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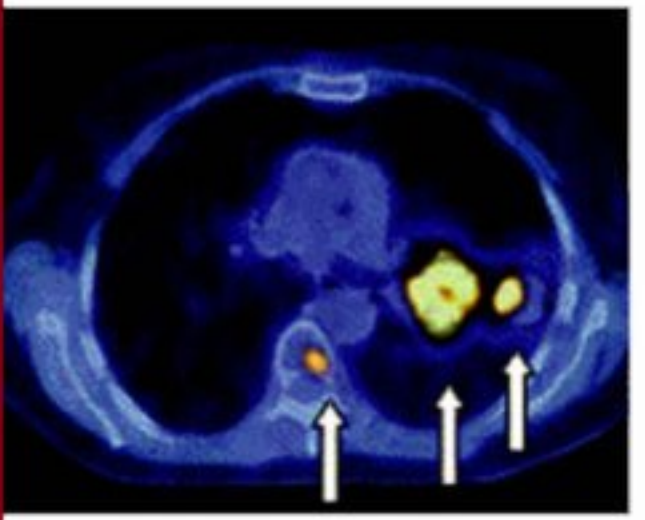

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Preface
Breast Cancer

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Breast cancer is one of the most devastating diseases affecting women in Western countries. Although progress has been made in the development of new therapeutic agents, approximately 40,000 patients in the United States alone will die of breast cancer in 2005. The diagnosis of breast cancer—especially in the early stages—is challenging, and mammography and ultrasound play an important role in screening asymptomatic women as well as in the initial workup of suspicious breast lesions.

Positron emission tomography (PET) has become widely available in the United States, and this first issue of the *PET Clinics* is devoted to the current status and potential future applications of molecular PET imaging in breast cancer. Higher glucose consumption in cancer cells compared with normal tissue has made F-18 fluorodeoxyglucose (FDG) the most commonly used PET radiopharmaceutical. The metabolic information from FDG-PET provides sensitive and specific information about the spread of disease but is limited in evaluating primary breast cancer. New and improved dedicated PET breast scanners have both higher sensitivity and spatial resolution. This necessitates a reconsideration of the potential clinical application of FDG-PET in primary breast cancer.

The development of integrated PET and CT scanners (PET/CT) was a milestone in the acceptance of metabolic PET imaging in the clinical workup of cancer patient. The coregistered metabolic and anatomic information from PET/CT is resulting in improved sensitivity and specificity compared with the single imaging procedures. FDG-PET and FDG-PET/CT have become an integral part of routine patient care in breast cancer within the past few years. New applications such as radiation therapy planning based on metabolic/anatomic information are on the horizon but still need careful evaluation and validation. PET tracers other than FDG targeting tumor cell proliferation and angiogenesis as well as radiolabeled receptor ligands are now increasingly being used to noninvasively characterize breast cancer.

There are further potential applications of FDG-PET beyond diagnostic staging. Changes in tumor glucose consumption occur early in the course of chemotherapy and ultimately predict treatment outcome. The use of FDG-PET for monitoring breast cancer therapy holds promise to reduce the number of ineffective therapies and unnecessary side effects and to facilitate the effective evaluation of new therapeutic approaches.

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F-18 Fluorodeoxyglucose-Positron Emission Tomography Imaging for Primary Breast Cancer and Loco-Regional Staging

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Breast cancer is the most common female malignancy in most European countries, North America, and Australia; it is less frequent in Asia and in Africa. In Europe, one out of every 10 to 15 women will develop breast cancer in her lifetime, and the risk is even higher in the United States, where it is one out of every eight women. Approximately 95% of breast cancer cases occur sporadically without any known genetic mutation, and the causal mechanisms underlying this disease have yet to be fully elucidated. Overall, 5-year survival rates are approximately 75%, with ranges of 92% for Stage I (pT1, pN0, M0) to 15% for Stage IV (M1) disease [1].

The main prognostic factors in patients who have breast cancer are lymph node status, tumor size, histologic grade, and the presence or absence of distant metastases. Most patients who have locally advanced disease have axillary lymph nodes involved with their tumors, but a subset of patients have large primary tumors without lymph node involvement. For patients who have lymph node metastases, more than four lymph nodes involved predict poorer survival [2]. The College of American Pathologists has recently considered prognostic and predictive factors in breast cancer and stratified them into categories reflecting the strength of published evidence [3]. Factors ranked in Category I included tumor, node, metastases (TNM) staging; histologic grade; histologic type; mitotic figure counts; and hormone receptor status. Category II factors included c-erbB-2 (Her2-neu), proliferation markers, lymphatic and vascular channel invasion, and p53. Factors in Category III included DNA

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ploidy analysis, microvessel density, epidermal growth factor receptor, transforming growth factor-alpha, bcl-2, pS2, and cathepsin D.

Invasive ductal carcinoma is the most common histological type (70%–80%), followed by invasive lobular carcinoma (6%–10%) and medullary carcinoma (~3%). The remaining tumors include a variety of histological types. Invasive breast cancer may be present as a single tumor, or as multifocal if tumors are growing in the same quadrant of the breast, and as multicentric if they are detected in different quadrants. The disease can occur in any part of the breast, but most frequently occurs in the upper outer quadrant. Locally advanced breast cancer remains a particular challenge, because the majority of patients who have this diagnosis develop distant metastases despite appropriate therapy. Patients who have locally advanced disease include primary tumors with direct extension to chest wall or skin (stage T4); advanced nodal disease, such as fixed axillary nodes or involvement of ipsilateral supraclavicular, infraclavicular, or internal mammary nodes; and inflammatory carcinomas.

Noninvasive breast cancer consists of two histological and clinical subtypes: ductal and lobular in-situ carcinomas. The carcinoma cells are confined within the terminal duct lobular unit and the adjacent ducts, but have not yet invaded through the basement membrane. Generally, lobular carcinoma in situ (LCIS) does not present as a palpable tumor and is usually found incidentally in breast biopsies, often multifocal and bilateral. Ductal carcinoma in situ (DCIS) is increasingly diagnosed because of microcalcifications seen on mammograms, and is more likely to be confined to one breast or even to one quadrant of the breast.

If breast cancer is suspected, a biopsy is necessary to confirm the diagnosis. The National Comprehensive Cancer Network has published guidelines for the work-up of women who have newly diagnosed breast cancer. The recommendations include history and physical examination, diagnostic bilateral mammogram and ultrasound and optional breast MRI, pathology review, and determination of estrogen receptor, progesterone receptor, nuclear grade and HER-2/neu status. To evaluate distant metastases, chest radiograph, ultrasound of the abdomen, bone scintigraphy, and CT or MRI may be indicated.

Detection of primary breast tumors

Improved methods to detect and diagnose breast cancer early are required to achieve a significant impact on morbidity and mortality. More than 80% of cancers are detected because of a suspicious mass, either by self-examination or routine breast examination. Clinical signs include a fixed, hard mass; asymmetry of the breast contour; a protrusion; a subtle dimpling of the skin (peau d' orange); or a bloody nipple discharge. Depending on the size of the breast and the density of breast tissue, most tumors are not palpable smaller than 1 cm in diameter. Breast carcinomas are often present as irregularly shaped, firm or hard, yet painless nodules or masses. Physical examination typically does not allow an accurate differentiation between a malignant and a nonmalignant mass. Therefore, imaging modalities are used to improve the diagnostic accuracy, and various new and innovative technologies are being investigated for advancing the early detection and diagnosis of breast cancer.

Screening-mammography allows the detection of breast cancer earlier than breast self-examination, and is generally credited with earlier diagnosis and an overall improvement in survival for patients who have newly diagnosed breast cancer. Mammography localizes and assesses the extent of a lesion as well as identifying other suspicious masses. Studies in large series have shown that mammography, using mediolateral oblique and craniocaudal projections, is a useful tool to improve early detection of breast cancer. Depending on the lesion size and the radiographic appearance and breast tissue density, sensitivity ranges from 54% to 58% in women under age 40, and from 81% to 94% in those over 50 [4,5]. Malignant and benign breast lesions often display similar radiographic appearance, resulting in a major limitation of mammography [6]. A Breast Imaging Reporting and Data System (BI-RADS) has recently been introduced to characterize mammography [7]. The categories are listed and explained in Box 1.

In some studies, approximately 6 to 8 out of 10 patients who have suspicious lesions in mammography and who undergo surgery have benign histology [6,8]. A recent multicenter analysis of 332,926 diagnostic mammography examinations [9] found the positive predictive value of a biopsy recommendation to be 31.5%, and that of a biopsy

***Box 1:* BI-RADS categories and definitions**

- **0:** More information is needed to give a final mammogram report.
- **1:** Mammogram is normal.
- **2:** Mammogram shows benign finding.
- **3:** Probably benign finding—short interval follow-up suggested.
- **4:** Suspicious abnormality—biopsy should be considered.
- **5:** Highly suggestive of malignancy—appropriate action should be taken.

performed to be 39.5% This means that currently almost two thirds have a negative biopsy. For screening mammography, the positive predictive value is even lower. About 10% of breast carcinomas are not identified in mammography, even when they are palpable [10]. One reason is that mammography is limited, because cancer can have photon absorption similar to that of normal breast tissue, especially in younger women who have radiographically dense breasts. Despite these limitations, mammography is viewed as the best tool currently available for screening and early diagnosis.

Ultrasound has become an important imaging modality in evaluating the breast [11]. Ultrasound is often used in addition to mammography, and provides differentiation between cystic lesions and solid tumors. In younger patients who have dense breasts, ultrasound can be superior in the detection of breast cancer in comparison with mammography. Breast cancer typically shows irregularly shaped hypoechoic masses, posterior acoustical shadowing, and ill-defined demarcation against the surrounding tissue. Doppler ultrasound may help distinguish benign from malignant breast disease; however, the diagnostic accuracy is often not sufficient enough to accurately characterize abnormal tissue, and to specifically exclude malignancy [12]. Another common application of ultrasound is to provide guidance for interventional procedures [12,13]. Less common uses include assisting in staging of breast cancer and evaluating patients who have implants. Recently, there has been an interest in using ultrasound to screen asymptomatic women for breast cancer, as is done with mammography. Further studies must be performed to assess if this reduces mortality from breast cancer. Although primarily used to image the female breast, ultrasound also can be used to evaluate breast-related concerns in men. Uses of contrast-enhanced ultrasound are still experimental and would add an invasive component to an otherwise noninvasive study.

MRI has become a valuable tool in breast disease, especially in cases that are difficult to diagnose. Recent progress in both spatial and temporal resolutions, the imaging sequences used, pharmacokinetic modeling of contrast uptake, and the use of dedicated breast coils has contributed to the advancement of this imaging technique. More recently, phased-array breast coils, pulse sequences engineered to saturate signal from fat-containing tissue (FATSAT), and gadolinium-based contrast agents have done so as well [14]. MRI has several distinct advantages for breast imaging. These include three-dimensional visualization of breast tissue, information about tissue vascularity, and chest wall visualization. Moreover, MRI allows evaluation of dense breast parenchyma that often limits the detection of breast cancer in mammography. The use of paramagnetic contrast agents has been found to be essential in characterizing breast masses. Signal enhancement following injection of intravenous (IV) contrast is a highly sensitive criterion to detect breast cancer, and sensitivity is more than 90% in most studies. Unfortunately, the high sensitivity of MRI for invasive breast carcinomas is coupled with a correspondingly low specificity [14,15]. To improve upon the disappointingly low positive predictive value of enhancing lesions on MRI, high-speed dynamic imaging of the breast must be performed in make use of the differential washout rates of contrast agent gadolinium (III)-diethyltriaminepentaacetic acid (Gd-DTPA) in benign and malignant breast lesions. Even with dynamic imaging, MRI has not proven to be a robust technique for discriminating benign from malignant tumors in the community setting. MRI of the breast offers higher sensitivity for the detection of multifocal or multicentric cancer, which is important in selecting patients appropriate for breast-conserving surgery. It is also a valuable tool for the screening of patients who have a high risk of breast cancer, or in whom there is axillary disease or nipple discharge and conventional imaging has not revealed the primary focus. Lesions detected on MRI are frequently visible on mammography or ultrasound in retrospect, if not prospectively, allowing for subsequent biopsy. Techniques are also now available to biopsy lesions only apparent on MRI of the breast. MRI can differentiate scar tissue from tumor, and is specifically useful in patients suspected for local recurrent disease. Studies suggest that MRI can identify responders and nonresponders to neoadjuvant chemotherapy with more accuracy [16]. It is the modality of choice for the assessment of breast implants for rupture, with accuracy higher than radiograph mammography and ultrasound. The most important limitations of MRI beside the low specificity are patient compliance, scan time, and cost.

Positron emission tomography imaging of breast cancer

Positron emission tomography (PET) is a noninvasive imaging technique that measures the concentration of positron-emitting radiopharmaceuticals within the body. Depending upon the radiolabeled tracer used, PET can be used to determine various physiological and biochemical processes in vivo. PET is highly sensitive, with the capacity to detect picomolar concentrations of radiotracer, and provides superior image resolution compared with conventional nuclear medicine imaging with gamma

cameras. Currently, PET imaging can target several biological features of cancer, including glucose metabolism, cell proliferation, perfusion, and hypoxia. Approximately 95% of clinical PET examinations are performed in patients who have known or suspected cancer, and virtually all of these are performed with a single radiotracer, the radiolabeled glucose analog, [F-18] 2-deoxy-2-fluoro-D-glucose (FDG). Following malignant transformation, various tumors are characterized by elevated glucose consumption and subsequent increased uptake and accumulation of FDG. PET imaging using FDG provides more sensitive and more specific information about the extent of disease than morphological/anatomical imaging alone. FDG-PET has become a standard imaging procedure for staging and restaging of many types of cancer [17]. In the United States, PET scans performed on patients who have head and neck cancer, follicular thyroid cancer, solitary pulmonary nodules, lung cancer, breast cancer, esophageal cancer, colorectal cancer, lymphoma, melanoma, and cervical cancer are generally considered reimbursable by third-party payers. The metabolic activity of neoplastic tissue assessed by PET offers additional information about cancer biology, and can be used for the differentiation between benign and malignant lesions, identification of early disease and staging of metastases, assessment of therapeutic effectiveness, and to determine tumor aggressiveness. The uptake mechanism and biochemical pathway of the glucose analog FDG has been extensively studied both in vitro and in vivo. The transport of the radiotracer through the cell membrane via glucose transport proteins, particularly glucose transporter type 1 (GLUT-1), and subsequent intracellular phosphorylation by hexokinase (HK) have been identified as key steps for subsequent tissue accumulation [18]. Because FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase, and the enzyme level of glucose-6-phosphatase is generally low in tumors, FDG-6-phosphate accumulates in cells and is visualized by PET.

Positron emission tomography imaging procedure and image analysis in the breast

To ensure a standardized metabolic state, including low plasma glucose levels, oncology patients must fast for at least 4 to 6 hours before administration of FDG. Blood glucose level before tracer injection should ideally not exceed 150 mg/100 ml. Intravenous administration of about 300 to 400 MBq (~10 mCi) F-18 FDG is used in most studies; however, Adler and colleagues [19,20] reported on a higher breast cancer detection rate using up to 750 MBq (~20 mCi) F-18 FDG. To avoid artificial tracer retention in the axilla region, the tracer should be injected into an arm vein contralateral to the suspected tumor. Most of the studies reported in literature are done in two-dimensional mode data acquisition, and the influence of three-dimensional mode on the results of breast imaging still needs to be studied. Imaging in prone position with both arms at the side and the breast hanging free is recommended to avoid compression and deformation of the breast. Data acquisition should be started approximately 60 minutes after tracer injection. Boerner and colleagues [21] showed increasing target-to-background ratios over time, suggesting a benefit to longer waiting periods between tracer injection and data acquisition. Lower image quality, due to radionuclide decay, has to be taken into account, however. Attenuation correction is recommended for optimal tumor localization as well as subsequent quantification of regional tracer uptake. The use of iterative reconstruction algorithms results in better image quality; an increase in diagnostic accuracy has not yet been reported. Visual image interpretation should include analysis of transaxial, coronal, and sagittal views. Breast cancer is typically present with focally increased FDG uptake, whereas benign tumors are negative in PET imaging. Proliferative mammary dysplasia may result in moderate but diffuse increased tracer uptake.

Attenuation-corrected PET images provide quantitative information about the tracer concentration in tissue. Various approaches of different complexity can be applied for quantitative PET analysis. Standardized uptake values (SUV) are frequently being calculated, providing a semiquantitative measure of FDG accumulation in tissue by normalizing the tissue radioactivity concentration measured with PET to injected dose and patient's body weight. Quantitative methods may be used to complement visual image analysis for differentiation between benign and malignant breast tumors; that is, by using an SUV-normalized scale for image display [22]. In particular, SUV correction for partial volume effects and normalization to blood glucose has been shown to yield the highest diagnostic accuracy for breast imaging. Corresponding threshold values for optimal tumor characterization have been published for various quantification methods [22]. Dynamic data acquisition allows calculation of the tracer influx constant, although this procedure is more complex and did not increase diagnostic accuracy.

Whole-body imaging can be improved by intravenous injection of furosemide (20–40 mg) to reduce tracer retention in the urinary system and butylscopolamine (20–40 mg) to reduce FDG uptake in the bowel [23]. Image evaluation requires an appreciation of the normal physiologic FDG

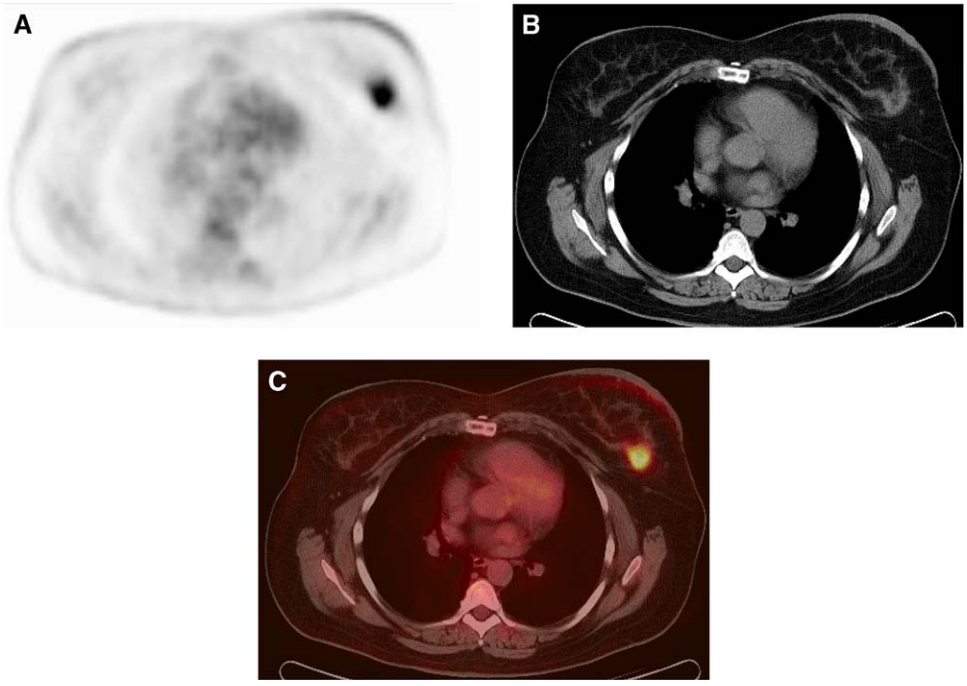

Fig. 1. Transaxial FDG-PET image (*A*), CT image (*B*), and fused PET/CT image (*C*), demonstrating a focal area of intense FDG uptake in the left breast.

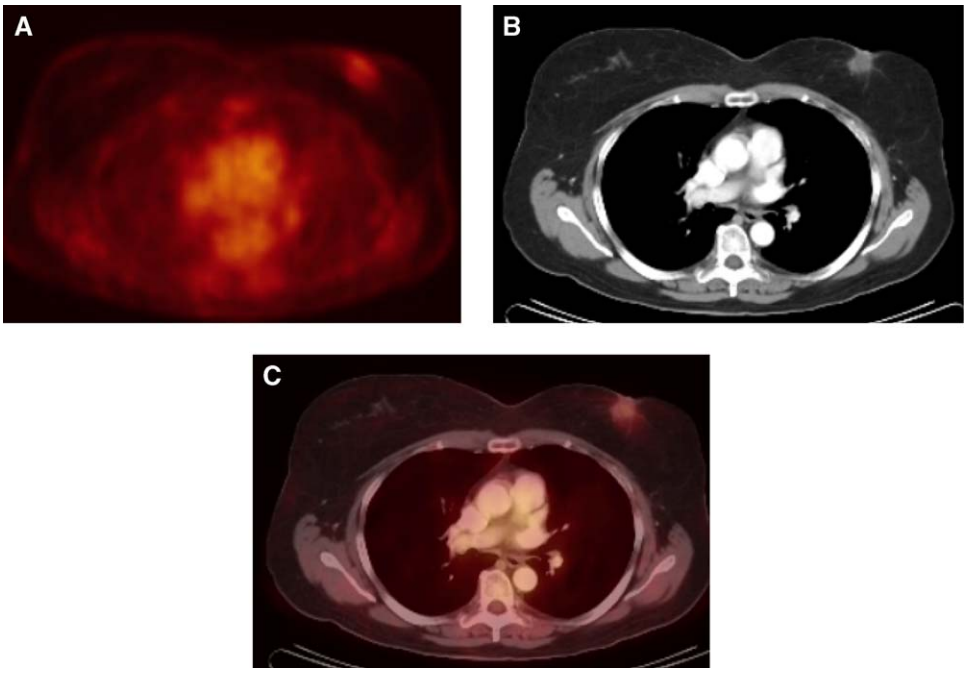

Fig. 2. Moderate FDG uptake in a local recurrence in the left breast. Transaxial FDG-PET (*A*), CT (*B*), and fused PET/CT (*C*).

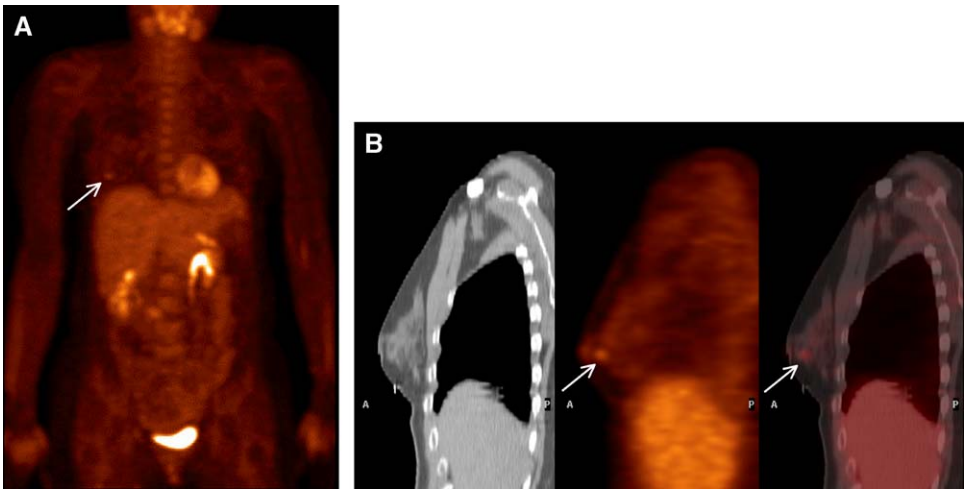

Fig. 3. Frontal maximum-intensity projection PET image (*A*) and sagittal slices from a PET/CT scan (*B*) show a mammographically occult 8-mm breast cancer detected incidentally by FDG-PET during a workup for presumed recurrent breast cancer in a patient with rising carcinoembryonic antigen. An ultrasound guided biopsy demonstrated an invasive ductal carcinoma, which was resected with clear margins.

uptake distribution and of variation between individuals, as well as consideration of artifacts and benign conditions that can mimic malignancy. Increased FDG uptake is found within the brain cortex, the myocardium, and the urinary tract. Low-to-moderate uptake is seen in the base of the tongue, salivary glands, thyroid, liver, spleen, gastrointestinal tract, bone marrow, musculature, and reproductive organs. Of particular importance is the inconsistent amount of normal uptake in glandular breast tissue. The most common normal cause of misinterpretation is related to muscle activity. Muscle tension may lead to increased FDG uptake, and physical activity immediately before or after tracer injection can lead to spurious muscle activity. In some patients, supraclavicular uptake has been shown to represent brown fat. Inflammatory and infectious processes also demonstrate increased FDG uptake, as well as some benign diseases, such as Paget's disease, Graves' disease, granulomatous disorders, healing fractures, and postradiation changes.

Positron emission tomography imaging of the breast

The first FDG imaging in breast cancer patients, using a collimated gamma camera, was reported in 1989 by Minn and Soini [24]. Shortly afterwards, Kubota and coworkers [25] reported on PET imaging with FDG in one case with local recurrence. In a first series of 10 patients who had locally advanced breast cancer, Wahl and colleagues [26] successfully identified all breast carcinomas. Subsequent studies including a limited number of patients, predominantly having advanced stages of disease, suggested a high accuracy of FDG-PET for the detection of primary breast carcinomas [**Figs. 1–7**] [19,24–26]. The largest patient group reported to date includes 144 patients who had 185 histologically confirmed breast tumors [27].

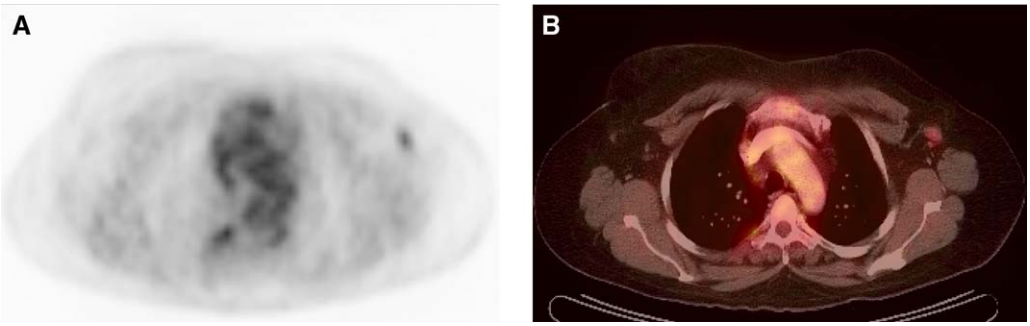

Fig. 4. Transaxial FDG-PET (*A*), and fused PET/CT image (*B*) with a small area of increased FDG uptake in a axillary lymph node metastasis.

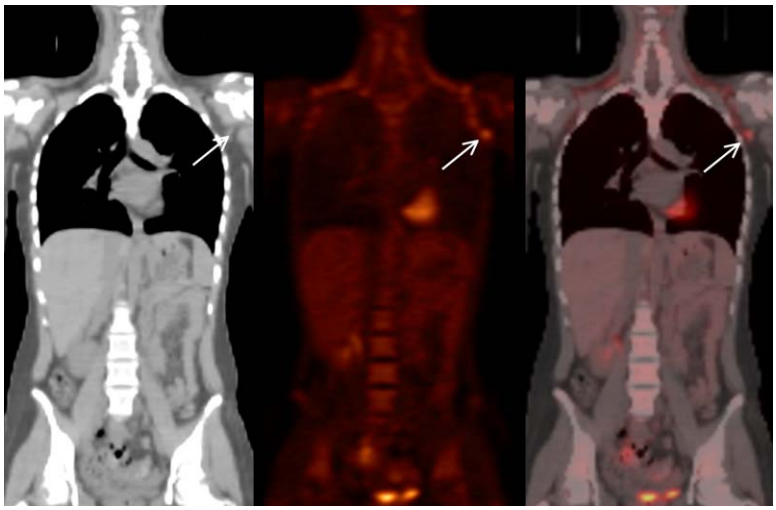

Fig. 5. Coronal PET/CT images demonstrate a false-positive axillary lymph node finding in a patient 2 weeks following a flu shot (*arrows*). There is also extensive, mild FDG uptake corresponding to metabolically active fat in the supraclavicular soft tissues.

PET detected breast cancer with an overall sensitivity of 64.4% by conservative image reading (regarding only definite FDG uptake as positive), and 80.3% by sensitive image reading (regarding equivocal as well as definite FDG uptake as positive). When applying sensitive image reading, however, specificity decreased from 94.3% to 75.5% [27,28].

Schirrmeister and coworkers [29] found similar results in 117 patients, with a sensitivity of 93% and specificity of 75%. The use of non-attenuation–corrected PET imaging combined with sensitive imaging reading may have contributed to the higher sensitivity and lower specificity in this study. A recent study compared MR imaging of the breast with FDG-PET [30] found a comparable diagnostic accuracy (88% versus 84%) for both methods in 32 patients. The sensitivity of FDG-PET was 79%, whereas MRI detected all primary breast carcinomas; however, the specificity of FDG-PET was higher (94% versus 72%). Baslaim and coworkers [31] evaluated the usefulness of FDG-PET for diagnosing and staging of inflammatory breast cancer. All 7 patients studied presented with diffuse breast enlargement, redness, and peau d'orange. PET showed diffuse FDG uptake in the involved breast, with intense uptake in the primary tumor as well as increased FDG uptake in the skin.

The ability of PET to detect breast cancer greatly depends on tumor size. Regarding small tumors, only 30 (68.2%) out of 44 breast carcinomas at

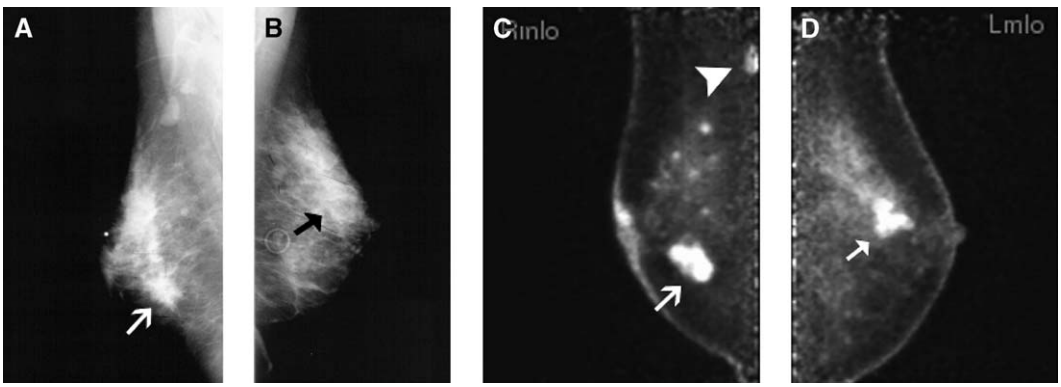

Fig. 6. Mediolateral radiograph mammograms of both breasts showed heterogeneously dense breast parenchyma with bilateral masses (*arrows*). Ultrasound-guided right breast biopsy showed invasive ductal carcinoma (*A, arrow*), whereas left breast ultrasound-guided biopsy showed papilloma (*B, arrow*). PEM of right breast showed dominant known invasive cancer (*C, arrow*) and smaller foci in upper breast, proving multicentric cancer with positive lymph node (*arrowhead*), and increased focal activity on left side (*D, arrow*) that was confirmed as DCIS at surgery.

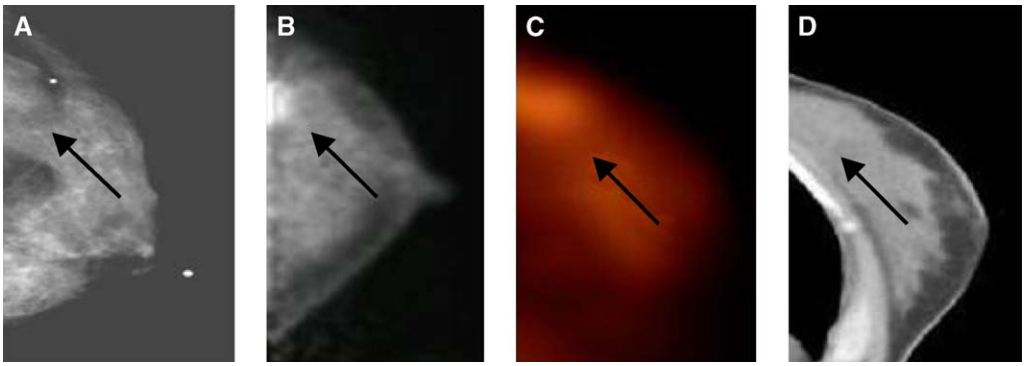

Fig. 7. (*A–D*) Mammogram, FDG-PEM, whole body PET, and CT in a patient with DCIS.

stage pT1 (<2 cm) were correctly identified, compared with 57 (91.9%) out of 62 at stage pT2 (>2–5 cm) [27]. Sensitivity for tumors less than 1 cm (pT1a and b) was only 25%, compared with 84.4% for tumors between 1 and 2 cm in diameter (pT1c). Table 1 provides more detailed information.

Invasive lobular carcinomas were more often false-negative (65.2%) than invasive ductal carcinomas (23.7%). These results are consistent with a previous report from Crippa and colleagues [32], who found higher glucose metabolism for invasive ductal carcinomas (median SUV of 5.6) versus invasive lobular carcinomas (median SUV of 3.8). This is of particular importance in the clinical application of PET, because lobular carcinomas are more difficult to diagnose by imaging procedures such as mammography, sonography, and MRI [33–35]. The identification of multifocal or multicentric breast cancer plays an important role in the decision of therapy, because it limits breast-conserving surgery. Only 9 (50%) out of 18 patients who had multifocal or multicentric breast cancer were identified by PET [27]. Nevertheless, Schirrmeister and colleagues [29] found that PET was twice as sensitive in detecting multifocal lesions (sensitivity 63%, specificity 95%) than the combination of mammography and ultrasound (sensitivity 32%, specificity 93%).

Table 1: **Sensitivity of FDG-PET and the size of breast cancer**

TNM	Size	n	Sensitivity
pTis		12	42%
pT1	<2.0 cm	44	68%
pT1a	<0.5 cm	4	25%
pT1b	>0.5–1.0 cm	8	25%
pT1c	>1.0–2.0 cm	32	84%
pT2	>2.0–5.0 cm	62	92%
	>2.0–3.0 cm	33	94%
	>3.0–4.0 cm	15	87%
	>4.0–5.0 cm	14	93%
pT3	>5.0 cm	14	100%

Data from Avril N, Rose CA, Schelling M, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. J Clin Oncol 2000;18(20):3495–502.

The diagnosis of in-situ carcinomas has increased over the past decade, mainly due to increased use of and technological improvements in mammography. There is little information available about the ability of PET imaging to detect noninvasive breast cancer. Tse and coworkers [36] studied 14 patients and found that one out of two false-negative cases had predominantly intraductal cancer with microscopic invasive foci. In 12 patients, (10 DCIS and 2 LCIS) none out of six in-situ carcinomas smaller than 2 cm could be identified [27]. For larger in-situ carcinomas, three (50%) out of six displayed increased FDG uptake. Although the number of patients studied was small, these data suggest that PET imaging cannot contribute to an improved diagnosis of noninvasive breast cancer.

Vranjesevic and colleagues [37] evaluated the influence of the breast tissue density on FDG uptake of normal breast tissue, and found significantly lower SUVs for primarily fatty breasts than for dense breasts. Benign conditions of the breast are more common, and are often difficult to differentiate from breast cancer in conventional imaging modalities. In general, benign breast masses display low FDG uptake. Only 3 out of 53 benign breast masses presented with focally increased tracer uptake, including one rare case of a ductal adenoma, one case with dysplastic tissue, and one fibroadenoma [27]. Fibroadenomas are common benign tumors, and only 1 out of 9 displayed increased tracer uptake. Moreover, dysplastic tissue often accounts for false-positive results in MRI, predominantly showing a diffuse pattern of little or moderate FDG uptake.

Biological features of breast cancer

FDG uptake in breast cancer shows considerable variation. To address that issue, the degree of tracer accumulation was recently correlated with various tumor characteristics [Table 2] [38]. Histologic sections of breast cancer specimens were analyzed for histologic type, microscopic tumor growth pattern, percentage of tumor cells, presence of inflammatory cells, density of blood vessels, histopathologic grading, tumor cell proliferation (mitotic rate and antibody binding of MIB-1), expression of estrogen and progesterone receptors, and expression of the glucose transporter protein Glut-1. Invasive ductal carcinomas displayed significantly higher FDG uptake compared with invasive lobular carcinomas. The SUVs for clearly defined lesions were higher compared with tumors with diffuse growth patterns. Lower densities of blood vessels corresponded to higher FDG uptakes. In addition, there was a positive correlation between FDG uptake and tumor cell proliferation, but only a weak relationship between FDG uptake and the percentage of tumor cells. There was no relationship between FDG uptake and tumor size; axillary lymph node status; percentage of necrotic, fibrotic and cystic compounds; presence of inflammatory cells; steroid receptor status; and expression of Glut-1.

Histologic and immunohistochemical tissue analysis could not fully explain the variation of FDG uptake in breast cancer. The study authors concluded that the degree of metabolic changes in malignant tumors is mainly caused by complex interactions between the cellular energy metabolism and the microenvironment of the tumor. Hence FDG-PET uptake can not be used to predict the biologic behaviors of breast cancer, such as differentiation, histopathologic grading, cell proliferation, or axillary lymph node status.

Table 2: **FDG-uptake versus histology/ immunohistochemistry**

SUV vs.	p	n
Histology (ductal versus lobular)	0.003	50
Tumor growth (nodular versus diffuse)	0.007	49
Grading	0.69	50
% tumor cells	0.06	50
Inflammatory cells	0.74	50
Capillaries	0.08	50
Proliferation (MIB-1)	0.009	40
Estrogen receptor status	0.47	42
Progesterone receptor status	0.29	42
Glut-1 transporter protein	0.21	45

Data from Avril N, Menzel M, Dose J, et al. Glucose metabolism of breast cancer assessed by 18F-FDG PET: histologic and immunohistochemical tissue analysis. J Nucl Med 2001;42(1):9–16.

Loco-regional staging

The axillary lymph node status is still considered the single most important prognostic indicator in patients who have breast cancer. Clinical examination is generally unreliable for staging the axilla [39]. Lack of conventional imaging techniques to determine the axillary lymph node involvement with acceptable accuracy has been the main reason for axillary lymph node dissection; however, up to 70% of patients who have stage T1 and T2 tumors have negative axillary lymph nodes [40]. The extent, morbidity, and cost of the staging procedure of axillary lymph node dissection are often greater than those of the surgical treatment of the primary tumor. In anatomical based imaging modalities, such as computed tomography, ultrasound, and MRI, the size of a particular lymph node is of crucial importance to determine the tumor involvement. Generally, lymph node enlargement over 1 cm in diameter is the decisive criterion. In contrast, metabolic imaging with FDG-PET is suggested to provide more specific information, based on detecting increased glucose consumption of cancer tissue. In 1991, Wahl and coworkers [26] studied 12 patients who had locally advanced breast cancer, and found increased FDG uptake in axillary metastases. In 50 patients, Adler and colleagues [20] reported a sensitivity of 95%, a negative predictive value of 95%, and an overall accuracy of 77% for axillary PET imaging. Greco and coworkers [41] studied 167 consecutive breast cancer patients, and axillary involvement was detected in 68 of 72 patients, resulting in a sensitivity of 94.4% and a specificity of 86.3%; overall accuracy of lymph node staging with PET was 89.8%. There is some controversy about the sensitivity of axillary PET imaging, however [42]. It is a well-known phenomenon that the true FDG uptake is underestimated in small cancer deposits because of the limited spatial resolution of current PET devices, (approximately 6–8 mm). Therefore it cannot be expected that PET will provide visualization of micrometastases. Avril and colleagues [43] studied 51 patients and found overall sensitivity and specificity for detection of axillary lymph node metastases to be 79% and 96%, respectively. In patients who had primary breast tumors larger than 2 cm (>stage pT1), the sensitivity increased to 94%, with a corresponding specificity of 100%. PET could not identify lymph node metastases in 4 out of 6 patients who had small primary breast cancer (stage pT1), however, which led to a sensitivity of only 33% in this group. Although the number of

patients studied is small, this study clearly points out that the current achievable spatial resolution of PET imaging limits the detection of micrometastases and small tumor-infiltrated lymph nodes. This conclusion is also supported by others; for example, by Schirrmeister and coworkers [29], who studied 117 breast cancer patients and found similar results (sensitivity 79%, specificity 92%). In a prospective multicenter study representing the largest patient cohort so far [44], 360 women who had newly diagnosed invasive breast cancer underwent PET imaging. Three experienced readers blindly interpreted PET images, and the results from 308 axillae were compared with histopathology. If at least one probably or definitely abnormal axillary focus was considered positive, the sensitivity for PET was 61% and the specificity was 80%. Patients who had false-negative PET had significantly smaller and fewer tumor-positive lymph nodes than true-positive cases. Semiquantitative analysis of axillary FDG uptake showed that a nodal standardized uptake value (lean body mass) of more than 1.8 had a positive predictive value of 90% but a sensitivity of only 32%. Finding two or more intense foci of tracer uptake in the axilla was highly predictive of axillary metastasis, but had a sensitivity of only 27%.

Sentinel node biopsy has become accepted as a reliable method of predicting the status of the axilla in early stages of breast cancer [40]. There are few studies available directly comparing the diagnostic accuracy of PET with sentinel node biopsy in breast cancer patients. In one study [45], 5 out of 15 patients had sentinel lymph node metastases, but PET identified only 1 of these patients. The size of missed metastases ranged from a small micrometastasis identified only by immunohistochemistry to an 11-mm, tumor-involved lymph node. Another study [46] included 24 clinically node-negative breast cancer patients who had primary tumors smaller than 3 cm, and axillary staging by PET was accurate in 15 of 24 patients (62.5%). PET was false-negative in 8 of 10 node-positive patients, and false-positive in 1 patient. The sensitivity and specificity of FDG-PET were 20% and 93%, respectively. The mean diameter of false-negative axillary lymph node metastases was 7.5 mm, and ranged from 1 to 15 mm. In 32 breast cancer patients who had clinically negative axillary nodes, sentinel lymph node biopsy was false-negative in 1 patient, whereas PET missed lymph node metastases in 11 patients, resulting in a sensitivity of 20% [47]. These studies clearly indicate the limitation of FDG-PET for axillary staging of small primary tumors. FDG-PET is not accurate enough in clinically node-negative breast cancer patients qualifying for sentinel lymph node dissection. On the other hand, among patients who have larger tumors, sentinel biopsy can be avoided in those who have positive FDG-PET, in whom complete axillary lymph node dissection should be the primary procedure. FDG-PET cannot replace the axillary dissection, not only because of the limited sensitivity, but also because the number of involved lymph nodes and extranodal extension cannot be determined. In patients who have locally advanced disease and who are undergoing primary chemotherapy, however, FDG-PET seems to be a reliable method to determine the extent of disease.

Recently, the intrathoracic lymph node status has been retrospectively analyzed comparing CT and PET [48]. In 73 consecutive patients who had recurrent or metastatic disease, PET was able to correctly identify 40% of the patients who had intrathoracic lymph node metastases, resulting in a sensitivity of 85% and a specificity of 90%. Only 23% of the patients had suspiciously enlarged lymph nodes in CT, leading to a sensitivity of 54% and a specificity of 85%. PET and CT were both positive in 22% of the cases. Therefore overall diagnostic accuracy of PET was higher (88%) than that of CT (73%). Despite the limitation in detection of small tumor deposits, FDG-PET is currently the most sensitive imaging modality to detect lymph node metastases, including parasternal and mediastinal nodes.

Positron emission mammography

Because of the limited resolution of conventional PET scanners (4.8 to 7.1 mm in plane resolution), the even more limited resolution achieved with current clinical protocols (1 cm or greater), and the loss of contrast due to scatter, conventional PET scanners are unlikely to detect the small carcinomas that are detectable with other imaging modalities such as mammography and MRI. Dedicated breast PET—positron emission mammography (PEM)—was developed to improve both resolution and contrast of breast lesions and thereby improve small lesion detectability, while reducing the cost of imaging [49]. By optimizing scanner geometry for breast imaging, a dedicated breast PET scanner can achieve much higher resolution than a whole body scanner, while maintaining higher count sensitivity and a marked reduction in scatter [50,51]. Radiographic mammography uses compression to reduce the mean radiographic travel path, thereby reducing scatter. In an analogous manner, incorporating compression into PET imaging reduces the mean travel path of gamma emissions, with a resulting reduction in scatter. Because scatter represents such a low proportion of incident photons, septa or collimation is unnecessary, and a three-dimensional acquisition with full three-

dimensional reconstruction is performed. An added benefit of compression is that images can be produced with a correspondence to radiograph mammograms, so PEM can be used to interrogate the functional status of abnormalities detected by mammography. Final output resolution of commercially available equipment is approximately 1.5 mm in plane. Resolution orthogonal to the imaging planes is dependant on the distance between the flat plate detectors (ie, the compressed thickness of the breast) and is generally not as good as in-plane resolution [52]. The dramatic improvement in resolution achieved results in the ability to detect smaller objects than would be detectable using a whole-body scanner (assuming identical object-to-background activity ratios) or to detect small objects with lower object-to-background activity ratios than would be detectable with whole body PET [19].

A recent multicenter study [52,53] demonstrated that high-resolution FDG-PEM detects in-situ components of cancers better than any other modality. This fact has been documented in retrospective surgical studies [52] as well as prospective imaging studies [53]. In the last-cited study, 93 consecutive subjects who had biopsy-proven breast cancer or suspicious breast lesions were recruited from four sites [53]. Only evaluable cases (eg, with proof of pathology) were shown to a blinded panel of imaging specialists for review. Patients who had Type I or poorly controlled Type II diabetes were excluded from participating in the study. Other diabetic patients were included, with the prospective decision that diagnostic performance of the PEM scans would be subsequently analyzed to determine whether diagnostic accuracy would differ in certain subsets of patients (eg, those who had diabetes or other medical conditions). Among index cancers in the 77 evaluable subjects reviewed, 39 (93%) out of 42 were PEM-positive. Including incidental lesions, 43 (90%) out of 48 malignancies were PEM-positive, including 10 (91%) out of 11 lesions of DCIS and 33 (89%) out of 37 invasive carcinomas. Three index malignancies (a 3-mm Grade II/III infiltrating and intraductal carcinoma, a 6-mm Grade I/III tubular carcinoma, and a 10-mm Grade I/III invasive ductal carcinoma with a positive axillary lymph node) were occult on FDG-PEM, but were visible mammographically. One contralateral 25-mm invasive lobular carcinoma was visible mammographically, but was only recognized by one of three PEM readers. Three DCIS foci (Grade II/III) were visible on FDG-PEM, but were mammographically occult. The combination of mammography, ultrasound, and FDG-PEM depicted 47 (98%) out of 48 cancers, with one case of contralateral Paget's disease caused by Grade II DCIS missed on all imaging modalities. FDG-PEM improved sensitivity when added to mammography, ultrasound, and clinical examination, without reducing accuracy.

One of three lesions with atypical ductal hyperplasia showed intense FDG uptake. Five (12%) of 41 other proven benign lesions showed intense FDG uptake, including two fibroadenomas, two fibrocystic changes, and one fat necrosis in a participant who had transverse rectus abdominis muscle (TRAM) flap reconstruction. The first two readers agreed on overall PEM assessment (ie, recommendation for biopsy or not) for 83% of the index lesions and 80% of the incidental lesions. Examining individual reader performance, at least one reader missed a malignancy in 8 index lesions and 3 incidental lesions. Examining all readings of index lesions, the average area under the receiver operating characteristic (ROC) curve was 0.91. Qualitatively high and asymmetric FDG uptake, as compared with radiograph mammograms, was the finding most predictive of malignancy. Although promising, additional prospective studies are needed to determine the clinical role of FDG-PEM imaging in the future.

Current clinical status of F-18 fluorodeoxyglucose-positron emission tomography in primary breast cancer

Breast cancer often displays only moderately increased FDG uptake, and considering the limited spatial resolution of FDG-PET, metabolic imaging results in a low sensitivity to detect small breast carcinomas, micrometastases, and small-tumor–infiltrated lymph nodes. The restricted sensitivity of FDG-PET does not allow the screening of asymptomatic women for breast cancer. Moreover, negative PET results in patients who have suspicious breast masses or abnormal mammography do not exclude breast cancer. Therefore, PET imaging may not be used as a routine application for evaluation of primary breast tumors, and currently cannot significantly reduce unnecessary invasive procedures in patients suspected of having breast cancer. Advances in technology such as the development of dedicated breast imaging devices (eg, PEM) may improve the detection of primary tumors with PET in the future. In patients who have locally advanced breast cancer, PET accurately determines the extent of disease, particularly the loco-regional lymph node status. In smaller tumors, the sentinel node biopsy has become the standard of care in many institutions.

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ELSEVIER SAUNDERS

POSITRON EMISSION TOMOGRAPHY

PET Clin 1 (2006) 15–24

Diagnosis of Recurrent and Metastatic Disease Using F-18 Fluorodeoxyglucose-Positron Emission Tomography

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Breast cancer is the most common non-skin cancer, and the second leading cause of cancer death in women [1]. 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]. Because optimal treatment of patients who have recurrent breast cancer depends on knowing the true extent of disease, accurate staging of these patients is an important public health problem. This is a useful application of FDG-PET when it is performed to complement conventional imaging (CI) such as CT, MRI, and bone scintigraphy. The additional metabolic information provided by FDG-PET increases the accuracy of detecting recurrent or metastatic lesions [2–12]. This is particularly true in the evaluation of anatomic regions that have been previously treated by surgery or radiation [13], in which the discrimination between post-treatment scar and recurrent tumor can be problematic. FDG-PET can also significantly impact the choice of treatment, especially in patients who have more advanced or recurrent disease [14,15].

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 [16]. For most clinical trial studies, local failure is defined as any recurrence of tumor in the ipsilateral chest wall or mastectomy scar; regional failure is defined as any recurrence of tumor in the ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes; and recurrence of tumor in any other site is considered as distant failure [17]. In general, systemic therapy is used at almost all disease stages; however, isolated loco-regional disease or single sites of metastatic recurrence are also treated with surgery and radiation therapy [18,19]. It is hoped that the potential of FDG-PET to provide more accurate and earlier detection of breast cancer recurrences will translate into more effective treatment strate-

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gies and better health outcomes for these patients in the future.

Loco-regional recurrence

Recurrence in the breast, skin of the breast, axillary nodes, chest wall, and supraclavicular nodes are the most common sites of first loco-regional recurrence after primary surgical resection [20,21]. The shift toward breast-conserving surgery and local radiation therapy for early breast cancer in recent years has heightened concern over loco-regional recurrence [22]. The incidence of loco-regional recurrence after breast conservation treatment ranges from 5% to 22% [23]. Independent risk factors associated with loco-regional recurrence in this group of patients include positive margins at surgical resection, tumors with extensive intraductal component, high grade ductal carcinoma in situ (DCIS), patient age under 40 years, and absence of radiation after breast conservation therapy [23,24].

Among patients treated with mastectomy, axillary node dissection, and adjuvant chemotherapy, the most common sites of loco-regional recurrence are the chest wall (68% of loco-regional recurrences) and supraclavicular nodes (41% of loco-regional recurrences) [**Fig. 1**] [25]. Recurrent disease at both of these sites is associated with poor prognosis in terms of survival after recurrence [26–28]. Factors that predict an increased risk of chest wall or supraclavicular node recurrence include four or more positive axillary nodes, tumor size 4 cm or larger, and extranodal extension of 2 mm or more [25]. Supraclavicular node recurrence is technically considered Stage IV disease, and is generally considered a harbinger to more widely disseminated disease; however, patients who have supraclavicular node involvement as the sole site of disseminated disease may benefit from aggressive local radiotherapy.

One clinical situation where FDG-PET has been shown to be helpful is in the evaluation of previously treated patients who have symptoms of brachial plexopathy. This debilitating condition can be secondary to tumor recurrence in the axilla or chest wall, or caused by scarring of tissue neighboring the brachial plexus from previous surgery or radiation. Because the signs and symptoms of loco-regional recurrence often overlap with the side effects of treatment [29,30] and patients who have tumor recurrence may benefit from surgical resection [31,32], it is important to distinguish one from the other. Hathaway and colleagues [33] showed the value of combining the functional information of FDG-PET and the anatomic information from dedicated MRI to decide whether patients would benefit from further surgery. Other studies [34] have confirmed these early findings.

Intrathoracic lymphatic recurrences

Lymphatic drainage to the internal mammary nodal chain is an important pathway of spread of disease, both at the time of initial diagnosis and

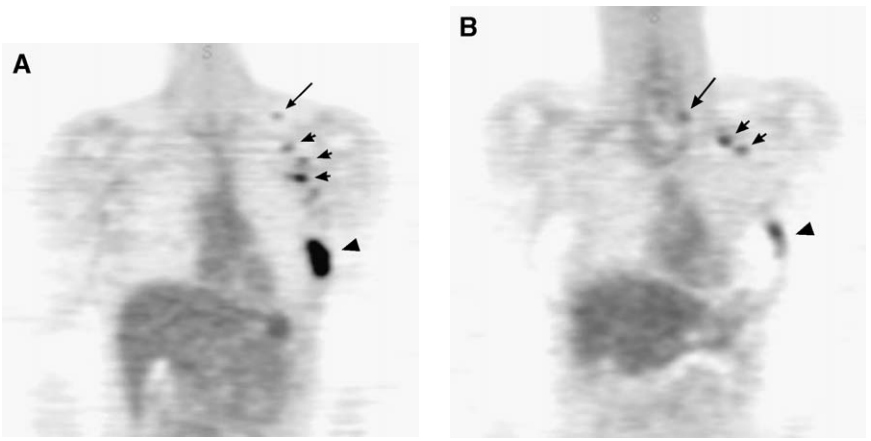

Fig. 1. A 49-year-old woman who underwent bilateral mastectomies and reconstruction with implants 7 years before recurrence of disease. She originally had extensive lobular carcinoma in situ with two small (2–3 mm) foci of invasive lobular carcinoma in the right breast. Sentinel node and limited low axillary lymph node dissection revealed no pathologically involved nodes, and surgical margins were negative. She received no adjuvant treatment, but opted for prophylactic left mastectomy. At time of recurrence, she presented with palpable left chest wall mass (biopsy-proven invasive ductal carcinoma) and axillary nodes. Coronal FDG-PET image (*A*) shows recurrent chest wall mass (*arrowhead*; standardized uptake value [SUV] = 8.2) lateral to breast implant, uptake in several axillary nodes (*small arrows*; maximum SUV = 4.5), and left supraclavicular node (*long arrow*; SUV = 2.1). At more anterior level, coronal FDG-PET image (*B*) shows uptake in a left internal mammary node (*long arrow*; SUV = 2.0) in addition to uptake in left axillary nodes (*short arrows*) and the left breast (*arrowhead*).

after primary treatment of breast cancer. Data from sentinel node lymphoscintigraphy series in patients who had early breast cancer at the author's institution reveal that overall prevalence of drainage to the internal mammary nodes is 17% [35]. This is a similar prevalence to that shown in early extended radical mastectomy series [36–38], in which metastasis to internal mammary nodes occurred in close to one in five women who had operable (Stage II–-III) breast cancer. Metastasis to internal mammary nodes can occur from tumor located anywhere in the breast; however, in the series of the author and colleagues, internal mammary drainage was significantly less frequent in tumors located in the upper outer quadrant (10%) compared with the other three quadrants and subareolar portion of the breast (17%–29%) [35]. Metastasis to the internal mammary and axillary nodes usually occurs synchronously but infrequently (4%–6% incidence) may be isolated to the internal mammary chain [36,39]. The prognosis of patients who have internal mammary and axillary nodal metastasis is significantly worse compared with patients who have only axillary node disease [40,41], suggesting that internal mammary nodal chain is a conduit for more widespread dissemination of disease.

The importance of internal mammary nodal detection and treatment remains controversial [42]. Unlike axillary nodes, internal mammary nodes are not routinely biopsied as part of an individual patient's staging work-up, and their status is generally unknown. There has been reluctance to biopsy internal mammary nodes because: (1) early radiotherapy trials (before the era of routine adjuvant chemotherapy) failed to demonstrate a clear benefit in survival with internal mammary chain radiation, and (2) there is a relatively high complication risk (pneumothorax and bleeding) associated with internal mammary nodal sampling. A recent large, prospective, randomized, radiotherapy trial [43] has shown a benefit in systemic relapse-free and overall survival from aggressive regional nodal irra-

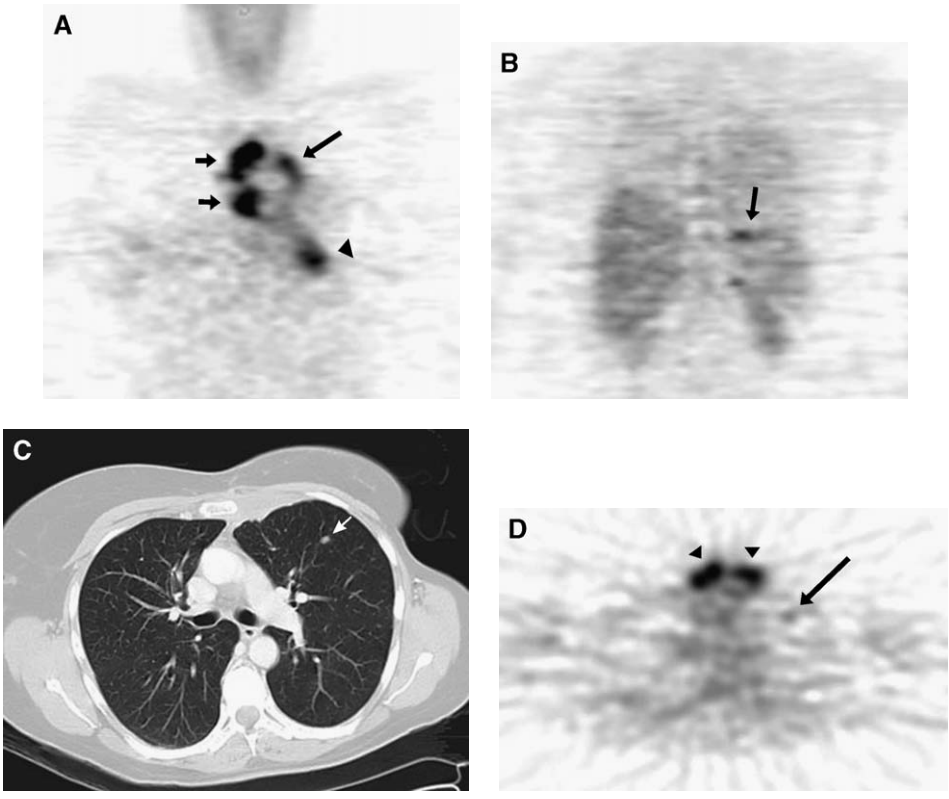

Fig. 2. A 46-year-old woman who presented with sternal pain 5 years after undergoing left mastectomy for invasive ductal carcinoma (T3, N0) followed by chemotherapy and radiation. Anterior coronal FDG-PET image (*A*) shows intense uptake in the left parasternal region (*long arrow*) and sternum (*short arrows*; maximum SUV = 9.4) consistent with disease in the internal mammary node chain with local spread to the sternum. Physiologic uptake in the anterior heart (*arrowhead*) is also present. A posterior coronal FDG-PET image of the chest (*B*) shows linear uptake along the supradiaphragmatic region (*arrow*; SUV = 4.1) consistent with pleural metastasis and axial FDG-PET (*C*) and CT (*D*) of the upper chest show a small lung metastasis (*arrows*; SUV = 2.0) in addition to sternal uptake (*arrowheads*).

diation (including internal mammary field) following lumpectomy or mastectomy, even in patients who had fairly limited spread to the axilla. These data suggest that eradication of residual loco-regional metastasis (including internal mammary nodal disease) has a strong systemic effect.

FDG uptake in the internal mammary nodal chain has been anecdotally reported in some of the studies that have focused on detection of primary tumor or axillary staging [44,45]. In one study of 85 patients who underwent FDG-PET before axillary node dissection [44], 12 (14%) had uptake in the internal mammary region, but there was no histological confirmation of these nodes. The author and colleagues' experience with imaging patients who have locally advanced breast cancer shows that the prevalence of internal mammary FDG uptake can be as high as 25%, and that the presence of internal mammary FDG uptake predicts treatment failure patterns of disease consistent with internal mammary nodal involvement and progression [**Fig. 2**] [46]. A preliminary study by Bernstein and coworkers [47] showed the feasibility of detecting internal mammary nodal metastases in early-stage patients using FDG-PET. FDG-PET may prove to be an ideal method of non-invasively staging this important nodal region, and may aid in the selection of patients who would potentially benefit most from directed internal mammary nodal radiotherapy; however, further work needs to be done to confirm FDG-PET findings with histopathology.

Neoplastic spread to mediastinal nodes is also common in patients who have advanced disease, and the mediastinum is a common site of recurrence in patients who have undergone axillary node dissection and radiation [**Fig. 3**]. As with internal mammary 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 who have non-small–cell lung cancer in which histologic analysis is used as the gold standard [48,49]. In the author and colleagues' retrospective series of 73 patients who had recurrent or metastatic breast cancer and who underwent both FDG-PET and chest CT [50], FDG uptake in mediastinal or internal mammary 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 who had 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 loco-regional recurrence by CI and clinical examination had mediastinal or internal mammary FDG uptake. Risk factors associated with mediastinal or internal mammary FDG uptake in these patients were recurrent chest wall invasion and three or more positive axillary nodes.

Distant metastases

The skeleton is the most common site of distant metastasis in breast cancer; nearly 70% of patients who have advanced disease have bone metastasis [51]. Bone scintigraphy is considered the most sensitive method of detecting and determining the extent of skeletal metastases; however, purely osteo-

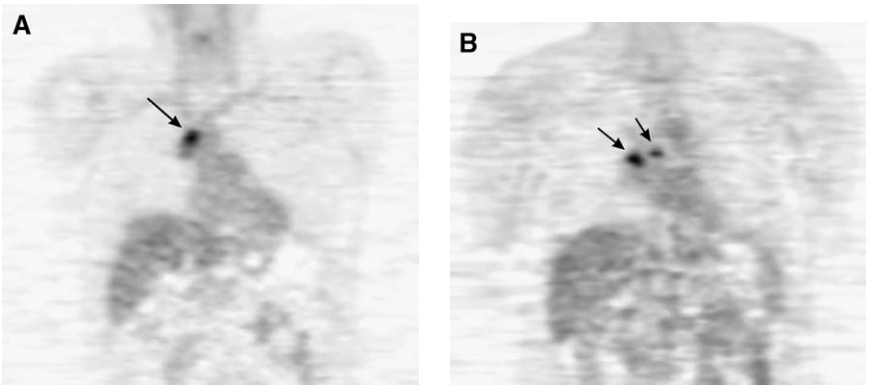

Fig. 3. A 65-year-old man with history of multiple chest wall recurrences of estrogen receptor-positive invasive ductal carcinoma of the right breast. He had undergone multiple chest wall resections, radiation, chemotherapy, and hormonal therapy for these episodes of recurrent disease. Anterior coronal image from FDG-PET (*A*) performed 11 years after original diagnosis of breast cancer shows a focus of uptake in the right anterior chest (*arrow*; SUV = 6.0) consistent with pathologic involvement of an internal mammary node. A more posterior coronal image (*B*) shows two foci of uptake (*arrows*) in the right hilum (SUV = 6.4) and the pretracheal region of the mediastinum (SUV = 5.0).

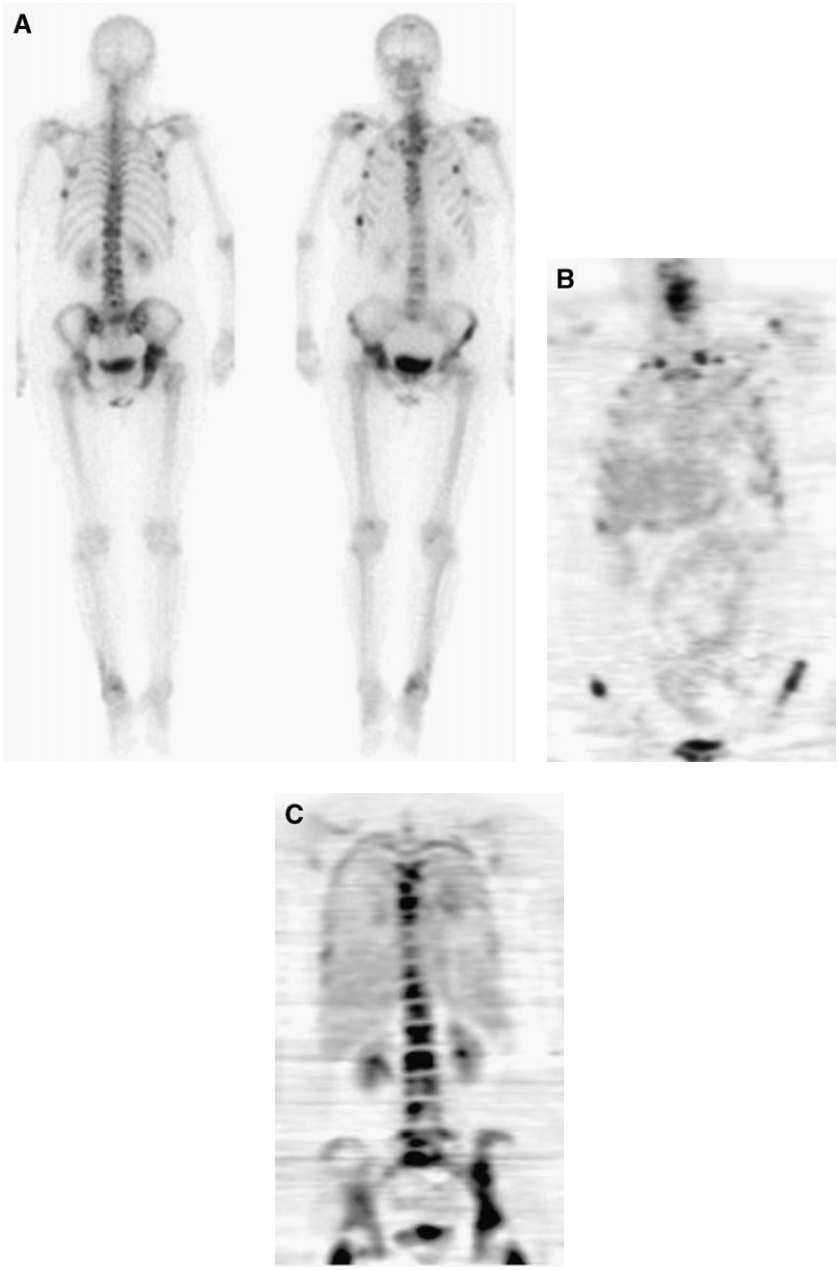

Fig. 4. A 43-year-old woman with bone-dominant metastatic breast cancer. The posterior and anterior projections of bone scan (*A*) show widespread foci of uptake in the axial skeleton and ribs consistent with metastatic disease. Anterior (*B*) and posterior (*C*) coronal images from FDG-PET performed 1 week after the bone scan show much more extensive involvement of the axial skeleton, with a predominant intramedullary uptake pattern in the spine. The pattern of uptake in the ribs is also different compared with the bone scan. The bone scan shows discrete foci in multiple ribs bilaterally that are not as apparent on FDG-PET; these sites represent areas of active cortical bone remodeling from either sclerotic metastases or pathologic fractures. The rib activity in the FDG-PET scan is more diffuse and less discrete, consistent with intramedullary metastases.

lytic lesions or metastases confined to the marrow cavity may be difficult to detect on bone scintigraphy, because of a lack of sufficient osteoblastic response [52]. Retrospective studies comparing the sensitivity of bone scintigraphy to FDG-PET in the detection of skeletal metastases in patients who have advanced disease have shown conflicting results [3,4,9,53–56]. Some studies have shown FDG-PET to be equal or superior to planar bone scintigraphy in the detection of skeletal metastases