6. Fluorodeoxyglucose-PET in Breast Cancer

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Similar to the previously discussed approved applications in oncology, FDG-PET in breast cancer has demonstrated superior diagnostic accuracy compared with conventional anatomic imaging for the detection of distant metastases. This increased accuracy in lesion detection has translated into improved staging, especially in cases with a high clinical suspicion or pre-test probability of distant metastases. In addition to staging and restaging, another application for FDG-PET covered by Medicare is in the evaluation of tumor response to therapy.

This chapter briefly reviews the basic classification and imaging aspects of breast cancer; describes the currently approved clinical indications, as defined by the Center for Medicare and Medicaid Services (CMS); and discusses the accuracy, strengths, and limitations of FDG-PET.

Epidemiology and Histopathology

Breast cancer is the most frequent tumor in women, with over 200,000 new cases each year in the US [1,2]. Women in the US have an approximately 1 in 7 lifetime risk of developing breast cancer. It is the second leading cause of cancer death in women with an approximately 15% mortality, or 40,000 deaths each year [1,2]. In men, only 1450 new cases occur each year in the US; however, mortality is approximately 450 each year [1,2].

Eighty percent of breast cancers are adenocarcinomas, 5–10% are lobular carcinomas, and 5% are medullary carcinomas. Other rare types of breast cancer include inflammatory breast carcinoma (1–3%), tubular carcinoma (2%), and Paget's disease of the breast (1%). Of the adenocarcinomas, approximately 20% are diagnosed at the early stage of intraductal carcinoma, also called ductal carcinoma in situ (DCIS).

Tumor Node Metastasis Staging

The tumor node metastasis (TNM) tumor staging of breast cancer is summarized in Table 6.1. Changes to the American Joint Committee on Cancer Staging (AJCC) in 2002 have been recently summarized [3]. New classifications

Table 6.1. American Joint Committee on Cancer TNM staging for breast cancer

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T0	N1	M0
Stage IIA	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
	T0	N2	M0
	T1	N2	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Sixth Edition (2002), published by Springer-Verlag, New York, www.springeronline.com.

have been added to incorporate lymph node metastases detected by sentinel lymph node biopsy and/or immunohistochemical staining or reverse transcriptase-polymerase chain reaction (RT-PCR). In addition, distinction is made between isolated tumor cells (≤0.2 mm) and micrometastatic disease (>0.2 mm and ≤2.0 mm). The number of positive lymph nodes is also incorporated into the nodal staging. Changes in staging criteria may influence the apparent survival data when comparing prognosis based on different staging criteria [4]. The more recent and more accurate pathologic staging may lead to an apparent increase in survival without true improvement [4].

Currently Approved Indications

In contrast to the other oncologic clinical indications, FDG-PET is currently not approved for the initial diagnosis of breast cancer. Mammography with ultrasound and biopsy is a highly sensitive approach for the majority of breast cancer initial diagnoses. Although the early reports of FDG-PET showed high sensitivity (>90%) for large lesions such as in locally advanced breast carcinoma [5,6], subsequent reports demonstrated significantly lower sensitivity in smaller primary lesions, predominately related to the limited PET image reso-

lution [7] (Figure 6.1). In a meta-analysis of the literature, FDG-PET on conventional whole-body scanners could not accurately classify a primary breast lesion as benign or malignant with sufficient sensitivity [8]. Promising devices currently under evaluation include novel PET instrumentation specifically designed for breast imaging which can improve sensitivity and accuracy for detection of smaller primary tumors [9–18]. See Figure 6.2 for a glimpse of a positron emission mammography (PEM) device and a representative FDG-PEM study.

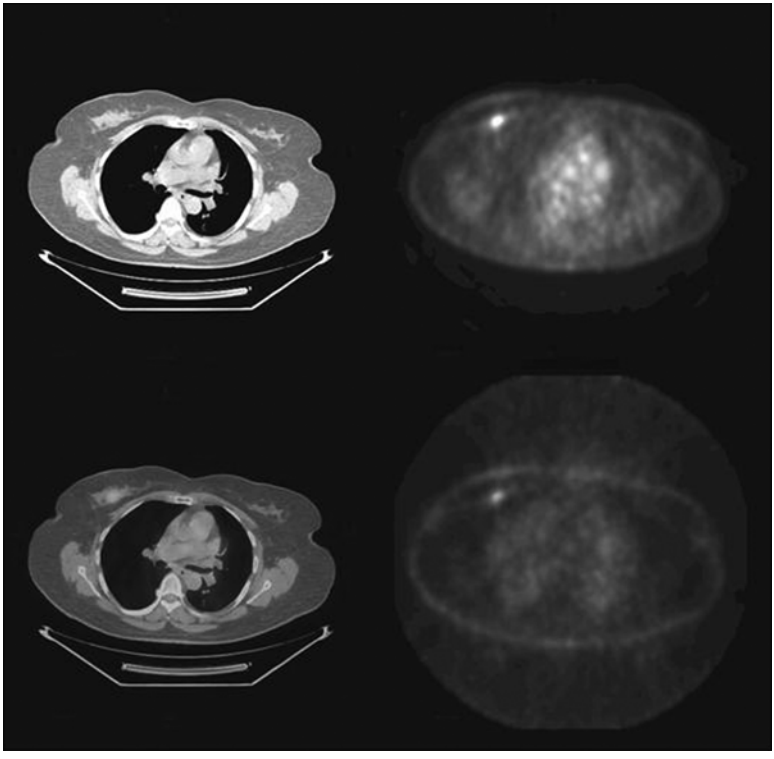

Figure 6.1. A 75-year-old woman who presented with a breast mass that was biopsied and demonstrated to be invasive ductal cancer. She was referred for a PET scan for initial staging, which was negative for disease other than the primary lesion in the right breast. The CT scan (upper left) reveals a right breast mass that is FDG avid on PET (upper right). The fused images (lower left) show the location of the cancer within the mass. The lower right image is the non-attenuation-corrected image.

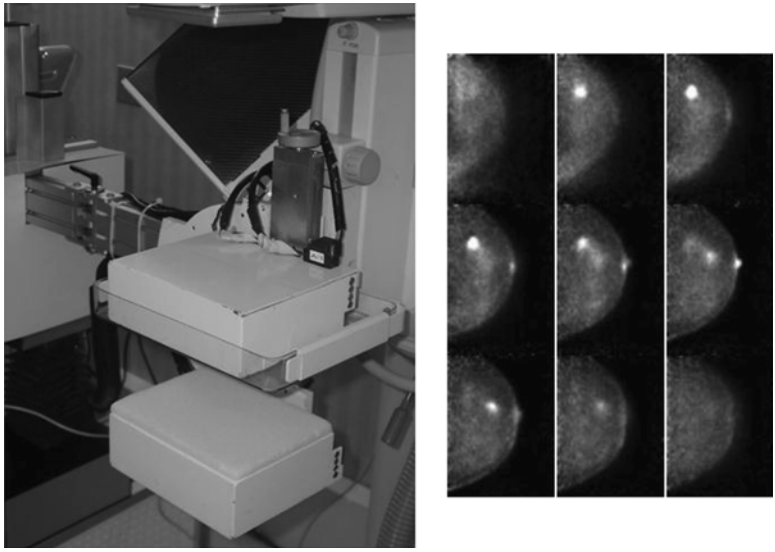

Figure 6.2. A positron emission mammography (PEM) device developed by Jefferson National Laboratory and being evaluated by Duke University Medical Center is shown on the left. The two detectors are placed on a mammography unit; the breast is positioned on the lower detector and the upper detector is lowered with the compression device for imaging. The tomographic images shown on the right reveal FDG accumulation in a large breast cancer.

Staging and Restaging of Breast Carcinoma

FDG-PET is currently approved for the staging and restaging of regional and distant metastatic disease. Advantages of FDG-PET include complete whole-body evaluation in a single study, and superior sensitivity and accuracy compared to conventional anatomic imaging modalities (Figure 6.3). Several review articles have summarized the higher accuracy of FDG-PET compared to conventional diagnostic modalities [19–22]. In a report of 60 patients with suspected breast cancer recurrence, FDG-PET sensitivity, specificity, and accuracy were 89%, 84%, and 87%, respectively, for the detection of local or regional recurrence [23]. For the detection of distant metastases, sensitivity, specificity, and accuracy were 100%, 97%, and 98%, respectively [23]. A meta-analysis of FDG-PET for detection of breast cancer recurrence or metastases in patients showed a pooled sensitivity of 90% (95% confidence interval = 86.8–93.2%), and a pooled false-positive rate of 11% (95% confidence interval = 7.8–14.6%) [24]. A number of other reports have shown significantly better sensitivity and accuracy of FDG-PET in detection of recurrence or distant metastases compared to conventional anatomic imaging modalities including CT [25–30]. Particular

utility is demonstrated in the detection of mediastinal or internal mammary lymph node metastases [25,31–33]. Figures 6.3 and 6.4 demonstrates the ability of FDG-PET to identify sites of distant metastases.

Although FDG-PET has shown excellent sensitivity in the detection of distant recurrence or metastases, early micrometastatic disease to axillary lymph nodes may not be detected. In a blinded, prospective, multicenter study of FDG-PET in primary staging of the axillary lymph nodes, the sensitivity was 61% with a corresponding specificity of 80% [34]. Sentinel lymph node biopsy and

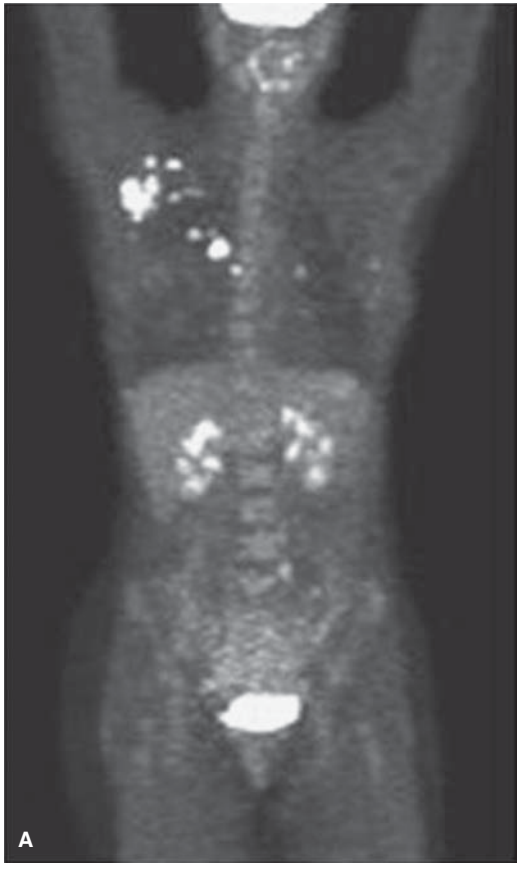

Figure 6.3. A 42-year-old woman with a history of breast cancer now with biopsy-proven axillary recurrence after mastectomy and radiation therapy. PET/CT scan was performed to determine extent of disease. Maximum intensity pixel projection image **(A)** demonstrates marked axillary nodal disease as well as disease in the right and left chest.

Continued.

focused histologic examination, which may include thin sectioning and immunohistochemical staining [35], provide higher sensitivity compared to FDG-PET for axillary lymph node staging after initial diagnosis. Although intense foci were highly predictive of metastatic disease, this finding was relatively infrequent among those with axillary metastases, and routine staging of the axillary lymph nodes by FDG-PET is currently not recommended [34]. Other studies have confirmed a relatively low sensitivity compared to sentinel lymph node biopsy [35], and results from other studies have been recently summarized [36]. Thus, sentinel lymph node biopsy with dedicated histologic examination is recommended for initial axillary lymph node staging in the majority of cases clinically presenting with early stage disease.

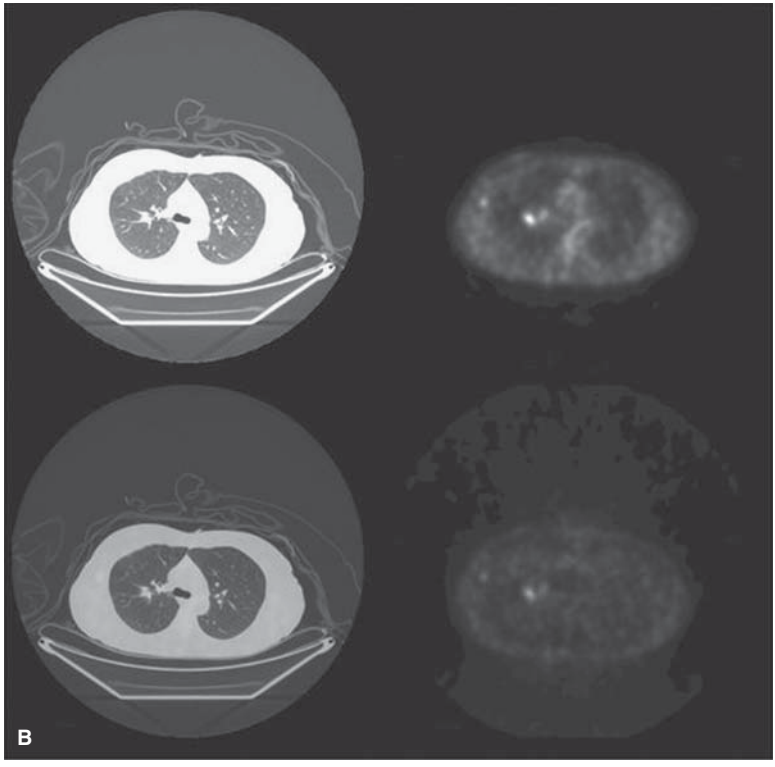

Figure 6.3. *Continued.* **(B)** Transaxial images of the chest demonstrate a lung metastasis (not obvious on CT) as well as hilar nodal metastases. The upper left image is the CT with lung windows, upper right is the attenuation-corrected PET image, the lower left is the fusion image, and the lower right is the non-attenuation-corrected PET image.

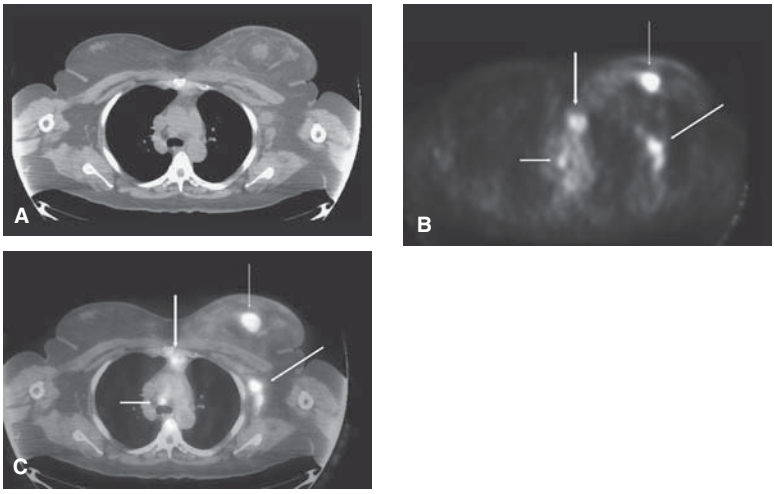

Figure 6.4. A 50-year-old woman presenting with inflammatory breast cancer. Left breast mass and palpable axillary lymph nodes. **(A)** Transaxial CT of the chest shows the left breast mass. **(B)** Transaxial PET at the same level shows intense FDG uptake in the breast mass (thin vertical arrow), in internal mammary lymph nodes (thick vertical arrow), in the left axillary lymph nodes (thick diagonal arrow), in the paratracheal lymph nodes (horizontal thick arrow), and in the soft tissues of the left breast. **(C)** Transaxial fusion of PET and CT co-localizes the same abnormalities described in **(B)**.

Evaluation of Response to Therapy

FDG-PET imaging is able to accurately predict response to therapy [26,33,37–40]. In a prospective study of patients with locally advanced breast cancer, FDG-PET was able to predict response to therapy after the first course of chemotherapy with a sensitivity of 100%, specificity of 91%, and overall accuracy of 88% [37]. A similarly designed study also showed a high sensitivity (90%) and a good specificity (74%) in prediction of response to chemotherapy after a single dose of chemotherapy [38]. Figure 6.5 demonstrates the ability of FDG-PET to predict response to chemotherapy.

FDG-PET after therapy has also demonstrated significantly higher accuracy in predicting disease relapse or death compared to conventional imaging [26,41,42]. Furthermore, preliminary results support the ability of FDG-PET to provide prognostic information in patients with bone-dominant metastatic disease [39,43].

FDG-PET can alter staging and patient management because of its high sensitivity and accuracy in detection of metastatic disease [33,44]. In a study of 125 patients with breast carcinoma, FDG-PET altered the therapeutic plan in 32% and directly supported the therapeutic plan in 27% of patients [33]. These

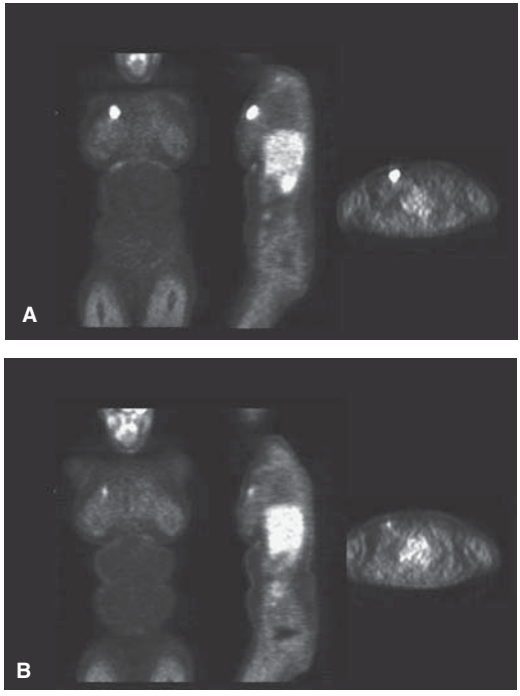

Figure 6.5. A 52-year-old woman with locally advanced, invasive intraductal breast carcinoma. **(A)** Prior to chemotherapy, FDG-PET (left) coronal, (middle) sagittal, and (right) transaxial images demonstrate intense uptake in the primary tumor. **(B)** After chemotherapy, FDG-PET (left) coronal, (middle) sagittal, and (right) transaxial images demonstrate marked reduction in tumor uptake compatible with tumor response to therapy.

results are very similar to an earlier study of FDG-PET that demonstrated a change in clinical stage (36%) and a greater than 30% change in patient management [44].

Potential Limitations

In patients with lobular breast carcinoma, FDG-PET has shown lower uptake and lower sensitivity in detection of the primary lesion [7,45]. Using a clinically relevant threshold for interpretation, 65% (15/23) of primary invasive lobular carcinomas were false negative [7]. A study of primary breast carcinoma also demonstrated a significantly lower FDG uptake in lobular compared to intra-

ductal carcinoma [45]. A specific comparison of FDG uptake in metastatic lesions of lobular compared to intraductal histology has not been yet reported.

A potential limitation in detection of bone disease is in lesions that are osteoblastic. In a study of 23 patients comparing FDG-PET and ^{99m}Tc MDP, FDG-PET detection of bone metastases was reported to have a significantly lower sensitivity in osteoblastic compared to osteolytic bone metastases [46]. Several lesions did not show FDG-PET uptake in osteoblastic lesions that were positive on conventional bone scintigraphy with ^{99m}Tc MDP [46]. Although some patients had radiation therapy, these authors concluded that a significant number of osteoblastic metastases without prior radiotherapy were false negative on FDG-PET imaging. A larger series without segregation of type of bone metastases has demonstrated that the overall sensitivity and accuracy of FDG-PET was higher than that of ^{99m}Tc MDP scintigraphy [47]. Figure 6.6 is an example of

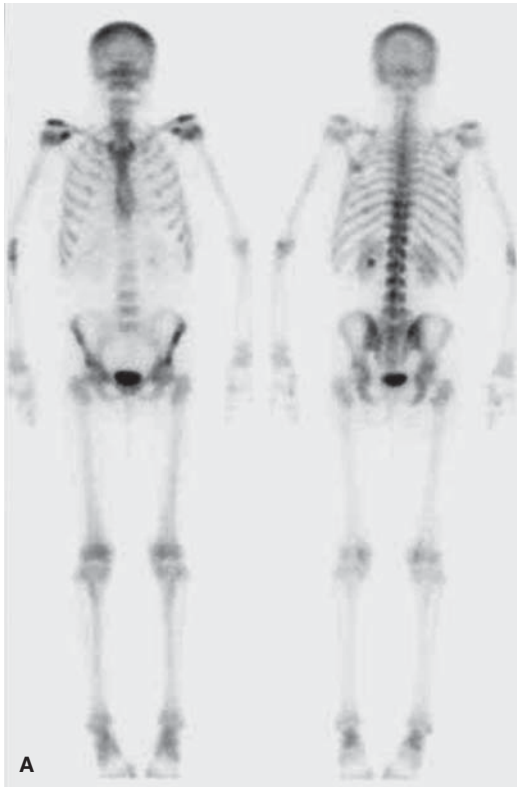

Figure 6.6. **(A)** Anterior and posterior whole-body planar images from a ^{99m}Tc methylene diphosphonate (MDP) bone scan in a patient with breast cancer demonstrates inhomogeneous uptake within the thoracolumbar spine. While this is suspicious for metastatic disease, it is not conclusive.

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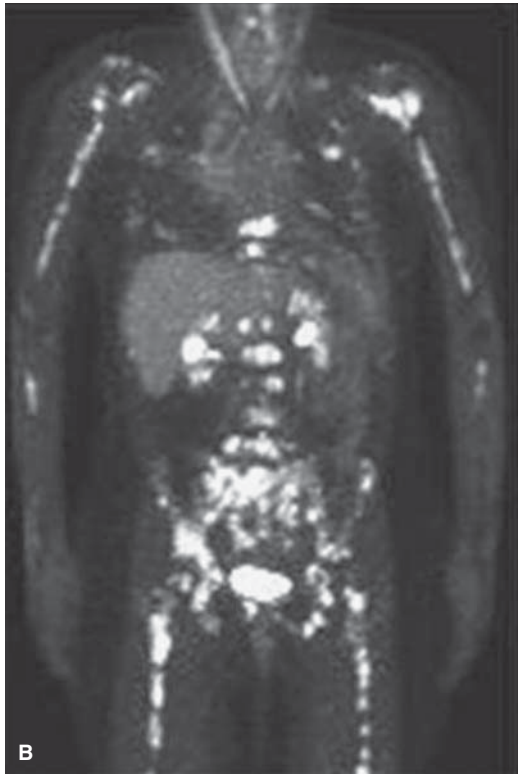

Figure 6.6. *Continued.* **(B)** Maximum intensity projection (MIP) image from an FDG-PET scan of the same patient obtained a few days following the bone scan demonstrates widespread osseous metastatic disease within the axial and proximal appendicular skeleton. Metastatic extent was significantly underestimated by the whole-body bone scan.

underestimation of osseous metastatic disease by bone scan compared to FDG-PET. Patients with osteoblastic bone metastases have better prognosis and survival, and thus, the clinical and biologic significance of reported decreased sensitivity in osteoblastic metastases requires further investigation [46].

As discussed previously, FDG-PET is unable to detect very small and micrometastatic disease to lymph nodes because of limitations in spatial resolution. Sentinel lymph node biopsy and histologic evaluation is preferable in the staging for early axillary lymph node metastases. Sensitivity and accuracy in detection of primary breast cancer are similarly lower for detection of smaller tumors [7]. Multifocal breast cancer has also shown a relatively low FDG-PET sensitivity of 50–63% in recent studies [7,30]. Some of the new dedicated devices may improve the sensitivity for small lesions and multifocal disease.

The specificity of FDG-PET is relatively high. In a number of studies, specificities of greater than 90% have been reported. Studies are now being performed with co-registered CT which may further improve specificity [48,49]. Cases of false positives have included breast fibroadenoma, inflammation, dysplastic tissue [7], degenerative disease, infection [50], chronic infection, and non-specific lymph node uptake [27]. Physiologic FDG breast uptake is normally higher in patients with dense breasts [51], and in lactating women [52].

Future Directions

New PET radiotracers are currently being investigated to further characterize the biologic properties of breast cancer metabolism, receptor status, blood flow, hypoxia, proliferation [53], and response to hormonal therapy [54]. For example, ^{18}F fluoride may be more sensitive than conventional planar bone scintigraphy with ^{99m}Tc MDP in the detection of skeletal metastatic disease, and in addition, may be able to detect osteoblastic disease which may not have FDG uptake [46,55]. Advances in combined PET/CT are promising for improving accuracy in radiotherapy planning, and for improving accuracy in staging [20,48,49]. Research is currently being performed to determine the feasibility of using ^{18}F-FDG in high doses for radiotherapy [56].

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