Role of Positron-Emission Tomography Scan in the Diagnosis and Management of Breast Cancer

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In 2008, more than 184,000 new patients were diagnosed with breast cancer, the most commonly diagnosed malignancy in women in the United States. Despite great advances over the past few years in screening, detection, and treatment, more than 40,000 women died from the disease in 2008.[1] Early breast cancer is considered a curable disease, but the curative potential of patients with locally advanced or metastatic disease is limited.

ABSTRACT: Positron-emission tomography (PET) scan is a widely used imaging modality in the management of various malignancies. There is considerable controversy regarding its use in breast cancer diagnosis and treatment. In this review, we discuss published data on the use of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG-PET) in the staging workup of locally advanced breast cancer, and management of locally recurrent and metastatic breast cancer. FDG-PET is a useful tool in staging advanced breast cancer and assessing the extent of disease involvement when metastasis is suspected. It might also aid in assessing early response to therapy. Future goals of improving PET scan accuracy in the management of breast cancer will be achieved through utilizing radiotracers, based on a better understanding of tumor biology and improvement in breast-specific PET scans.

In 2008, more than 184,000 new patients were diagnosed with breast cancer, the most commonly diagnosed malignancy in women in the United States. Despite great advances over the past few years in screening, detection, and treatment, more than 40,000 women died from the disease in 2008.[1] Early breast cancer is considered a curable disease, but the curative potential of patients with locally advanced or metastatic disease is limited.

Imaging in Breast Cancer

Various imaging modalities have contributed to the evolution of breast cancer care. Early detection by mammography is a key element in the improvement of survival in breast cancer patients.[2] Ultrasonography is frequently used to differentiate benign cysts from solid lesions, and to assess axillary lymph node involvement. It also serves as a localizing imaging modality when biopsy is recommended.[3] Magnetic resonance imaging (MRI) of the breast yields better visualization of denser breasts and the chest wall, and is currently recommended for women who are at high risk for developing breast cancer (eg, those with a strong family history or known inherited susceptibility to the disease).[4]

PET Scan

In this review, we focus on the role of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)-PET in the diagnosis and management of breast cancer. FDG is a radioactive glucose analog with a short half-life. Tumor cells have a rapid growth rate and thus utilize more glucose. When a patient is injected with FDG, it is taken by these tumor cells, but not metabolized. The proportion of FDG trapping is dependent on the rate of glucose metabolism. The level of uptake is quantified and reported as a standardized uptake value (SUV).[5,6] FDG is given intravenously 1 hour before the scan in a very small dose, which has no pharmacologic effect. To avoid false-positives due to elevated blood glucose levels, the patient is asked to fast overnight and a normal blood glucose level must be documented.[7] FDG-PET has the advantage of providing functional information compared with just the anatomic characterization provided by conventional imaging studies. FDG-PET is used for diagnostic staging, recurrence evaluation, and to assess response to therapy in multiple malignancies. A strong body of clinical evidence supports its use in non–small-cell lung cancer, Hodgkin and aggressive non-Hodgkin lymphoma, colorectal carcinoma, and melanoma.[8] Its role in advanced nonmetastatic, locally recurrent, and metastatic breast cancer will be discussed in this review.
PET/CT Fusion

Since 2005, PET/computed tomography (CT) fusion scanners have largely replaced traditional PET scans with the promise of better ability to detect cancer and lower false-positive rates. PET/CT fusion studies have the advantage of anatomic characterization in addition to the functional information provided by PET.[9,10] Furthermore, it would be less likely to mistake the normal physiologic accumulation seen in some PET studies when no corresponding lesion is observed on the CT portion.[11]

Different Radiotracers

Improvement in the knowledge of cancer biology and its metabolic pathways has led to the utilization of other metabolic radiotracers in PET scans. 16b-[18F]-Fluoro-17b-estradiol (FES) is an estrogen receptor (ER) ligand used for the detection of ER-positive breast cancer. Patients with higher FES uptake and metabolic flare after estradiol challenge were more likely to respond to endocrine treatment and had a better overall survival in a recent study.[12] Another radiotracer that has been evaluated in ER-positive breast cancers is carbon-11–labeled tetrahydroisoquinoline derivative, which is a selective estrogen receptor modulator.[13]

Hypoxia is associated with more aggressive tumors as well as resistance to chemotherapy and radiation in some cancers. 18F-labeled fluoromisonidazole (FMISO) is a radiotracer that measures tissue hypoxia, and is currently being studied in breast cancer.[14]

Breast Positron-Emission Mammography

Positron-emission mammography (PEM) is a new technology that was developed to overcome the limitation of whole-body PET in detecting smaller breast lesions and to improve visualization of fibrodense breast tissue and breasts with fibrocystic disease. With PEM, two high-resolution detector heads are placed on opposite sides of a compressed breast, and the data is integrated with conventional mammography. PEM has shown promising results in detecting primary ductal carcinoma in situ and recurrent breast disease, as well as for directing biopsy of suspicious lesions.[15,16]

Role of PET Scan in Early-Stage Breast Cancer

The role of FDG-PET in the routine workup and management of early breast cancer remains limited due to its low sensitivity in detecting smaller tumors and the high cost. In a large prospective clinical series (N = 144), the sensitivity of detecting tumors more than 1 cm in diameter was 91%, but the sensitivity dropped to 57% when looking at tumors smaller than 1 cm, and to 25% when looking at carcinoma in situ.[17]

On the other hand, FDG-PET might provide information about the growth pattern and prognosis of primary breast cancer. In a clinical study by Crippa et al, higher SUV values were associated with higher histologic grades and cellular proliferation.[18] In another clinical trial of 70 patients, higher uptake was associated with a statistically worse relapse-free and overall survival.[19] Nevertheless, there is no consensus on how to utilize this information.

Axillary Lymph Node Staging

TABLE 1
Tumor involvement in the axilla has a significant prognostic value in disease survival and recurrence in breast cancer. FDG-PET sensitivity in detecting axillary node involvement appears to vary—from as low as 20% in some studies to as high as 100%—but the specificity remains relatively high at 85% to 100% (Table 1).[20-23] In an older study (N = 124), FDG-PET scan detected axillary nodal disease in all of 44 patients but with a high false-positive rate.[24] In a more recent multicenter prospective study (N = 308), however, FDG-PET had a sensitivity of 61% with a specificity of 80% in detecting axillary lymph node involvement.[25] Another clinical trial showed that sensitivity appears to improve with higher-stage lymph node involvement (for pN1, 41%; pN2, 67%; and pN3, 100%).[26] Sentinel lymph node biopsy seems to have a higher sensitivity and remains the standard of care for diagnosing axillary lymph node involvement.[27]

**Internal Mammary Nodes**

Internal mammary node involvement occurs in approximately 25% of patients at the time of diagnosis and is usually associated with a worse outcome. These nodes are not routinely biopsied due to their inaccessibility. FDG-PET is more sensitive in detecting internal mammary nodes than conventional CT, as evidenced by a study that showed a sensitivity of 85% compared to 50% with CT with pathologic confirmation.[28]

**Metastatic Workup for Locally Advanced Breast Cancer**

**Bone Disease**

Bone scintigraphy is currently the most commonly used method to investigate bone metastasis. However, other inflammatory conditions such as degenerative arthritis, fractures, and Paget's disease might lead to false-positive bone scintigraphy findings.[29] Ohta et al compared PET scan with bone scintigraphy in 51 patients with bone metastasis. PET had a similar sensitivity to bone scintigraphy (78%), but had a better specificity (98% vs 81%).[30] FDG-PET might have an advantage over bone scan by visualizing the metabolic activity of tumor cells rather than detecting the osteoblastic response to destruction by these cells.[31] For example, FDG-PET has a superior ability to detect osteolytic bony lesions, which have a greater metabolic activity. These lesions are associated with more aggressive disease and a worse prognosis.[32] Moreover, bone scans are positive when there is an osteoblastic response, and thus, they might remain positive even after successful treatment. Nonetheless, FDG-PET scan appears to have a lower rate of sensitivity compared to bone scan in detecting osteoblastic lesions.[29] Taking all of these data into account, it appears that the role of FDG-PET scan is to complement the information obtained from a bone scan rather than replace it.

**Visceral Metastasis**
Evaluating for distant visceral metastasis is an essential element of the complete workup in patients with locally advanced breast cancer or worrisome symptoms. Current imaging modalities that are being used to evaluate for distant metastasis include ultrasonography, computed tomography, and bone scintigraphy.

Dose et al compared FDG-PET with conventional imaging studies to detect distant metastases in 50 breast cancer patients. FDG-PET had a sensitivity of 86% and a specificity of 86%, compared with 36% and 95% for conventional imaging. FDG-PET was superior in detecting pulmonary and mediastinal lymph node metastasis compared to chest x-ray, but was comparable in detecting bone and liver metastases compared with bone scintigraphy and ultrasound of the abdomen.[33] Another recent study looked at 119 patients with clinical suspicion for metastatic disease (69 patients with newly diagnosed locally advanced disease and 50 patients with a previous history of breast cancer). These investigators found that FDG-PET had a sensitivity of 87% and a specificity of 83% compared with 43% and 98%, respectively, for conventional imaging.[34] Furthermore, FDG-PET can potentially alter the staging of advanced breast cancer.[35] A retrospective study of 125 patients with advanced breast cancer who underwent PET and conventional imaging showed that PET scan resulted in a change of the clinical stage in 67% of patients (43% upstaged and 24% downstaged). In 32% of patients, this resulted in a change in treatment plan.[36] In another clinical study of 175 patients with locoregional recurrence, FDG-PET detected distant metastasis in 16% of patients; 24% had evidence of distant metastasis within 18 months.[37]

FDG-PET appears to have a limited role in detecting brain metastases due to the high uptake in surrounding tissue. However, combined PET/CT studies with contrast enhancement appear to have a better sensitivity in detecting these lesions.[38] MRI of the brain and CT with contrast enhancement remain the standard diagnostics studies in detecting brain metastases.

Detection of Local Recurrence

About one-third of patients diagnosed with primary breast cancer will have local or distant disease recurrence within 10 years from the time of surgery.[32] Early discovery of recurrent disease will likely affect the treatment plan and prognosis. Conventional imaging techniques have a limited role in surveillance and detection of recurrence. The role of FDG-PET in routine clinical surveillance and when recurrence is suspected is controversial. TABLE 2

Goerres et al compared FDG-PET with MRI in 32 patients with a suspected chest wall, contralateral breast, or locoregional recurrence. FDG-PET appeared to have a superior sensitivity of 100% compared with 79% for MRI, but had a lower specificity of 72% compared with 94% for MRI. FDG-PET detected additional distant metastases in five patients.[39] Another prospective study was done to evaluate FDG-PET role in detecting suspected relapse in 25 women. Abnormal FDG-PET uptake was noted in 43 areas. FDG-PET had a high sensitivity of 95%, but a low specificity of only 20%. A total of 22 sites were correctly identified as areas of relapse, and 21 additional sites of metastasis were discovered (Table 2).[40] By providing information on functional activity of the suspected tissue, FDG-PET can help differentiate postsurgical or radiation scar from local recurrence.[21,41] For example, FDG-PET can assist with distinguishing brachial plexopathy related to radiation scarring from plexopathy secondary to disease recurrence.[42] Nonetheless, tissue biopsy remains the gold standard for investigating suspected recurrence, and it should not be replaced by PET scan.

Response to Therapy
Neoadjuvant Treatment

It might be difficult to assess response to treatment in patients who receive neoadjuvant chemotherapy using conventional methods because the tumor can be slow to regress in size on conventional imaging. Physical examination and clinical assessment might not be good indicators of response to treatment either.[43,44] Changes in the metabolic activity of the tumor precede change in size and can help in detecting nonresponders in the early stages of treatment.[21,45]

A prospective study utilized serial FDG-PET/CT to predict pathologic response after neoadjuvant chemotherapy in patients with stage II or III breast cancer. Patients who responded to treatment had a significant decrease in SUV uptake. FDG-PET/CT had a sensitivity of 89% with a specificity of 95% in predicting pathologic response after two cycles of neoadjuvant chemotherapy.[46]. Similarly, Smith et al evaluated FDG-PET during treatment in 30 patients with large (> 3 cm) primary breast tumors or advanced breast cancer. FDG-PET uptake values were calculated before the first, second, and fifth dose of treatment as well as after the last dose. FDG-PET had a sensitivity of 90% in predicting complete pathologic response after the first cycle of chemotherapy.[47]

It is important to note that studies using serial PET scans had a higher sensitivity in assessing response to treatment, compared with studies using a single PET scan. Burcombe et al evaluated complete pathologic response in 10 patients who had a good clinical response after receiving neoadjuvant chemotherapy. While no patients had abnormal uptake on FDG-PET prior to surgery, nine of them were found to have residual invasive carcinoma ranging from 2 to 20 mm in size.[48]

Response to Systemic and Hormonal Therapy in Metastatic Breast Cancer

Patients with advanced breast cancer who receive antiestrogen therapy can develop worsening of their pain or swelling as well as elevated tumor markers, calcium levels, or alkaline phosphatase levels in the beginning of their treatment. This phenomenon, which is also referred to as “tamoxifen flare” or “metabolic flare,” is a good indicator of response to treatment.[32] Similarly, assessing the metabolic activity after antiestrogen treatment might provide guidance regarding response to therapy. Mortimer et al noted a greater degree of ER blockade in patients who had a decrease in SUV value on their FDG-PET scan. They concluded that PET scan can be used to predict response to tamoxifen therapy in advanced breast cancer patients.[49]

FDG-PET can provide prognostic information in patients undergoing chemotherapy for metastatic breast cancer.[50] Couturier et al studied 20 patients with hormone-refractory or hormone receptor-negative metastatic breast cancer. Semiquantitative analysis of FDG-PET metabolic response predicted short-term and overall survival when assessed after three cycles of chemotherapy (Table 3).[51]

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<td>Use of PET in Breast Cancer Patients With Distant Metastasis</td>
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Abnormal Tumor Markers and PET Scan

The role of tumor markers in detecting disease recurrence is evolving and has not been clearly defined. Patients with elevated serum tumor markers and equivocal CT scans might benefit from
FDG-PET imaging. A study that looked at 39 asymptomatic patients with elevated tumor markers detected recurrence in 94% of these patients (31 out of 33), whereas conventional imaging detected only 18% of these patients.[52] This can be attributed to the increased sensitivity of PET in detecting skeletal and lymph node recurrences compared to conventional imaging.

Another recent study done at our cancer center examined the relationship between PET scan, circulating tumor cells, and CA 27.29 tumor marker, and found a statistically significant correlation. CA 27.29 had a high positive predictive value of 90%, but had a relatively low sensitivity of 59% in detecting metastatic disease shown on PET scan. In the same study, the authors also looked at the correlation between PET scan and circulating tumor cells. Cancer cells that have detached from the primary tumor and are circulating in the peripheral blood might play an important role in tumor seeding in distant sites of metastasis. In this study, the authors noted that detection of more than 5 cells per 7.5 mL of blood had a positive predictive value of 100% with 100% specificity of having an abnormal PET scan.[53]

Conclusions

In summary, the contribution of FDG-PET to the management of breast cancer patients is evolving. Currently, the use of FDG-PET in early breast cancer is limited due to the low sensitivity in detecting small tumors. Clinical trials are investigating the role of positron emission mammography in screening, diagnosis, and management of early-stage breast cancer. Its role in assessing tumor prognostics and biology is investigational. It is inferior to sentinel lymph node biopsy in assessing lymph node involvement. Patients who present with a possible local recurrence might benefit from PET scanning, as it might help in deciding whether further workup is warranted.

FDG-PET is superior to traditional imaging modalities in assessing distant metastasis. It provides information that is supplemental to bone scintigraphy in the case of bone metastasis. FDG-PET is useful in assessing response to chemotherapy in both the neoadjuvant and advanced breast cancer settings. It is also helpful in identifying metastatic sites when tumor markers are elevated. Improvement in PET scan accuracy is potentially achievable by having a better understanding of the tumor microenvironment and by utilizing better targeted radiotracers.

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