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## PET and PET/CT for Breast Cancer

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### LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the different mechanisms of FDG metabolism in tumor cells.
- List the indications of PET and PET/CT in breast cancer patients.
- Explain the limitations of PET in the diagnosis of primary breast cancer and axillary lymph node staging.
- Select which patients with suspected bone metastasis will benefit from PET scan or bone scan.

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**B**reast cancer is the most common malignancy to occur in women in the U.S. Approximately one woman in nine will have breast cancer during her lifetime.<sup>1</sup> Detection is increasing due to regular screening and self-examination, and treatment has changed over last the decade, progressively becoming less radical. Neoadjuvant chemotherapy is increasingly used as primary treatment of locally advanced breast cancer. Therefore, a comprehensive imaging modality that detects tumor in early stages, defines the extent of disease, monitors treatment response, and predicts tumor behavior in patients with breast cancer will be extremely useful.

During the past decade, the application of PET scanning has improved the management of cancer patients remarkably. Fluorine-18 FDG is the glucose analog most widely used as a radiotracer in clinical practice. The clinical value of PET and PET/CT is expanding for diagnosis, initial staging, monitoring of patient response to chemotherapy, and determination of metastatic disease in patients with breast cancer.

### PRINCIPLES AND TECHNIQUE

PET imaging uses positron-emitting radionuclides such as carbon-11, nitrogen-13, oxygen-15, and F-18, which can replace their stable nuclei respectively in biologically active molecules. These radionuclides decay by positron emission. After being emitted from the nucleus, a positron will combine with a nearby electron through a process known as annihilation. Annihilation converts the mass of both parti-

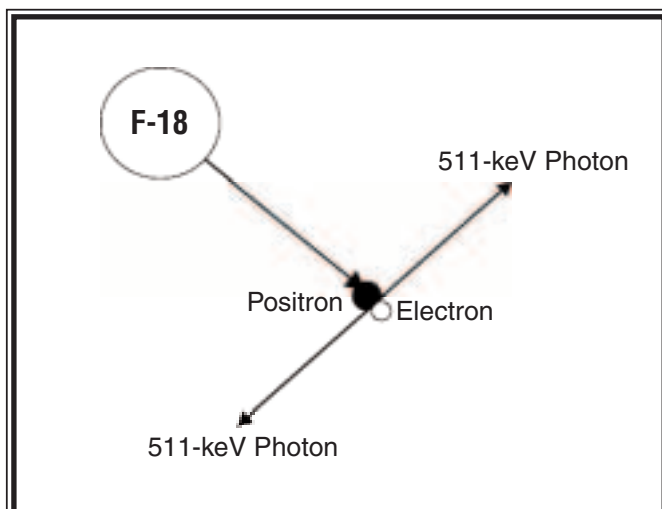


Figure 1. F-18 decay by positron emission. After being emitted, a positron meets an electron through a process known as annihilation. Annihilation converts the mass of both particles into energy in the form of two antiparallel 511-keV gamma rays.

cles into energy in the form of two antiparallel 511-keV gamma rays (Figure 1). The detectors in a PET scanner are arranged in a ring in order to detect these gamma rays.

At present, F-18 FDG is the most commonly used positron-emitting radiopharmaceutical for PET imaging. F-18 FDG is a radioactive analog of glucose that is able to detect altered glucose metabolism in disease processes. Like glucose, FDG is transported into cells by means of a glucose transporter protein and begins to follow the glycolytic pathway.<sup>1</sup> Once inside the cell, F-18 FDG is phosphorylated into F-18 FDG-6-phosphate. F-18 FDG-6-phosphate cannot continue through glycolysis, however, because it is not a substrate for enzyme glucose-6-phosphate isomerase. As a result, F-18 FDG-6-phosphate is biochemically trapped within the cell (Figure 2).

This process of metabolic trapping constitutes the basis of PET imaging. PET imaging makes it possible to calculate a specific uptake value, normalized to the injected dose, that is called a standardized uptake value (SUV). The SUV provides an approximate indicator that correlates with FDG metabolism. A lesion with an SUV greater than 2.5 is considered to have a high probability of malignancy.

**PATIENT PREPARATION AND ACQUISITION**

All patients should fast for a minimum of four hours before the study, and the blood glucose level should be lower than 150 mg/dL. Normal blood glucose level is very important in diabetic patients, as an increased glucose level can alter distribution of F-18 FDG. F-18 FDG is administered in a dose of 5 to 10 mCi through a peripheral vein. The patient is asked to refrain from talking, walking, and performing any other muscular activity after FDG injection.

Most of the time, no contrast is used for the CT portion of the PET/CT study, and no additional patient preparation is required. If contrast is used for a PET/CT study, however, the precautions normally

taken for contrast CT should be observed. Sequential overlapping emission scans of the neck, chest, abdomen, and pelvis should be acquired on the PET or PET/CT scanner 60 minutes after the injection of tracer.

**PET/CT OR PET ALONE?**

PET has been shown to improve the management of cancer patients significantly. But in some instances, it is difficult to interpret a PET scan alone, due to poor anatomic localization, especially in head and neck, abdominal, and pelvic regions.

than 1 cm was 57% (13/22), while it was 91% (155/170) in tumors larger than 1 cm. The specificity of FDG-PET in differentiating benign from malignant lesions was almost 90% in most of these studies, with inflammatory conditions accounting for most of the false-positive results.

Using SUV thresholds of 2 to 2.5, discrimination of benign from malignant lesions can be obtained with about 90% accuracy. Dehdashti et al found a significantly higher SUV of  $4.5 \pm 2.8$  in malignant lesions as compared with an SUV of  $1.05 \pm 0.41$  in benign lesions.<sup>3</sup> They achieved a sensitivity of 88% and specificity of 100% by using an SUV of 2 as a cutoff value for diagnosis of malignancy. Similarly, Avril et al reported in their initial study that malignant lesions had an SUV 2.5 times greater than benign lesions.<sup>4</sup> By correcting for partial volume effect, sensitivity improved from 75% to 92%, while specificity decreased from 100% to 97%.

The only PET/CT study that has aimed at staging breast cancer patients reported a sensitivity, specificity, and accuracy of 93.3%, 90.9%, and 100%, respectively, for the diagnosis of the primary tumor and 80%, 90%, and 86.7%, respectively, for detection of lymph node metastases. This suggests that PET/CT diagnosis of both primary tumor and axillary lymph node involvement is more accurate than diagnosis using mammography, ultrasound, or PET alone.<sup>2</sup>

False-negative results are reported in small lesions (<1 cm) and in slowly growing and well-differentiated histologic subtypes of tumors such as tubular and in situ carcinoma, and in lobular carcinomas.<sup>5,6</sup> The ultimate role of FDG-PET in imaging primary breast lesions is not clear. It is not suited for screening purposes, as its accuracy does not appear comparable to the standard practice of mammography supplemented by ultrasonography and histologic analysis of specimen obtained from image-directed core needle biopsy. Because of its high positive predictive value, how-

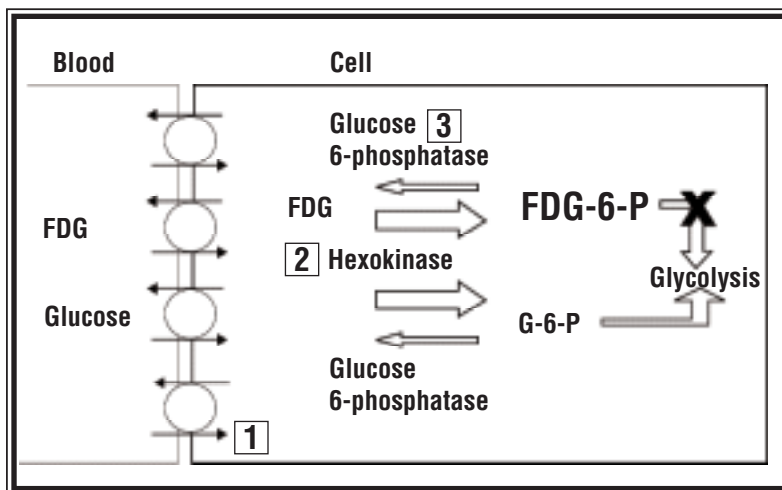


Figure 2. Three different mechanisms of FDG metabolism in comparison with glucose in a neoplastic cell. 1: Increased GLUT receptors in tumor cells. 2: Increased hexokinase. 3: Decreased glucose 6-phosphatase enzyme.

The normal physiologic accumulation of FDG in these regions can be misinterpreted as a pathologic area, leading to false-positive results.

PET/CT provides better accuracy in localizing pathologic areas of FDG uptake.<sup>2</sup> In addition, CT data are used for attenuation correction instead of PET transmission, thereby shortening acquisition time by more than 10 minutes for each patient.

**DIAGNOSIS OF PRIMARY BREAST CANCER**

Several investigators have assessed the role of F-18 FDG-PET in detecting primary breast cancer and in distinguishing malignant from benign disease. Most of the larger prospective studies using FDG-PET in patients with unconfirmed, suspicious breast lesions have yielded very encouraging results, showing sensitivities and specificities ranging from 80% to 100% and 75% to 100%, respectively. The sensitivity for detecting tumors smaller

ever, PET may be useful in selected groups of patients with breast implants, dense breasts, and suspected local recurrence.

### AXILLARY LYMPH NODE STAGING

Sentinel lymph node dissection is a well-established procedure for detecting axillary lymph node metastasis from primary breast cancer.<sup>7</sup> The sensitivity of PET in detection of axillary lymph node metastasis varies from 20% to 100% compared with sentinel lymph node biopsy or axillary node dissection (Figure 3). In a recent series that included a substantial proportion of patients with smaller primary tumors, the sensitivity of FDG-PET in detecting axillary metastases was significantly less when only one node was positive versus several positive nodes and when the primary tumor had infiltrating lobular versus ductal histology.<sup>8</sup> These more recent studies underscore the limitation of PET's ability to detect small-volume axillary disease in early-stage breast cancer.

The results of these studies suggest that FDG-PET should not replace axillary node sampling for routine staging of the axilla. FDG-PET can miss micrometastasis in lymph nodes, as there are fewer numbers of tumor cells, which may or may not have increased glucose metabolism to be detected. In any case, FDG-PET and any other imaging modalities are expected to have a higher false-negative rate than sentinel lymph node biopsy and histological examination of tissues.

In contrast to the variable sensitivity of FDG-PET, almost all studies have shown specificities of higher than 90% and some approaching 100% for determining the status of axillary lymph nodes. In our experience, FDG-PET has limitations in detecting lymph node metastases when compared with sentinel lymph node biopsy, but it was highly specific for staging axilla.<sup>1</sup> Therefore, FDG-PET may be complementary to sentinel lymph node mapping and other standard axillary procedures in patients with more advanced tumors and/or equivocally palpable axillary nodes.

### DETECTION OF REGIONAL AND DISTANT METASTASIS

FDG-PET can contribute significantly to the clinical management of patients who

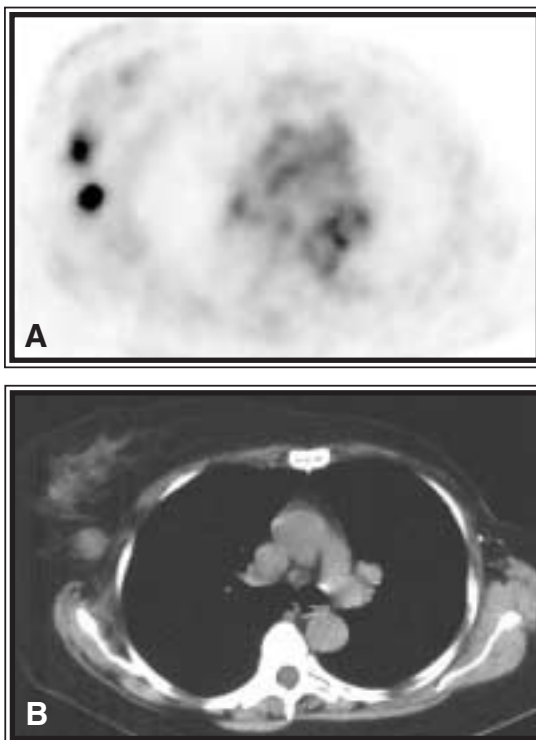


Figure 3. A: PET shows focal areas of intense FDG uptake in right breast and right axillary lymph node, suggestive of primary breast cancer with axillary lymph node metastasis. B: CT image of chest shows irregular density in right breast and enlarged right axillary lymph node.

have been treated previously by surgery or radiation and where a question persists of discrimination between post-treatment scar and recurrent tumor. PET can help define the extent of disease in suspected recurrences when CT or MRI is equivocal or negative. FDG-PET has been shown to be superior to conventional diagnostic imaging for detecting distant metastases in breast cancer.

A particular clinical problem in breast cancer patients after initial treatment is brachial plexopathy. Since either tumor recurrence or treatment-induced scarring can cause symptoms, it is important to differentiate between these two conditions. FDG-PET is a very sensitive method for the detection of brachial plexus metastases in breast cancer patients. Hathaway et al showed the value of combining functional information from FDG-PET and anatomic information from dedicated MR imaging to decide whether patients would benefit from further surgery.<sup>9</sup> Metastases to internal mammary and axillary nodes are usually synchronous, and prognosis is significantly worse when internal mammary nodes are involved.<sup>16</sup>

Jones et al demonstrated the feasibility of detecting internal mammary nodal metastases in early-stage patients using FDG-PET.<sup>10</sup> Eubank et al investigated 33 patients for detection of recurrent or metastatic disease and demonstrated superior sensitivity of 85% with FDG-PET as compared with 54% with CT.<sup>11</sup> In another study, Gallowitsch et al evaluated FDG-PET for detection of recurrence or distant metastases in 62 breast cancer patients.<sup>12</sup> The authors reported sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 97%, 82%, 87%, 96%, and 90%, respectively, for FDG-PET compared with 84%, 60%, 73%, 75%, and 74%, respectively, for CT.

In bone metastases, FDG-PET has produced variable results when compared with bone scan, depending upon the type of metastatic lesion.<sup>13</sup> In some patients, bone scan has better sensitivity in detecting radiologically sclerotic or mixed sclerotic/osteolytic lesions. PET also has a limited role in detecting bone metastasis in the skull due to high physiologic uptake in the brain. Bone scintigraphy has lower sensitivity in pure lytic lesions or metastases confined to the marrow cavity, however, because of lack of sufficient osteoblastic response. FDG-PET has shown higher specificity but lower sensitivity for detecting bone metastases as compared with bone scan. Cook et al showed that FDG-PET detected more lesions than bone scintigraphy except in a subgroup of patients with osteoblastic metastases.<sup>13</sup>

These studies imply that FDG-PET is not a substitute for bone scans, but the two modalities are complementary to one another. PET using the F-18 fluoride ion has shown superior results compared with bone scan and may play a role in breast cancer bone metastasis staging in the future.

### MONITORING TREATMENT RESPONSE

Neoadjuvant chemotherapy is the standard therapy for patients with locally advanced breast cancer. It is associated with a good response rate in more than 70% of these patients, leading to a complete pathologic remission rate of about 10% to 15%. Early assessment of neoadjuvant chemotherapy response would

greatly benefit patient management by assuring continuance of therapy in responders and instituting alternative therapy in nonresponders.<sup>16</sup> FDG-PET has been reported to detect metabolic changes in breast cancer as early as eight days after initiation of chemotherapy. Significant decline in FDG uptake was noted in responders, while uptake was persistent in nonresponders.

Several studies have differentiated responders from nonresponders after the first course of chemotherapy using FDG-PET imaging.<sup>14,15</sup> Two separate investigators have evaluated FDG-PET in predicting complete macroscopic pathologic response to therapy, defined as the absence of gross viable tumor in the surgical specimen post-therapy, after a single cycle of chemotherapy. These exciting results suggest a possible role for PET in the early evaluation of response to therapy.

Bassa et al found that FDG-PET was useful in evaluating response to chemotherapy for primary locally advanced

breast cancer.<sup>16</sup> The investigators showed a good correlation of persistence of FDG uptake after completion of chemotherapy and poor prognosis. Another study investigated the factors influencing the response to chemotherapy in locally advanced breast cancer patients using FDG and O-15 water. The authors hypothesized that low tumor perfusion and high FDG metabolism correlated with the poor response to chemotherapy.<sup>17</sup> Two preliminary studies show the potential value of FDG-PET in evaluating the response of patients with advanced breast cancer.<sup>18,19</sup> A significant reduction was noted in axillary nodal FDG uptake after neoadjuvant chemotherapy. In another study, patients who showed a clinical response had an average decrease in lesion SUV of 72% after chemotherapy compared with no change in lesion SUV from baseline in nonresponders.<sup>20</sup> Stafford et al used serial FDG-PET to evaluate the response of skeletal metastases to therapy and demonstrated strong correlation be-

tween the quantitative change in SUV and overall clinical assessment of response and change in tumor marker.<sup>21</sup>

**SUMMARY**

PET or PET/CT is currently the single most useful diagnostic modality in breast cancer patients, especially those with recurrent or metastatic disease. PET/CT can influence the planning of a treatment modality at staging and in patients with suspected locoregional recurrence. PET seems to be highly useful in predicting tumor response to chemotherapy and can differentiate between responder and nonresponder earlier in the course of treatment than any conventional method currently available.

PET has limitations in detecting small tumors (<1 cm), well-differentiated tubular carcinoma, in situ carcinoma, and lobular carcinomas. In the future, PET is likely to better characterize tumor biology and thereby individualize treatment.

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**REFERENCES**

1. Kumar R, Alavi A. Fluorodeoxyglucose-PET in the management of breast cancer. *Radiol Clin North Am* 2004;42:1113-1122.
2. Zangheri B, Messa C, Picchio M, et al. PET/CT and breast cancer. *Eur J Nucl Med Mol Imaging* 2004;31 Suppl 1:S135-142.
3. Dehdashti F, Mortimer JE, Siegel BA, et al. Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and in vitro receptor assays. *J Nucl Med* 1995;36:1766-1774.
4. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol* 1996;14:1848-1857.
5. 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;18:3495-3502.
6. Eubank WB, Mankoff DA. Evolving role of positron emission tomography in breast cancer imaging. *Semin Nucl Med* 2005;35:84-99.
7. Kumar R, Jana S, Heiba SI, et al. Retrospective analysis of sentinel node

- localization in multicentric palpable and non-palpable breast cancer. *J Nucl Med* 2003;44:7-10.
8. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. *J Clin Oncol* 2004; 22:277-285.
9. Hathaway PB, Mankoff DA, Maravilla KR, et al. Value of combined FDG PET and MR imaging in the evaluation of suspected recurrent local-regional breast cancer: preliminary experience. *Radiology* 1999; 210:807-814.
10. Jones A, Bernstein V, Davis N, et al. Pilot feasibility study to assess the utility of PET scanning in the pre-operative evaluation of internal mammary nodes in breast cancer patients presenting with medial hemisphere tumors. *Clin Positron Imaging*. 1999;2:331.
11. Eubank WB, Mankoff DA, Takasugi J, et al. 18fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. *J Clin Oncol* 2001;19:3516-3523.

12. Gallowitsch HJ, Kresnik E, Gasser J, et al. F-18 fluorodeoxyglucose positron-emission tomography in the diagnosis of tumor recurrence and metastases in the follow-up of patients with breast carcinoma: a comparison to conventional imaging. *Invest Radiol* 2003;38:250-256.
13. Cook GJ, Houston S, Rubens R, et al. Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. *J Clin Oncol* 1998;16:3375-3379.
14. Schelling M, Avril N, Nahrig J, et al. Positron emission tomography using [(18)F]fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000;18:1689-1695.
15. Smith IC, Welch AE, Hutcheon AW, et al. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. *J Clin Oncol* 2000;18:1676-1688.
16. Bassa P, Kim EE, Inoue T, et al. Evaluation of preoperative chemotherapy using PET with fluorine-18-fluorodeoxyglucose in breast cancer. *J Nucl Med* 1996;37(6):931-938.
17. Mankoff DA, Dunnwald LK, Gralow JR, et al. Blood flow and metabolism in

- locally advanced breast cancer: relationship to response to therapy. *J Nucl Med* 2002;43:500-509.
18. Tseng J, Dunnwald LK, Schubert EK, et al. 18F-FDG kinetics in locally advanced breast cancer: correlation with tumor blood flow and changes in response to neoadjuvant chemotherapy. *J Nucl Med* 2004;45:1829-1837.
19. Chen X, Moore MO, Lehman CD, et al. Combined use of MRI and PET to monitor response and assess residual disease for locally advanced breast cancer treated with neoadjuvant chemotherapy. *Acad Radiol* 2004;11:1115-1124.
20. Gennari A, Donati S, Salvadori B. Role of 2-[18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) in the early assessment of response to chemotherapy in metastatic breast cancer patients. *Clin Breast Cancer* 2000; 1:156-161.
21. Stafford SE, Gralow JR, Schubert EK, et al. Use of serial FDG PET to measure the response of bone-dominant breast cancer to therapy. *Acad Radiol* 2002;9:913-921.



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