Clinical Utility of PET Scanning in Breast Cancer Management

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Abstract

The utilization of imaging to stage patients with breast cancer continues to evolve from a reliance on conventional techniques, such as the scintigraphic bone scan and computed tomography (CT), to more advanced hybrid molecular imaging, such as 18F-fluorodeoxyglucose positron-emission tomography–CT (FDG PET-CT). Although FDG PET has proven to be a powerful imaging technique, appropriate usage is critical to optimize healthcare delivery. While FDG PET should not be used routinely for initial detection of breast cancer or for detection of axillary nodal involvement, FDG PET in appropriate higher-risk populations has great value in definitive whole-body initial staging, in the differentiation of recurrent tumor from post-therapy sequela, and in the restaging of patients with recurrent tumors. FDG PET scanning also is emerging as a potent tool in prognostic stratification and for assessing early response to therapy. The use of any advanced imaging technique, including FDG PET, is strongly discouraged for routine surveillance of patients with asymptomatic breast cancer who have achieved a complete response. While more research is under way in other molecular-based radiotracers and imaging techniques, this review will focus on the utility of the most common and available molecular-imaging technique, FDG PET, in the diagnosis, staging, and restaging of breast cancer.

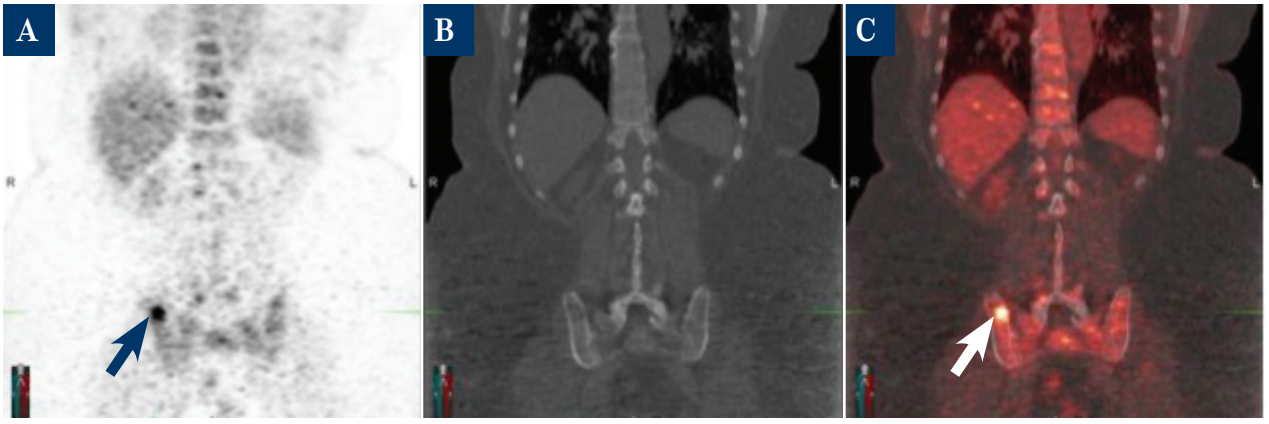
Key words: FDG, breast cancer, PET, staging, therapy response

Positron-emission tomography (PET) has proven useful in the evaluation of many cancers. However, as with all imaging modalities, PET is best used in the proper clinical scenarios. Although many types of PET radiotracers have been developed to noninvasively interrogate in vivo tumor metabolism, the most widely used US Food and Drug Administration (FDA)–approved PET radiotracer, 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG), is based on glucose metabolism. FDG is transported into the cell via glucose transporters, but unlike glucose, FDG is not metabolized but is irreversibly phosphorylated by hexokinase and trapped within the cell. Because glucose transport is upregulated in most cancers in a phenomenon termed the *Warburg effect*, FDG PET exploits greater uptake of FDG within most cancer cells versus normal tissue in order to visualize tumors. Biologic correlates of FDG uptake in breast cancer include mitotic activity index, histologic grade, tumor cell density, as well as other markers of aggressiveness.[1-3] For example, FDG uptake is greater with triple-negative breast cancer (TNBC) and HER2 positivity, and lower with luminal A subtypes. While FDG uptake positively correlates with pathologic complete response to neoadjuvant chemotherapy for patients with breast cancer, FDG uptake inversely correlates with prognosis.[4,5]

Awareness of key principles of FDG PET usage is important for clinicians who order FDG PET for their patients with breast cancer. Most PET scanning today is performed on a combined PET-computed tomography (CT) hybrid instrument, which allows co-registration of metabolic data from the PET scan with anatomic data from the CT scan. Patients should be fasting except for water for at least 4 to 6 hours to optimize the study. Lack of fasting or elevated blood glucose will raise insulin levels and drive FDG into muscle and away from tumor tissue. Recent chemotherapy or marrow stimulation with granulocyte colony-stimulating factors within 2 to 4 weeks before may spuriously lower FDG uptake in tumors. Although FDG uptake has high positive predictive value (PPV) for breast cancer, false-positive uptake has been described with dysplasia, fibroadenomas, silicone leakage, and fat necrosis, among other inflammatory and infectious etiologies.[6] False-negative results on whole-body FDG PET imaging may be secondary to small lesions (<1 cm), tubular or lobular carcinoma, or carcinoma in situ.

For primary breast lesions, because whole-body FDG PET has lower sensitivity for the detection of small lesions, it is not recommended as a primary staging modality. In a study by Avril et al,[7] while PET imaging detected 92% of pT2 lesions, only 68% of pT1 lesions (<2 cm) were detected. In addition, 65% of lobular carcinomas in that series had false-negative results compared with ductal carcinomas (24% false-negative). Yet, because of its

FIGURE 1. Bone Marrow Aspirate.



A 65-year-old asymptomatic patient with infiltrating ductal carcinoma; clinical stage IIA, T2 N0 grade 2, status post-lumpectomy with positive sentinel node biopsy. Coronal PET (A), CT (B) and fused PET-CT (C) images show unsuspected metastasis in right ilium (arrow) proven on subsequent biopsy.

high PPV for identification of tumors, whole-body FDG PET may be useful in uncommon problem-solving cases for which magnetic resonance imaging (MRI) is not available. Similarly, if incidental breast focal activity is noted on FDG PET in the evaluation of other cancers, further investigation is warranted.[8-10] Although beyond the scope of this review, investigation is ongoing on the clinical utility of such specialized PET techniques as positron-emission mammography (PEM) with dedicated small-field devices in the evaluation of primary breast cancer. There is evidence to suggest that while PEM with FDG has lower sensitivity for small breast lesions compared with MRI, specificity is higher than with MRI.[11,12] More specialized radiotracers, such as ^{18}F-fluoroestradiol, may also become available for use with PET or PEM for more complete, noninvasive, metabolic interrogation of breast lesions.

Initially there had been speculation that FDG PET could potentially obviate nodal dissection for locoregional axillary nodal staging, but this has not proven to be the case. While FDG PET does have high PPV in the detection of axillary nodes, there is insufficient sensitivity to detect small-volume disease compared with the sentinel node procedure.[13,14] Yet, whereas FDG PET is not recommended for initial axillary nodal staging, many studies have demonstrated the superiority of FDG PET compared with conventional imaging such as CT or MRI for mediastinal, internal mammary, and supraclavicular nodal involvement.[15,16] In one study by Eubank et al,[15] PET scanning demonstrated accuracy of 88% compared with CT staging accuracy of 70%, upstaging 10 of 33 patients. FDG PET scanning, therefore, is especially useful to help guide radiation therapy planning decisions.[17-19]

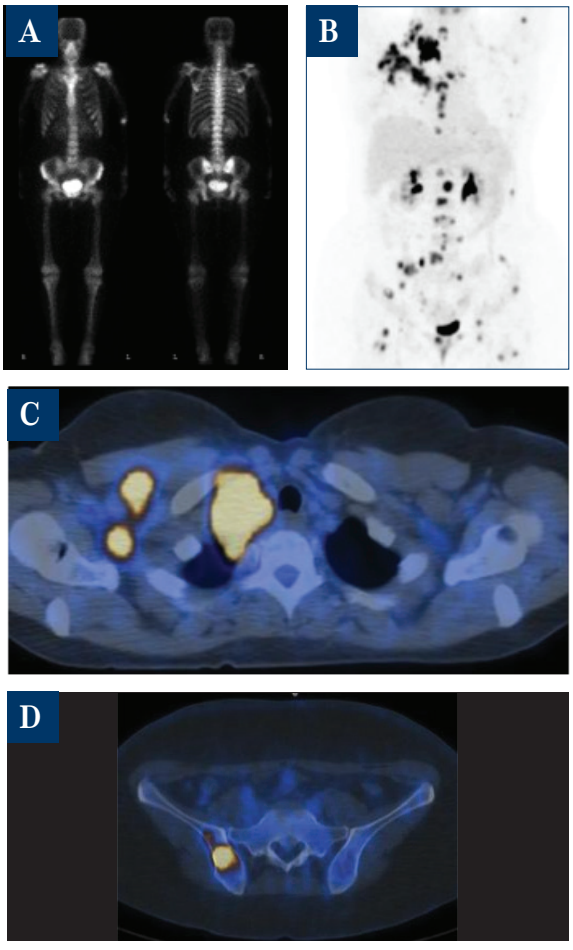
The greatest utility for FDG PET imaging is for whole-body staging, including the detection of distant metastasis (**Figure 1**). In a retrospective study of 225 patients, Niikura et al[20] reported 97.4% sensitivity and 91.2% specificity for FDG PET imaging compared with a combination of conventional techniques with 85.9% sensitivity and 67.3% specificity.[20] Yet, rapid growth in the use of FDG PET has been reported even in early-stage breast cancer, in which FDG PET is not indicated for asymptomatic patients because of low baseline prevalence for metastatic disease.[14,21] According to National Comprehensive Cancer Network (NCCN) guidelines, FDG PET is considered optional for locally advanced (clinical stage 3a), recurrent, or stage 4 disease, but is not indicated for clinical stages 1, 2, or operable stage 3.[22] Most third-party payers reference these guidelines. However, there is compelling evidence that even at clinical stage 2b, whole-body staging of patients with FDG PET has excellent utility. In a prospective study of 254 patients with breast cancer, Groheux et al[23] reported stage modification due to N3 disease and/or distant metastases detection in 16.1% of patients with clinical stage 2b disease.[23] In another retrospective study of 134 asymptomatic women younger than 40 years, distant metastases were discovered in 17% of patients initially staged with 2b disease.[24]

Finally, in a prospective study by Cochet et al[25] of 142 patients with T2 or larger breast lesions in which standard conventional staging was followed by FDG PET, not only did FDG PET scanning have greater prognostic significance compared with conventional imaging, but the addition of FDG PET resulted in 21% upstaging and 16% downstaging. In patients with inflammatory breast cancer, there is broad consensus as to the added value of

FDG PET for complete staging.[26-28] Yet, with less FDG avid breast tumor histology, such as lobular carcinoma, recent evidence suggests that FDG PET imaging may not contribute much to systemic staging compared with conventional imaging.[29] The long-term impact of treatment changes based on PET scanning, however, remains unknown.

There has been some controversy as to the role of FDG PET versus routine bone scanning for the detection of skeletal metastasis. In a study of 89 patients who underwent both FDG PET and bone scans, whereas FDG PET had inferior performance compared with bone scanning for purely osteoblastic lesions, FDG PET outperformed bone scanning for osteolytic, mixed, and CT-silent lesions.[30] The addition of CT to PET, as in most modern PET-CT scanners, also reveals osteoblastic lesions that may not be metabolically active on FDG PET alone. Thus, most imaging specialists support the use of FDG PET over bone scan for initial staging, and then recommend bone scan or ^{18}F-NaF PET-CT if there is still clinical suspicion after a negative or equivocal FDG PET scan (**Figure 2**). Finally, lesions on bone scan may appear worse, when in fact the lesions are healing (flare phenomenon). Although metabolic flare has been reported with FDG PET scanning in response to hormonal therapy, it is considered rare with other systemic therapy. Thus, in general, FDG PET more accurately reflects metabolic response to therapy.[30-33]

FIGURE 2. Widespread Metastatic Breast Cancer.



A 33-year-old female with infiltrating ductal carcinoma, post-partial right mastectomy, axillary dissection, chemotherapy, and radiation therapy. (A) Bone scan is unrevealing, but (B) PET scan (maximum intensity projection) demonstrates unsuspected widespread disease, including (C) soft-tissue (axial-fused PET-CT) and (D) bone (axial-fused PET-CT) involvement.

FDG PET has also proven useful for monitoring response to chemotherapy in the neoadjuvant and metastatic settings. Wahl et al[34] first reported that response on FDG PET imaging performed mid-therapy could discriminate between responders and nonresponders. The current overall consensus is that: (1) early- or mid-therapy FDG PET during neoadjuvant therapy is the best predictor of ultimate response; (2) poor response on FDG PET is highly predictive of therapy failure; and (3) the absence of FDG uptake is not sensitive for histologic complete response since minimal residual disease might not be detected. In addition, initial uptake and optimal response criteria on FDG PET imaging depend on histologic subtype, and type and even sequence of neoadjuvant chemotherapy.[35-41]

Although more work in well-controlled trials to define precise indices for response criteria is required, lack of response on FDG PET imaging has utility in predicting poor clinical response to therapy, and provides prognostic information that may result in modification of chemotherapy or encourage closer post-therapy surveillance.[42] Finally, in patients with metastatic disease in which early identification of nonresponders may avert futile chemotherapy, FDG PET scanning is a highly accurate technique to assess response at the end of therapy and to monitor overall biologic behavior, especially in lesions that are difficult to follow with anatomic imaging, such as bone metastasis.

FDG PET is highly valuable in the setting of recurrence (**Figure 3**). With conventional imaging, it can be difficult to differentiate recurrent cancer from postsurgical and radiation sequelae. However, FDG PET performs well in this regard, with excellent diagnostic performance in the detection and staging of recurrent breast cancer. FDG PET scanning has proven accurate on or off hormonal therapy, and may alter management in up to 51% of patients. Although FDG PET is not recommended for routine surveillance of asymptomatic patients after a complete response to therapy, whole-body restaging with FDG PET imaging has proven value over conventional imaging for patients with rising tumor markers or otherwise clinical suspicion of recurrence.[43-46]

Conclusion

Although whole-body FDG PET imaging does not have sufficient utility in the detection of primary disease, and is not optimized to take the place of the sentinel lymph node procedure for initial axillary staging, FDG PET scanning has efficacy superior to that of conventional imaging for the detection of locoregional and metastatic spread in the appropriate patient population, and has better diagnostic performance for detection of skeletal metastasis compared with routine bone scanning. Thus, FDG PET can serve as a one-stop shopping imaging technique for patients who would benefit from whole-body staging, such as in clinical stage 2b-or-above disease, or for patients with clinical suspicion of distant disease. FDG PET imaging can also provide prognostic information and monitor response to therapy. Although minimal residual tumor cannot be reliably excluded, FDG PET does have high PPV for predicting the presence of residual tumor. Finally, FDG PET is effective at detecting and restaging recurrent tumor, surpassing the diagnostic performance of conventional imaging. However, PET scanning should not be used for routine surveillance in asymptomatic patients who have achieved a complete response.

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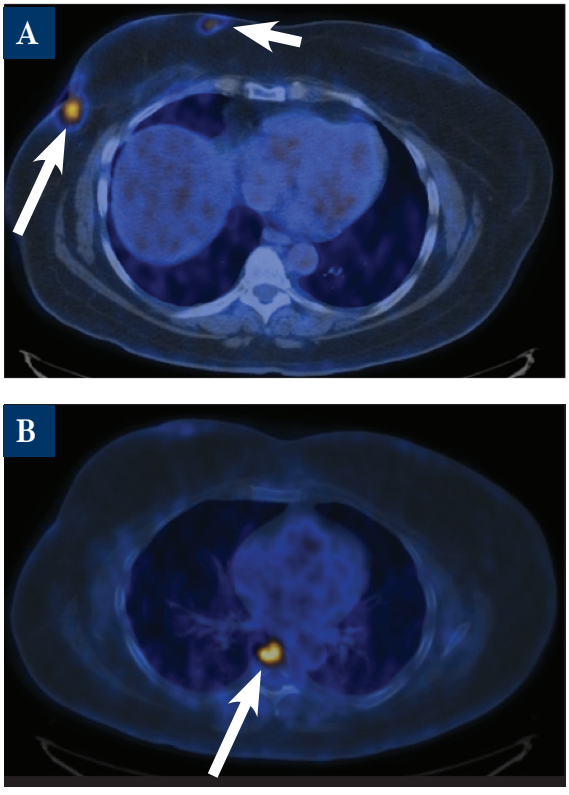
FIGURE 3. Recurrent Cancer With Skin Implant and Vertebral Body Lesion.



Axial-fused PET-CT scan showing cancer recurrence in the right breast (long arrow in A) and skin implant (short arrow in A), with an unexpected vertebral body metastasis (arrow in B)

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