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REVIEW ARTICLE

FDG-PET and Beyond: Molecular Breast Cancer Imaging

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INTRODUCTION

Positron emission tomography (PET) scanning has gained widespread acceptance for the diagnosis, staging, and management of a variety of malignancies, including breast cancer. This has heralded an exciting new era of molecular imaging research of which using FDG as the primary PET tracer is only the beginning. The fundamental strength of PET over conventional imaging is the ability to convey functional information that even the most exquisitely detailed anatomic image cannot provide. As the standard PET radiotracer in current clinical use, FDG is a glucose analog that is taken up by cells in proportion to their rate of glucose metabolism. The increased glycolytic rate and glucose avidity of malignant cells in comparison to normal tissue is the basis of the ability of FDG-PET imaging to accurately differentiate cancer from benign tissue irregardless of morphology.[1] The level or intensity of FDG uptake on PET is semiquantified and reported as the standardized uptake value (SUV). A multitude of new PET tracers are under development, many of which are aimed at targeting cellular processes that are more specific than glucose metabolism. In relation to breast cancer, these tracers include thymidine analogs such as [F-18]fluoro-L-thymidine (FLT) that target DNA replication as a measure of cell proliferation, annexin V derivatives that evaluate apoptosis, estrogen receptor (ER) tracers such as 16 α-[F-18]fluoroestradiol-17β (FES), and engineered antibody fragments that directly target HER-2/*neu* receptors. In addition to new tracers, scanner technology is also rapidly evolving. Chief among these is the advent of the dual modality PET/CT scanner, which at the very least increases patient convenience by permitting PET and computed tomography (CT) imaging in a single appointment. But perhaps more importantly, initial studies indicate that the sum of the two modalities is better than either used separately and also may be an extremely useful tool in preradiation therapy planning.[2,3] Other new scanning devices are also being developed, including small gantry PET scanners designed specifically for breast imaging, and handheld PET probes for direct intraoperative localization of tracer-avid tumor foci.

FDG-PET AND PET/CT

Oncologists have utilized FDG-PET with a great deal of success in imaging lung cancer, lymphoma, and melanoma, and its use in breast cancer can also be very helpful when used judiciously in many common clinical situations. As of November 2004, the Centers for Medicare & Medicaid Services (CMS) approves of coverage for FDG-PET scanning for the following indications in breast cancer: as an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence of metastasis; and as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced

and metastatic breast cancer when a change in therapy is anticipated.

However, currently CMS has not yet decided to cover FDG-PET for initial diagnosis of primary breast cancer and the staging of axillary lymph nodes since research studies for these indications have had mixed results. Nevertheless, the role of FDG-PET in clinical diagnosis and management of breast cancer patients is increasing and evolving, and the range of the CMS coverage will likely be expanded in the near future.

Initial Diagnosis

Noninvasive breast cancer has been previously shown to be poorly imaged by FDG-PET[4] and the majority of FDG-PET research studies in the literature have been performed on patients with invasive breast cancer. Surveying across several studies, Wu and Gambhir[5] reported that the overall sensitivity, specificity, and accuracy of FDG-PET in the detection of primary invasive breast cancer are 90%, 92%, and 93%, respectively. There are significant variations between studies, with earlier small studies in selected patient groups reporting 100% sensitivity and accuracy, which is in contrast to larger series conducted by Avril et al[4] and Schirrmerister et al[6] showing FDG-PET sensitivity varying in the range of 84% to 93%. The overall specificity of FDG-PET is relatively high, but false-positives do occur in some benign inflammatory conditions and fibroadenoma.[7,8]

The two major contributing factors that explain the varied statistical results between studies are histopathology and size of the lesion. Invasive breast cancer includes multiple histologic types including infiltrating ductal, infiltrating lobular, and combined infiltrating ductal and lobular carcinoma. Infiltrating ductal carcinoma has a higher level of FDG uptake and therefore is detected at a significantly higher sensitivity than infiltrating lobular breast cancer.[4,9] This difference in FDG uptake between the two histologic types suggests that tumor aggressiveness is not the sole determinant of FDG uptake but that the mechanism of the variable FDG uptake by breast cancer cells is likely modulated by multiple factors including glucose transport-1 expression, hexokinase I activity, tumor microvessel density, amount of necrosis, number of lymphocytes, tumor cell density, and mitotic activity index.[10]

Not surprisingly, several studies show that breast tumor size significantly affects FDG-PET scan results. Early studies of lesions larger than 1 cm show that FDG-PET can detect such tumors with both a sensitivity and specificity in the range of 96% to 100%.[11,12] However, a more recent series showed that FDG activity was very low or nondetectable in patients with tumor sizes ranging from 0.4 to 1.5 cm.[13] These small lesions are at the limit of the resolution of modern PET systems, which is approximately 6 mm (with the newest PET/CT systems having a spatial resolution as good as 4 mm), and lesions in this size range and smaller will be below the threshold of detectability.

In short, the results of FDG-PET for the initial detection and diagnosis of primary breast cancer vary, largely due to heterogeneity of the disease and tumor size. Although some nuclear medicine physicians expected that FDG-PET would serve as a "metabolic biopsy" as a means of screening, this is not yet the case for breast cancer. Improvements in spatial resolution and scanner sensitivity, as well as the advent of dual modality PET/CT scanning, may lead to FDG-PET being more useful for breast cancer diagnosis.[3] FDG-PET may also play an important adjunctive role in selected patients with dense breasts where mammography has a much poorer sensitivity.[14] Finally, new PET scanners utilizing a small gantry size, designed exclusively for breast imaging, are being developed that may significantly increase spatial resolution and sensitivity.[15]

Initial Staging

The performance of FDG-PET imaging in breast cancer staging can be separated into two general categories: (1) staging of axillary lymph nodes where PET has met with decidedly mixed results; and (2) staging of mediastinal and internal mammary lymph nodes and distant metastatic disease where FDG-PET has consistently performed well.

Axillary lymph node involvement in breast cancer patients is an indicator of prognosis and an important factor in determining medical management and therapy. Since conventional anatomic imaging cannot reliably detect axillary nodal metastases, patients with invasive breast cancer routinely undergo lymphoscintigraphy and axillary lymph node dissection (ALND) for accurate staging. This practice is under debate, as the identification of axillary nodal involvement may not improve overall survival rate, and because ALND is associated with a high incidence of morbidities. Therefore, FDG-PET has been extensively studied for noninvasive staging of the axilla. These results have been promising but mixed. Although PET has an overall sensitivity of 88%, specificity of 92%, and accuracy of 89% when surveying across the multitude of prior reports,[5] several of the studies achieved higher sensitivity at the expense of lower specificity or vise versa. This has led to a wide variation in results. For example, Adler et al[16] tried to achieve high sensitivity by using 20 mCi (740 MBq) of FDG (two times the regular dose for an adult patient), and they reported 95% sensitivity in 50 patients, but the specificity in the same series was only 66%. In contrast, a more recent study by Guller et al[17] evaluated 31 patients using histopathologic correlation of sentinel lymph nodes as the gold standard and the overall sensitivity, specificity, and negative predictive values were 43%, 94%, and 67%, respectively. Further discussion of these findings and a tabulated summary are presented below.

Studies of PET for Axillary Node Staging: A Tabulated Summary

A literature search identified nine studies that have looked at the sensitivity and specificity of FDG-PET scanning in assessing axillary node status. The search was confined to English language, prospective studies with at least 12 human subjects and with either sentinel node biopsy (SNB) or axillary node dissection (AND) as the reference standard, and with PET scan interpreters blinded to the results of the pathologic axillary node assessment. Table 1 summarizes the results of the eight studies using AND as the reference standard.

The largest of these studies, by Wahl et al,[22] suggested that FDG-PET may fail to detect tumor in the axilla when there are few and small nodal metastases, but may be highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified. This would suggest that for patients with a highly positive PET, SNB might be omitted as AND will still be required. Earlier studies suggesting a high sensitivity of FDG-PET for the detection of axillary metastases did not employ the more sensitive methods of serial sectioning and cytokeratin immunohistochemistry currently employed in the assessment of sentinel lymph nodes. With increasing numbers of trials and larger sample sizes, more recent studies are beginning to consistently suggest that FDG-PET may not have a sufficiently high negative predictive value to justify forgoing AND. In addition, however, there have been studies of FDG-PET together with both SNB and AND in patients with early-stage breast cancer. Such studies have explored the possibility that the combination of SNB and FDG-PET may together have a high enough sensitivity to allow avoidance of AND, when neither alone is sensitive enough.

Four studies have compared FDG-PET with the reference standards of SNB, or SNB plus AND, with the results presented in Table 2. These studies suggest that PET is even less sensitive in detecting metastases identified by SNB than those identified by AND. This is presumably because SNB, with its more detailed pathologic examination of a small number of nodes, is more likely to detect micrometastatic disease that cannot be identified with FDG-PET.[22] A review article regarding PET versus SNB suggests that PET in its current format is not yet sensitive enough to replace SNB, but that its high specificity may be useful in determining the extent of local and systemic disease.[24]

Staging Mediastinal and Internal Mammary Lymph Nodes and Distant Disease

In contrast to the mixed results of FDG-PET in axillary lymph node staging, many studies have consistently demonstrated that FDG-PET is superior to CT in the detection of internal mammary and/or mediastinal lymph nodal metastases.[7,25,26] In studies comparing PET to CT staging directly, the overall sensitivity, specificity, and accuracy in detection of mediastinal and internal mammary nodal metastases by PET was 85%, 90%, and 88% versus 54%, 85%, and 73% by CT.[5] These data are promising for FDG-PET to play a role in staging internal mammary and mediastinal lymph node involvement, which is an important prognostic factor in patient management (Fig 1).

FDG-PET has also proved effective in detecting distant lesions and providing staging information even at the time of initial diagnosis. Several investigators have shown that PET is relatively sensitive (84% to 93%), and has a good negative predictive value (greater than 90%) in the evaluation of distant metastases.[27-29] Whole-body FDG-PET is able to detect metastases involving the liver, lymph nodes, bone, lung, and bone marrow (Fig 2). Specificity and positive predictive values are not quite as high, in the range of 55% to 86% and 82% respectively, largely due to false-positive findings caused by muscle uptake, inflammation, blood-pool activity, and bowel uptake.[29] In respect to bone metastases where Tc-99m MDP bone scanning has been the established standard, recent studies independently show that FDG-PET identified bone metastases with similar sensitivity and higher accuracy relative to Tc-99m MDP bone scanning.[30,31] Further, a report by Garcia et al[32] and a preliminary study at our center suggests that FDG-PET, and particularly dual modality PET/CT, may in fact be superior to bone scanning in the evaluation of lytic bone metastases.[33]

In addition to traditional whole-body PET scanning, new strategies for using FDG-PET for lymph node staging

Table 1. Results of Studies Using Axillary Node Dissection as the Reference Standard

Study	No. of Patients	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Prevalence* (%)
Smith[18]	50	88	97	95	92	42
Greco[19]	167	94	86	84	95	43
Schirmeister[6]	85	79	92	82	79	40
Yutani[13]	38	50	100	100	73	42
Adler[16]	50	95	66	63	95	38
van der Hoeven[20]	23	57	100	100	60	61
Lovrics[21]	74	46	98	86	89	—
Wahl[22]	360	61	80	62	99	—

*Prevalence of positive axillary nodes.

Table 2. Studies Comparing FDG-PET with the Reference Standards of SNB and AND

Study	Reference Standard	No. of Patients	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Prevalence* (%)
Van der Hoeven[20]	SNB	47	0	97	0	61	38
Lovrics[21]	SNB + AND	74	41	98	90	78	—
Kelemen[23]	SNB	15	20	90	50	69	33
Guller[17]	SNB	31	43	94	86	67	45

Abbreviations: FDG-PET, [F-18]fluorodeoxyglucose positron emission tomography; SNB, sentinel node biopsy; AND, axillary node dissection.
*Prevalence of positive axillary nodes.

are being developed. For example, an exciting system being tested at our institution is the intraoperative use of a handheld positron probe. Under this protocol, a patient is brought to the operating room immediately after FDG-PET scanning. The handheld positron probe directs the surgeon to lymph nodes and lesions that have intense FDG (positron) radioactivity and perhaps increase sampling accuracy for malignancy.

Treatment Monitoring, Tumor Recurrence, and Restaging

FDG-PET is a metabolic imaging modality that has high sensitivity in the detection of therapy-induced glucose metabolic rate changes that may not be evident in anatomic images, particularly early after treatment. This concept has naturally led to the evaluation of PET for treatment monitoring. Many groups of investigators[34-43] have reported that as early as after the first cycle of chemotherapy, FDG-PET can reliably differentiate responding and nonresponding breast cancers. For example, Schelling et al[40] reported that in a group of 22 patients, all responders were correctly identified with a sensitivity of 100% and specificity of 85% using a decrease in FDG intensity (SUV) of greater than 55% compared to baseline. Using a similar protocol, Stafford et al[42] evaluated the response to chemotherapy in 24 patients with stage IV breast cancer. They also observed a good correlation between the FDG SUV changes and clinical response ($P < .01$). An additional phenomenon has been reported in ER-positive tumors where metastases may actually show increased FDG intensity as a predictive response to successful antiestrogen treatment, described as ''metabolic flare''. This transient increase in FDG activity after hormone therapy initiation may be the result of an initial stimulation of tumor growth by estrogen-like agonist effects induced by increased levels of the hormone.[44-46] The metabolic flare typically occurs 7 to 10 days after treatment initiation and may be the earliest and most accurate predictor of hormonal therapy response. It should be noted that all of these studies involve relatively small numbers of patients. Clearly, more patients need to be evaluated, although there is at least preliminary evidence that FDG-PET may be used for early therapy evaluation of patients with locally advanced and/or metastatic breast cancer.

FDG-PET can be very helpful in evaluating asymptomatic, already treated breast cancer patients who may pose a diagnostic challenge for detecting occult recurrences. In a large series of 132 patients being evaluated for disease recurrence, Pecking et al[47] reported that FDG-PET detected lesions in 106 patients, with an overall sensitivity of 94% and a positive predictive value of 96%. Many authors have had similar results.[5] Moreover, FDG-PET has outperformed conventional imaging modalities in evaluating disease recurrence. As an example, Suarez et al[48] studied 45 patients who were in complete remission but with progressive elevated tumor markers, and found that FDG-PET used alone detected recurrent disease in 24 patients, which was superior to the combination of several anatomic imaging modalities (CT, magnetic resonance imaging, ultrasound, and x-rays) that only detected recurrence in 21 patients. Published data consistently demonstrate that FDG-PET has a similar or superior diagnostic accuracy, as compared with other conventional imaging modalities, in the detection of occult recurrent breast cancer in patients with rising tumor markers. More recent studies have focused on the added value of dual modality PET/CT. A study by Pelosi et al[2] of mixed tumor populations that included breast cancer demonstrated that PET/CT has an even higher sensitivity than PET alone in restaging (96% *v* 92%). Additional initial studies in breast cancer and PET/CT have yielded similar results.[49]

An emerging application of PET/CT may be in radiation treatment planning. Fused PET and CT images provide radiation oncologists with two pieces of critical information with a single study: the extent of viable tumor and its exact location. Initial studies in patients with varied tumor types have confirmed that using PET/CT both in pretreatment planning and in follow-up evaluations have a significant impact on radiotherapy management in up to 56% of patients.[50,51] Certainly, evaluation of PET/CT for radiation treatment planning is still in the nascent stages lacking rigorous randomized trials, but nevertheless shows early promise.

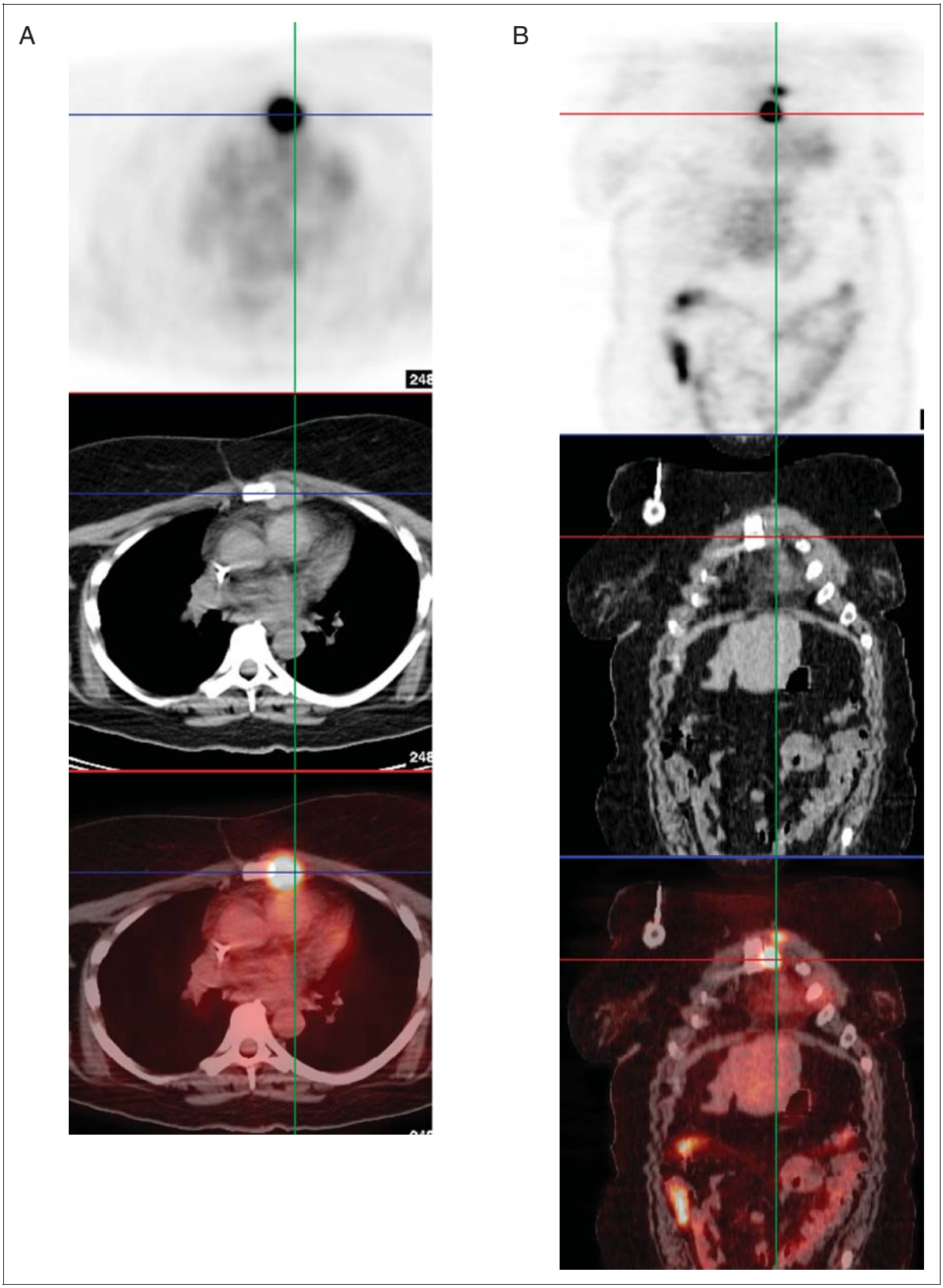

Fig 1. FDG PET/CT detection of internal mammary lymph nodes. (A) Top to bottom: FDG-PET, CT, and fusion PET/CT coregistered transaxial images; (B) top to bottom: FDG-PET, CT, and fusion PET/CT co-registered coronal images.

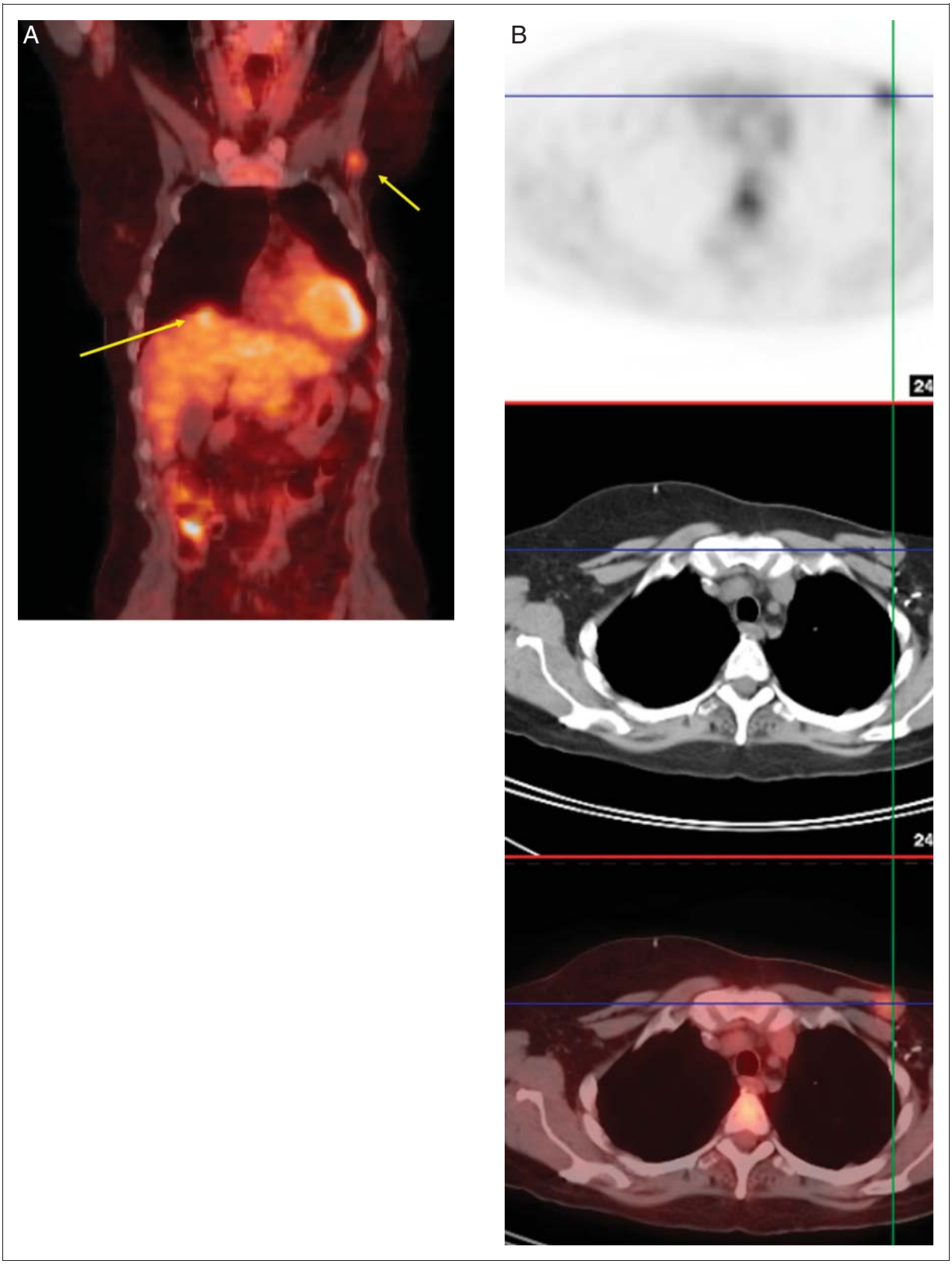

Fig 2. FDG PET/CT detection of breast cancer local recurrence and distant disease. (A) Fusion PET/CT image coronal view demonstrating local recurrence of breast cancer in the left chest wall and in the liver, both of which were not detected on CT alone; (B) top to bottom: FDG-PET, CT, and fusion PET/CT coregistered transaxial images demonstrating left chest wall recurrence.

BEYOND FDG: NEW TRACERS AND STRATEGIES ON THE HORIZON

Although FDG continues to play a role in the diagnosis, staging, and management of various tumors, including breast cancer, a host of new radiopharmaceuticals are being developed that target specific molecular components. New PET tracers are being developed and studied that allow for assessment of cell proliferation, apoptosis, estrogen receptors, and HER-2/*neu* expression and are exciting new avenues for future clinical usage in the coming years.

Cellular Proliferation Imaging

While imaging glucose metabolism with FDG has been quite successful thus far, there has been a continual search for a tracer that more specifically monitors tumor growth and, perhaps more importantly, cancer cell death in order to develop an imaging modality that can follow treatment response accurately. This is the driving notion behind the development of radio-labeled thymidine compounds. Thymidine is incorporated into DNA and therefore thymidine uptake and retention in the tumor serves as a specific marker of cell proliferation.

Earlier studies using [C-11]thymidine PET imaging using mixed tumor populations, including lung cancer and sarcoma, have shown a good correlation between mammalian thymidine activity and tumor response to therapy. A more recent pilot study using FLT in breast cancer by Smyczek-Gargya et al[52] showed that FLT has a tumor-to-background ratio similar to FDG in breast cancer but provides cell proliferation data rather than merely measuring glucose metabolism. Because of this factor, the most promising avenue appears to be the application of FLT in following treatment response. Pio et al[53] reported that FLT may be helpful in this clinical setting and at a relatively early stage of treatment in breast cancer.

There are additional aspects of FLT imaging that require further study. FLT clearly has lower background activity in the mediastinum when compared to FDG and therefore, presumably, can detect metastases in this region with a higher sensitivity. This aspect has not been studied in breast cancer but has already been suggested in FLT lung cancer research.

Imaging Apoptosis With Annexin V Derivatives

A technique to image-programmed cell death would be useful both in clinical care and in drug development. The most widely studied agent for the in vivo study of apoptosis is radiolabeled annexin V,[54] and the PET version of this tracer, [F-18]-labeled annexin V, is undergoing initial testing in various tumor types. Data in regards to breast cancer are so far scarce, but data in brain glioma have been encouraging.[55] Moreover, testing of the technetium-labeled annexin derivative has already promoted potential applications of apoptosis imaging as a marker of early response to therapy in cancer, acute cerebral and myocardial ischemic injury and infarction, immune-mediated inflammatory disease, and transplant rejection.[54]

Estrogen Receptor Imaging

Determining the presence of positive ERs in malignant breast tumors is an important step in the initial work-up of breast cancer because it is a major determinant in therapeutic strategy and is an indicator of prognosis. One of the most fertile new areas of PET research involves the development of specialized PET tracers that allow for in vivo quantification of ERs and active functionally. A variety of agents have been developed in this arena of which FES has shown very promising results. Studies have shown that using FES-PET to quantify the level ER expression closely correlates with results from a standard primary breast lesion in vitro assay. Some authors have even suggested that FES-PET imaging may be more helpful than a primary lesion biopsy since PET imaging can assess not just ER expression of the primary breast tumor, but the metastastic lesions as well. Further, PET is also an in vivo exam that can quantify receptor functionality rather than merely existence.[46,55]

Therefore, PET ER imaging has several potentially powerful uses. FES-PET can be used to quantify the entire volume of ER-positive disease of all of the lesions in a patient. Further, studies using FES-PET have already shown that there is heterogeneous FES uptake within the same tumor and between metastatic lesions. Both of these applications could possibly predict prognosis and guide treatment strategies. Furthermore, a higher level of FES activity in advanced tumors predicts a greater chance of response to tamoxifen.[46] Promising studies by Mankoff et al[56] have shown comparable results. Studies using FES-PET scanning during tamoxifen therapy demonstrates a direct correlation of increasing ER blockade (decreased FES uptake) with ongoing tamoxifen therapy. Greater levels of blockade are closely associated with successful therapy.[46] An effective overall strategy may be to use both FDG and FES-PET as a baseline scan to help decide treatment strategies. FDG-PET can be used to stage and detect metastatic disease while the correlative FES-PET can determine if antiestrogen therapy will be effective in treating those metastases. A post-treatment restaging FDG-PET can then be used to assess response (Fig 3).[45,46,56]

Engineered Antibodies for Receptor Imaging

Antibodies are also a potential tracer for targeting cell-surface receptors. Although primarily explored for imaging with gamma cameras and SPECT (single photon emission computed tomography), newer small animal studies and clinical trials are starting with positron-labeled antibody fragments. Monoclonal antibodies developed against a specific antigen target are problematic because their relatively slow clearance from blood leads to images with very high background signals, even up to 1 week after

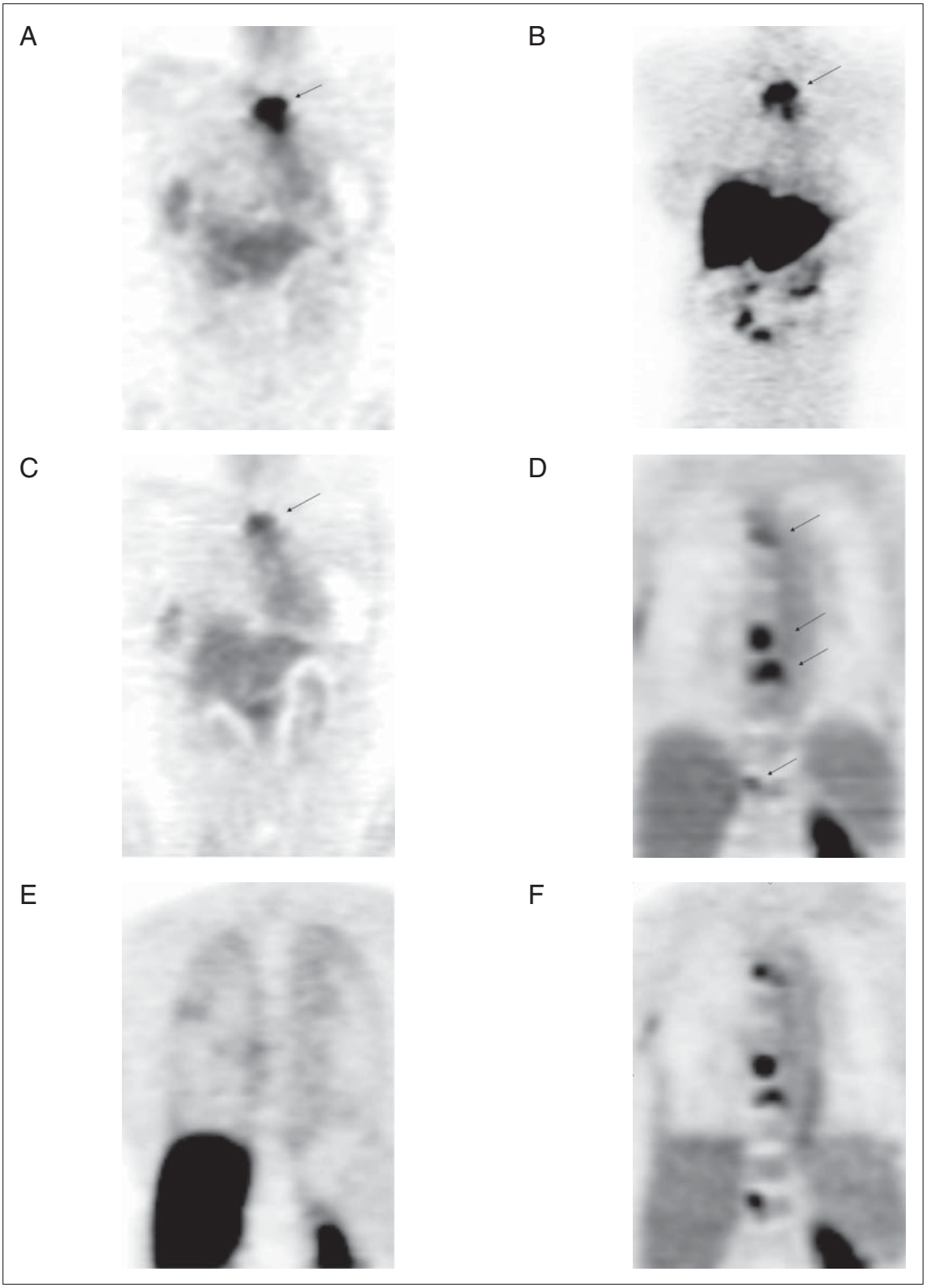

Fig 3. Estrogen receptor imaging using [18F]fluoroestradiol (FES) -PET scanning may predict breast cancer response to hormonal therapy. A comparison of two patients with newly diagnosed breast cancer undergoing hormonal therapy. (A) A patient with a sternal metastasis found by FDG-PET scanning prior to treatment (arrow); (B) accompanying FES-PET that reveals that the sternal metastasis is strongly estrogen receptor–positive; (C) follow-up FDG-PET scan of this patient after 6 weeks of letrazole therapy demonstrating decreased FDG activity consistent with a good response to the antiestrogen therapy as predicted by FES-PET scan. (D) A second patient with an initial FDG-PET scan demonstrating several spinal metastases and (E) the accompanying FES-PET scan that shows no evidence for estrogen receptor activity in these spinal lesions; (F) follow-up FDG-PET scan after 6 weeks therapy with multiple antiestrogen agents reveals the same spinal metastases without response to the hormonal therapies. Reprinted from Eubank WB, Mankoff DA: Current and future uses of positron emission tomography in breast cancer imaging. Semin Nucl Med 34:224-240, 2004. Copyright 2004 with permission from Elsevier.

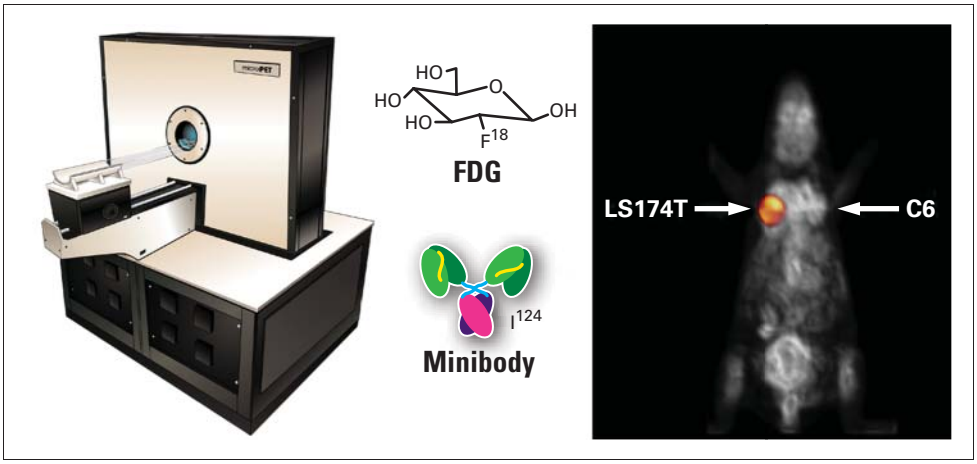

Fig 4. Small animal [F-18]fluorodeoxyglucose (FDG)/iodine-124 minibody imaging. Micro positron emission tomography (PET) imaging of a mouse 1 hour after tail-vein injection of FDG (gray scale) superimposed with microPET imaging of the same mouse imaged 18 hours after injection of an iodine-124 (≈4-day half-life) labeled minibody (color scale) that is targeted against carcinoembryonic antigen (CEA). The mouse carries two tumor xenografts, a C6 rat glioma as a negative control and an LS174T line that expresses CEA. The minibody signal is seen almost exclusively from only the LS174T tumor because 18 hours after tracer injection, most background has already cleared.

injection of the antibody. Efforts have been made to systematically construct engineered antibody fragments, such as minibodies and diabodies,[57,58] against carcinoembryonic antigen. These agents show much more rapid blood clearance (due to their smaller size) at the expense of some affinity for carcinoembryonic antigen as compared with intact antibodies. Humanized versions of these engineered antibody fragments have been labeled with ^{64}Cu and ^{124}I, and mouse tumor xenograft imaging has been performed with microPET (Fig 4).[58] Clinical PET trials with these agents are now starting. The engineered antibody fragments have the ability to be adapted for targeting other tumor cell-surface targets (eg, HER-2/*neu*)[59] and it remains to be seen what advantages these tracers have in the clinical setting over existing tracers such as FDG. Further reviews of antibodies and engineered antibody fragments for imaging are provided elsewhere.[58]

CONCLUSION

Molecular imaging of breast cancer continues to rapidly expand, and improvements in both instrumentation and newer, more specific tracers should help to make molecular imaging a critical component in the breast cancer oncologists' arsenal. Individualized management may soon be possible with the help of advances in molecular imaging. Regulatory issues and relatively slow CMS reimbursement may prove to be the limiting factor in helping make various approaches more generally available. Moreover, larger prospective studies are needed to delineate an effective strategy and guideline for incorporating PET imaging in standard clinical practice. In the future, new methods need to be investigated to link in vitro assays (eg, proteomics) with in vivo imaging, and may help to provide much more certainty in breast cancer management.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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