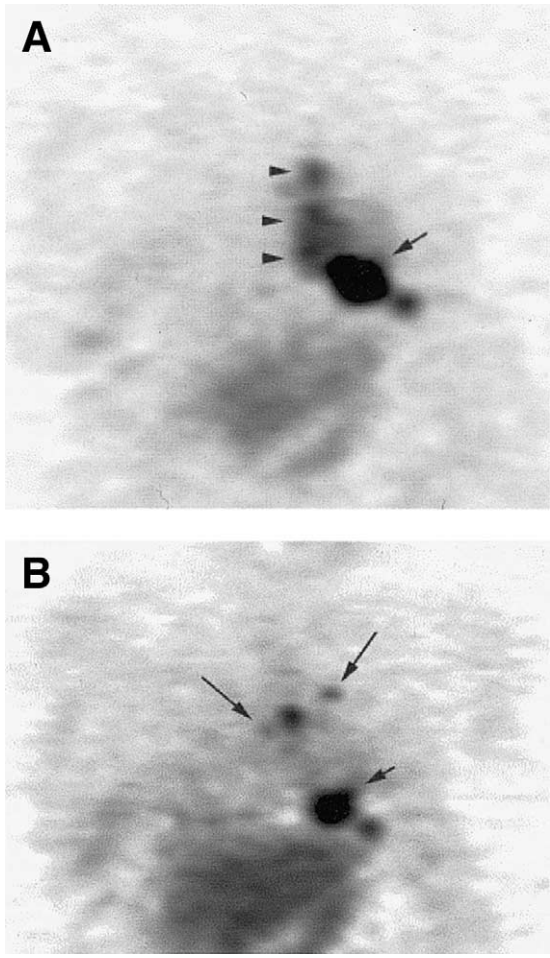

Fig 6. A 61-year-old woman developed a recurrence in the left parasternal chest wall 9 years following mastectomy and standard adjuvant systemic and radiation treatment (although internal mammary regions not included in field) for an infiltrating ductal carcinoma of the left breast. This mass was partially excised and histology of the lesion revealed similar characteristics as the original primary tumor. Postexcision positron emission tomography using F-fluorodeoxyglucose (FDG-PET) was performed to define extent of disease and evaluate for potential further surgical resection. The pattern of FDG uptake is consistent with locoregional spread from an internal mammary node recurrence. An anterior coronal image from FDG-PET (A) shows midline uptake of tracer (arrowheads; maximum SUV of 4.5), likely representing sternal involvement. A more posterior coronal image (B) shows two hypermetabolic foci (long arrows) on either side of midline consistent with bilateral internal mammary node metastases (maximum SUV of 2.9 and 2.2 on left and right sides, respectively). The large focus of intense uptake in the left anterior chest wall (short arrow in A and B) is likely due to contiguous spread of disease to adjacent rib or the excisional biopsy site.

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

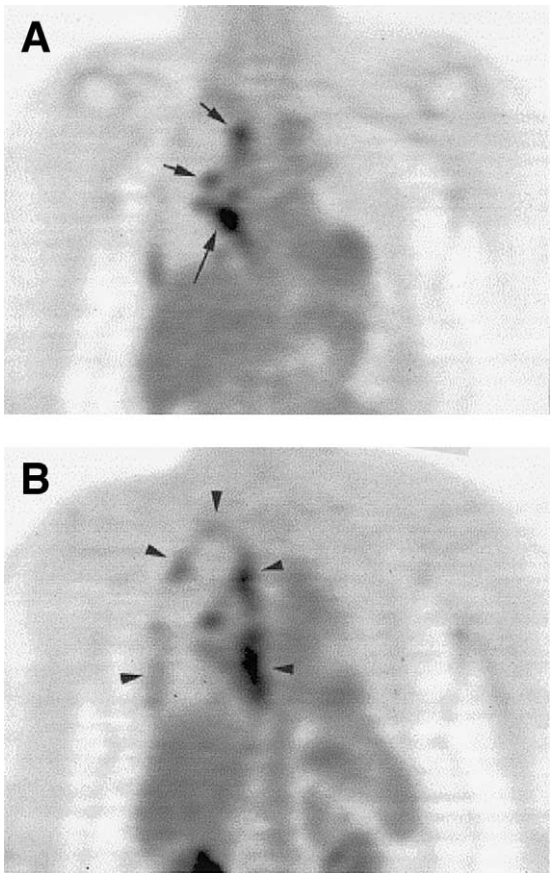

Fig 7. A 58-year-old woman with a 5-year history of pulmonary metastases from ER positive infiltrating ductal right breast carcinoma being treated with two different aromatase inhibitors in succession. Patient had worsening cough and chest pain. Computed tomography chest and bone scan (not shown) showed no clear-cut progression. Positron emission tomography using F-fluorodeoxyglucose was performed to evaluate for extent of disease and it showed multiple sites of intrathoracic disease. An anterior coronal image (A) shows multiple foci of F-fluorodeoxyglucose uptake corresponding to right hilar and mediastinal nodes (small arrows; maximum SUV of 8.4 in right hilum) and right middle lobe (long arrow, maximum SUV of 8.4) consistent with known metastases. A more posterior coronal image (B) shows linear uptake encasing the right hemithorax (arrowheads) consistent with pleural metastasis.

FDG-PET in detecting nodal and skeletal recurrences than CI. 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.[71,76,78] In a retrospective study of 39 patients comprised mainly of asymptomatic patients with rise in tumor markers,[71] FDG-PET detected recurrences in 31/33 (94% sensitivity) patients whereas CI was positive in only 6/33 (18% sensitivity) patients. 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.[81] In a study of 23 breast cancer patients with known skeletal metastases who underwent both bone scintigraphy and FDG-PET, Cook and coworkers[82] 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 [F-18]-fluoride PET may provide similar and likely improved bone metastasis detection in breast cancer and other tumors compared with bone scintigraphy[83,84] 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,[85] 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,[86] the extent of disease was changed in 67% (increased in 43% and decreased in 24%) of patients and changes in the therapeutic plan were induced or supported in 57% 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, and patients with known metastases being evaluated for response to therapy. In our study, these two subgroups of patients with advanced disease were most likely to

benefit from staging with FDG-PET. Future prospective trials will help to further define the role 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.[87] 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.[88-92] Significant reductions 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.[88] Two separate investigations[91,92] 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 [O-15]-water can estimate regional blood flow within a tumor; low tumor perfusion may be one factor responsible for poor response to intravenous chemotherapy.[93] 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 predicts complete pathologic response and disease-free survival.[30] We found a strong 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 following two 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.[94] 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 early evidence that using FDG-PET to monitor response to treatment in sites of disease other than the primary tumor may be helpful.[92,95] Smith and coworkers[92] 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[95] 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 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.[81,96,97] In a retrospective study, we evaluated the response of skeletal metastases to therapy using serial FDG-PET[98] 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 8). 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.[96] Mortimer and coworkers[99] 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.

Although FDG-PET has shown promise in assessing response to therapy, other tracers may provide advantages over FDG in this application. These are described as part of the following section.

BEYOND FDG: FUTURE DIRECTIONS IN PET BREAST CANCER IMAGING

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. New PET tracers and imaging approaches will help not only in breast cancer staging, but more importantly in guiding treatment by identifying therapeutic targets, by identifying factors associated with resistance to therapy, and by making early assessments of therapeutic response. Breast cancer is perhaps the best current clinical example of a tumor where therapy can be tailored to tumor biology. PET will be used increasingly and with a variety of tracers to aid in biologically directed, individualized treatment selection for breast cancer patients. Some promising examples are highlighted below.

Imaging Response, PET Cellular Proliferation Imaging

Decreased tumor proliferation is an early event in response to successful treatment.[100] This underlies the use of labeled thymidine and analogs to image cellular proliferation and early response to treatment.[39] Thymidine is incorporated into DNA, but not RNA; therefore

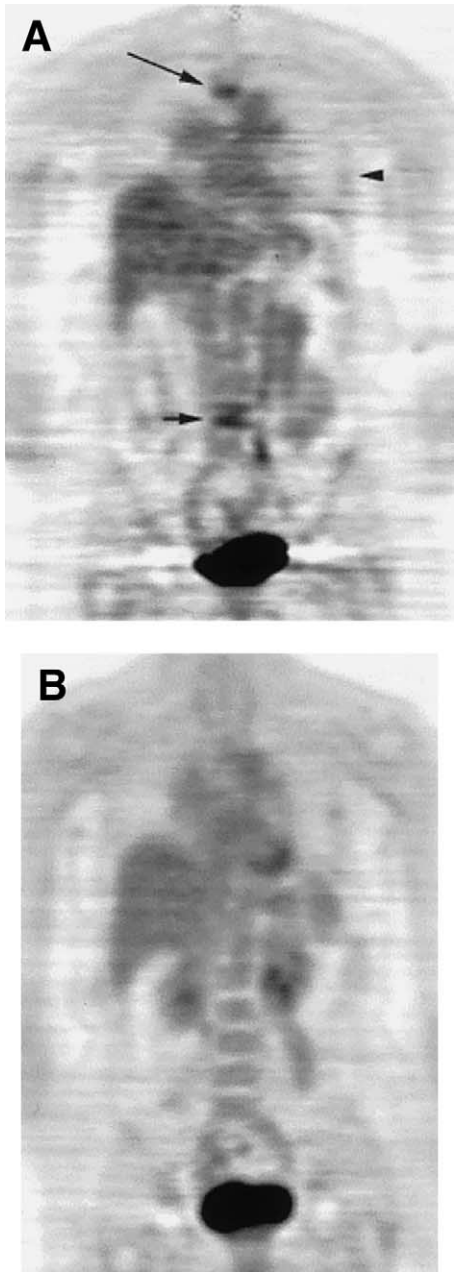

Fig 8. A 60-year-old woman with bone-dominant metastases that developed one year after completion of 5-year course of adjuvant tamoxifen for ER/PR positive infiltrating ductal primary tumor. Coronal image from baseline positron emission tomography using F-fluorodeoxyglucose (FDG-PET; A) shows uptake at T3 level (long arrow, maximum SUV of 3.8), at L4 level (short arrow, maximum SUV of 5.2) and mild uptake in left rib (arrowhead, maximum SUV of 3.0). Coronal image from FDG-PET after two courses of chemotherapy (B) showed resolution of foci in the spine and some decrease in SUV of the left rib lesion consistent with good response to therapy.

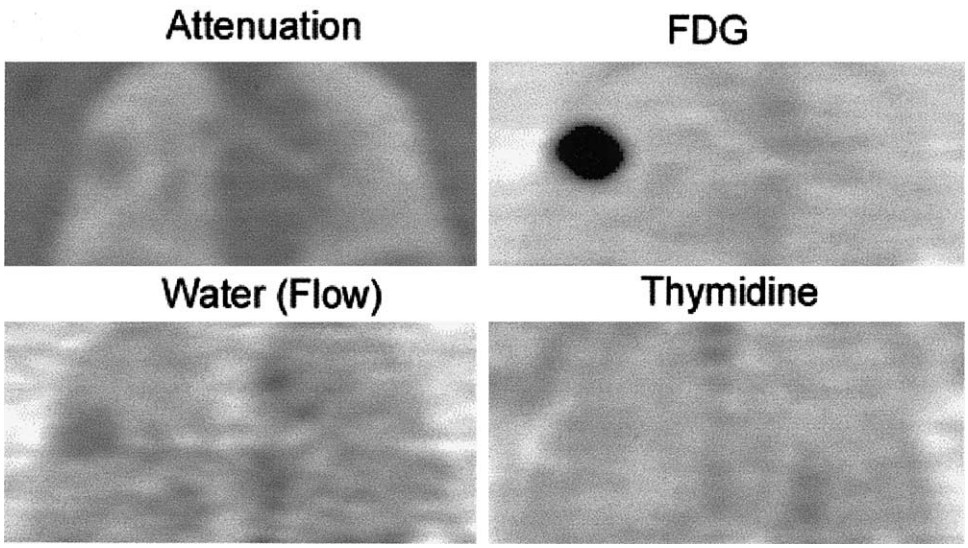

Fig 9. Image of patient with a large, biopsy-proven breast cancer lung metastasis in the right lung, seen clearly on the positron emission tomography transmission images (upper left). The patient underwent pretherapy imaging using [O-15]-water, [C-11]-thymidine, and F-fluorodeoxyglucose (FDG) on the same day. The patient had high FDG uptake (upper right, maximum SUV > 20), but only modest blood flow, illustrated by the summed [O-15]-water study (lower left). Thymidine imaging showed virtually no thymidine retention (lower right, summed image) and low calculated thymidine flux, suggesting a minimally proliferating tumor. The patient had a fairly minimal response to cytotoxic chemotherapy. This interesting case illustrates several points: 1) high FDG uptake does not necessarily indicate tumor proliferation and 2) cell proliferation can help characterize breast cancer and predict response. In this case, low tumor proliferation portended slow growth, but poor response to cytotoxic chemotherapy.

thymidine uptake and retention in the tumor serves as a specific marker of cell growth.[101,102] Recent studies using [C-11]-thymidine and PET show promise in assessing response,[39,103] especially early response. Our laboratory is beginning to study the use of [C-11]-thymidine in breast cancer (Fig 9). Because of the short half-life of C-11 (approximately 20 minutes) and the extensive metabolism of thymidine, [C-11]-thymidine is not practical for routine clinical use outside of academic centers. This spurred the development of [F-18]-labeled, nonmetabolized thymidine analogs to image tumor proliferation. The most promising thus far is [F-18]-fluoro-L-thymidine (FLT).[104,105] Studies in lung cancer have shown that FLT uptake correlates with in vitro measures of proliferation performed on biopsy specimens.[106] Several laboratories have ongoing studies using FLT PET to measure response in several different tumor types, including breast cancer.[107] Imaging cellular proliferation holds great promise as a method for early assessment of response to systemic therapy.

Identifying Factors Associated With Resistance, Imaging Tumor Hypoxia

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.[108,109] 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.[110] 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,[111] 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.[112] Several PET agents specifically designed to image tumor hypoxia have been tested for hypoxia imaging[113] and of these, [F-18]-fluoromisonidazole has the largest current body of preclinical validation studies and clinical experience.[113,114] A preliminary study at our center that included large primary and metastatic breast cancers showed that approximately one third of tumors had one or more areas of severe hypoxia by [F-18]-fluoromisonidazole PET.[112] PET hypoxia 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.

Measuring the Therapeutic Target, PET Imaging of ER Expression in Breast Cancer

The majority of breast cancers express ER and ER expression is an indicator of prognosis and predicts the

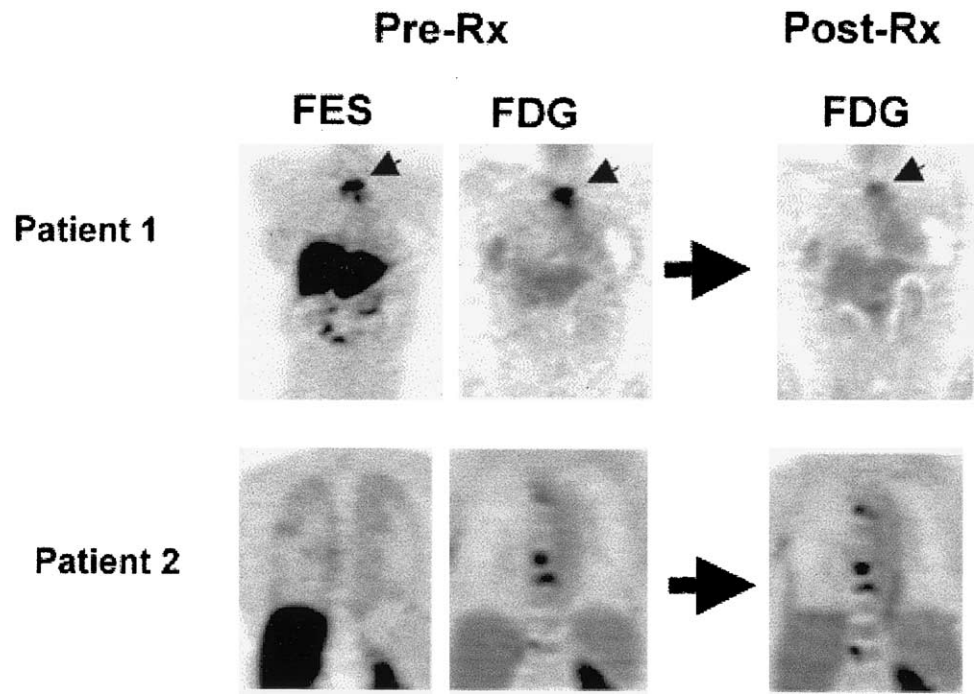

Fig 10. Images illustrating the correlation between 16 α-[F-18]-fluoroestradiol-17β (FES) uptake and subsequent response to hormonal therapy. Coronal images of FES uptake (left column) and F-fluorodeoxyglucose (FDG; middle column) uptake pretherapy, along with FDG uptake posthormonal therapy (right column), are shown for two patients (top and bottom row). The patient in the top row is a 44-year-old woman who was previously treated with adjuvant tamoxifen and had a sternal recurrence of breast cancer 4 years after primary tumor treatment. Her lesion had high pretherapy FES uptake in the lesion (arrow; image also shows liver and bowel uptake, both normal findings). FDG images taken before and after 6 weeks of letrozole treatment show a significant decline in FDG uptake, with subsequent excellent clinical response. The patient in the bottom row is a 69-year-old woman with newly diagnosed metastatic breast cancer that had not previously been treated. Her primary tumor was ER+ by immunohistochemistry and showed FES uptake (not shown). However, her pretherapy FES uptake showed no uptake at bone metastases documented by multiple imaging modalities, including positron emission tomography using F-fluorodeoxyglucose (FDG-PET). The patient received multiple hormonal treatments with no response of the bone metastases, indicated by the posttherapy FDG-PET, despite response by the primary tumor. The patient ultimately had progression of bony metastases and died to her disease.

likelihood of responding to antiestrogen therapy.[115,116] 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.[116] However, in vitro measurements of ER do not discriminate between functional and nonfunctional receptors and provide only an estimate of hormone sensitivity.[117] 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.[118] Here again is a clinical problem to which PET imaging is ideally suited. A variety of agents has been tested for PET-ER imaging[119] and new compounds continue to be evaluated.[120] The close analog of estradiol, the labeled estrogen 16 α-[F-18]-fluoroestradiol-17β (FES)[121] 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[122] and in preliminary data by immunohistochemistry.[123] FES-PET provides sufficient image quality to image metastatic lesions with high sensitivity in patients with ER positive tumors[124] at an acceptable radiation dose to the patient.[125]

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 heterogenous FES uptake within the same tumor and between metastatic lesions, both qualitatively and quantitatively.[32,126] 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 (Fig 10).

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[127] studies by Mortimer, Dehdashti and colleagues[99,128] 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.[129] 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.[124] High degrees of ER blockade in the primary tumor (about 50% decrease in SUV from baseline) also portend a good response to therapy.[99] 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.

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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