Assessment of Axillary Lymph Node Involvement in Breast Cancer Patients With Positron Emission Tomography Using Radiolabeled 2-(Fluorine-18)-fluoro-2-deoxy-d-glucose

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Background: The presence of metastatic tumor cells in the axillary lymph nodes is an important factor when deciding whether or not to treat breast cancer patients with adjuvant therapy. Positron emission tomography (PET) imaging with the radiolabeled glucose analogue 2-(fluorine-18)-fluoro-2-deoxy-d-glucose (F-18 FDG) has been used to visualize primary breast tumors as well as bone and soft-tissue metastases. Purpose: This study was undertaken to evaluate before surgery the diagnostic accuracy of PET for detection of axillary lymph node metastases in patients suspected of having breast cancer. Methods: Women who were scheduled to undergo surgery for newly discovered, suspected breast cancers were referred for PET imaging of the axilla region. The women were first clinically examined to determine the status of their axillary lymph nodes (i.e., presence or absence of metastases). Fifty-one women were intravenously administered F-18 FDG and were studied by PET imaging. Attenuation-corrected transaxial and coronal images were visually evaluated by two nuclear medicine physicians (blinded to the patient's medical history) for foci of increased F-18 FDG uptake in the axilla region. All patients underwent surgery for their suspected breast cancers. Axillary lymph node dissection was also performed on all patients with breast cancer, with the exception of four patients who received primary chemotherapy for locally advanced breast cancer. A single pathologist analyzed breast tumor and lymph node tissue specimens. Results: The overall sensitivity (i.e., the ability of the test to detect disease in patients who actually have disease) and specificity (i.e., the ability of the test to rule out disease in patients who do not have disease) of this method for detection of axillary lymph node metastases in these patients were 79% and 96%, respectively. When only patients with primary breast tumors larger than 2 cm in diameter (more advanced than stage pT1; n = 23) were considered, the sensitivity of axillary PET imaging increased to 94%, and the corresponding specificity was 100%. Lymph node metastases could not be identified in four of six patients with small primary breast cancers (stage pT1), resulting in a sensitivity of only 33%. Axillary PET imaging provided additional diagnostic information in 12 (29%) of 41 breast cancer patients with regard to the extension of disease to other sites (i.e., other lymph nodes, skin, bone, and lung). Conclusions: PET imaging with F-18 FDG allowed accurate and noninvasive detection of axillary lymph node metastases, primarily in patients with breast cancer more advanced than stage pT1. Detection of micrometastases and small tumor-infiltrated lymph nodes is limited by the currently achievable spatial resolution of PET imaging. Implications: In clinical practice, PET imaging cannot substitute for histopathologic analysis in detecting axillary lymph node metastases in breast cancer patients. PET imaging, however, improves the preoperative staging of the disease in breast cancer patients and, therefore, might alter therapeutic regimen options. [J Natl Cancer Inst 1996;88:1204-9]
their patients with axillary lymph node metastases receive adjuvant therapy. No imaging technique is currently available for accurate evaluation of axillary lymph node involvement. Therefore, axillary lymph node dissection is performed in the majority of breast cancer patients as a necessary diagnostic procedure to evaluate locoregional tumor extension.

Imaging by positron emission tomography (PET), using the radiolabeled glucose analogue 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (F-18 FDG), allows visualization of a wide variety of tumors because of the enhanced tracer uptake by malignant tissues as compared with surrounding benign tissues (3,4). It is well known that malignant tissue is characterized by an enhanced glycolytic rate, since Warburg (5) first reported increased glucose metabolism of cancer cells. The mechanism of cellular uptake of FDG is thought to reflect transport and phosphorylation of glucose. FDG is phosphorylated by hexokinase and is trapped intracellularly as FDG-6-PO4 with a slow rate of dephosphorylation in most tissues (6). Since the majority of tissue activity represents FDG-6-PO4 at the time of PET imaging, regional radioactivity is proportional to the exogenous glucose utilization. Increased F-18 FDG uptake, representing a marker of increased glucose utilization, has been successfully used to detect malignant brain tumors, head and neck cancer, lung cancer, pancreatic cancer, liver metastases, lymphomas, and other cancers (7-16).

Some studies have also demonstrated increased F-18 FDG uptake in primary breast cancer and in bone and soft-tissue metastases (17,18). These studies, however, are limited in scope because only a small number of patients were investigated and most of these patients had advanced disease.

The aim of the present study was to evaluate before surgery the diagnostic accuracy of PET imaging for detection of axillary lymph node metastases in women with suspected breast cancer.

### Patients and Methods

#### Patient Population

Women with newly discovered breast tumors who were scheduled to undergo surgery were referred for PET imaging of the breast. After PET imaging was performed, a PET scan of the axilla region was done if the patients were able to tolerate this additional procedure. Patients were ineligible for inclusion in this study if they were pregnant, had diabetes mellitus, or were younger than 18 years. The study protocol was approved by the Committee for Human Research at the Technische Universität München. Written informed consent was obtained from all patients. Fifty-one women fulfilled the inclusion criteria for this study and underwent PET imaging of the axilla. Patient characteristics are shown in Table 1.

#### PET Imaging

Patients were required to fast for at least 4 hours before they underwent the scanning procedure in order to minimize blood insulin levels and glucose utilization of normal tissue and to ensure standardized glucose metabolism in all patients. Imaging was performed by use of a whole-body PET scanner (ECAT 951R/3I; Siemens CTI, Knoxville, TN). This imaging device consists of 16 rings of bismuth germanate (BGO) detectors, yielding 31 transverse slices 3.4 mm apart. Transmission scans with germanium-68 rod sources were performed for 15 minutes, yielding about 4 million counts per slice. Emission data corrected for random events, dead time, and attenuation were reconstructed with filtered back-projection (Hanning filter with cutoff frequency of 0.4 cycle). The image pixel counts were calibrated to activity concentration (Bq/mL). The resulting in-plane image resolution of transaxial images was approximately 8 mm (full width at half maximum [FWHM]), with an axial resolution of approximately 5 mm FWHM.

F-18 was produced with an 11-MeV cyclotron RDS 112 (Siemens CTI) by the acceleration of protons onto an oxygen-18 H2O target. The radiolabeled glucose analogue F-18 FDG was produced by use of a synthetic procedure modified from the method of Hamacher et al. (19). The patients were in a prone position with both arms at their sides when we studied them. Imaging involved two gantry positions. Initially, the primary tumor was imaged from 40 to 60 minutes after intravenous administration of about 270-390 MBq F-18 FDG, followed by data acquisition over the axilla from 60 to 80 minutes after tracer injection. After acquisition of the emission data, transmission scans were performed as a "windowed scan" (i.e., selecting transmission data from the sinogram) and were used for appropriate attenuation correction.

#### Image Analysis

Attenuation-corrected PET images were normalized for the injected dose of F-18 FDG and the patient’s body weight, resulting in parametric images representing regional standardized uptake values (SUVs) (J).

\[
SUV = \frac{\text{tissue concentration (Bq/g) \times injected dose (Bq)/body weight (g)}}{
\text{SUV-normalized images were printed on an x-ray film with a linear gray scale, ranging from SUVs between 0 and 4 with the use of a background threshold of 5%}. Transaxial and coronal parametric SUV images were visually analyzed for the presence or absence of axillary lymph node metastases, respectively. In cases where focally increased F-18 FDG uptake was observed, PET scans were considered positive. In cases where there was no abnormal F-18 FDG uptake, scans were classified as negative. Both observers reached a consensus interpretation for each patient.

#### Clinical Examination

Axillary lymph node status (i.e., absence or presence of metastases) was ascertained by clinical examination of the patient before PET imaging and was classified as "negative" for metastases if no palpable lymph nodes were present or as "positive" for metastases if either enlarged, palpable lymph nodes or conglomerate masses in the axilla were detected.

#### Histopathologic Evaluation

All patients underwent surgery for suspected breast cancer. In patients found to have breast cancer, excluding four patients who underwent primary chemotherapy because of locally advanced breast cancer, axillary lymph node

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.*</th>
</tr>
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<tr>
<td>Age, y</td>
<td>49.9 ± 10.3</td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>18-74</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
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<tr>
<td>Perimenopausal</td>
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<td>Postmenopausal</td>
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<tr>
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</tr>
<tr>
<td>Malignant</td>
<td>41</td>
</tr>
<tr>
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<td>30</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Medullary breast carcinoma</td>
<td>2</td>
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</tbody>
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*Unless otherwise specified, values = number of patients.
dissection was performed and the lymph nodes were analyzed for the presence of metastases. Tissue specimens were analyzed by one pathologist (W. Nathrath) using the current histologic classification of breast cancers and axillary lymph node status of the International Union Against Cancer (20). Level I of axillary lymph nodes was defined as lymph nodes located lateral to the lateral border of the pectoralis minor muscle, whereas level II lymph nodes were found behind the pectoralis minor muscle, and level III lymph nodes were medial to the medial border of the pectoralis minor muscle.

Statistical Analysis

The following statistical parameters were calculated by use of the following formulas:

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \quad \text{specificity} = \frac{TN}{TN + FP}
\]

Positive predictive value = \( \frac{TP \times 100}{TP + FP} \), negative predictive value = \( \frac{TN \times 100}{TN + FN} \)

\[
\text{Accuracy} = \frac{TP + TN}{TP + FP + FN + TN}
\]

In these formulas, TP = true-positive, TN = true-negative, FP = false-positive, and FN = false-negative. In addition, 95% confidence intervals were calculated by use of the Ciba Geigy Scientific tables.

Results

Histologic Examination

Benign breast tumors were found in 10 of 51 patients. In 37 of 41 breast cancer patients, axillary lymph node dissection, including levels I and II, was performed. (For histology of breast tumors, see Table 1.) Four patients with advanced disease did not undergo axillary lymph node dissection. They were considered positive because they showed clinical evidence of extensive lymph node involvement and received primary chemotherapy. Axillary lymph node dissection was negative in 17 breast cancer patients, whereas 20 patients were found to have lymph node metastases by histologic examination. The median number of lymph nodes removed was 18.

Clinical Examination

Eighteen patients had palpable lymph nodes, which had features suggestive of axillary lymph node metastases. These 18 patients included four patients who presented with conglomerate axillary lymph node masses. Among all patients, the clinical findings turned out to be true-positives in 14 patients and to be false-negatives in 10 patients, which resulted in a sensitivity of 58% and a specificity of 85% (Table 2).

PET Findings

Fig. 1, A, shows an example of a transaxial PET image representing lymph node metastases in the left axilla and the retrosternal region. Fig. 1, B, shows a coronal PET image of the upper thorax, demonstrating multiple lymph node metastases including level III of the axilla, confirmed as stage pN2 after histologic examination.

Visual analysis of PET images by two observers classified 31 PET scans as negative. In the other 20 PET scans, focally increased F-18 FDG uptake in the axilla region was observed, resulting in an overall sensitivity of 79% and a corresponding specificity of 96% for the detection of lymph node metastases (Table 2). If we considered only patients with primary breast

| Table 2. Results of clinical examination and axillary positron emission tomography (PET) imaging analyzed by two independent observers blinded to results of patient's history* |
|---------------------------------|----------------|----------------|
|                                  | Clinical      | Axillary       | Breast cancer |
|                                  | examination   | PET imaging    | stage pT1     | stage greater than pT1 |
|                                  | (n = 51)      | (n = 51)       | (n = 18)      | (n = 23)               |
| No. of patients                  |               |                |               |
| True-positive                    | 14            | 19             | 2             | 17                     |
| True-negative                    | 23            | 26             | 12            | 5                      |
| False-positive                   | 4             | 1              | 0             | 0                      |
| False-negative                   | 10            | 5              | 4             | 1                      |
| Sensitivity, %†                  | 58            | 79             | 33            | 94                     |
| 95% confidence interval          | 36-78         | 57-93          | 4-78          | 72-100                 |
| Specificity, %‡                  | 85            | 96             | 100           | 100                    |
| 95% confidence interval          | 66-96         | 81-100         | 73-100        | 47-100                 |
| Positive predictive value, %§    | 78            | 95             | 100           | 100                    |
| 95% confidence interval          | 30-70         | 75-100         | 15-100        | 80-100                 |
| Negative predictive value, %¶    | 70            | 84             | 75            | 83                     |
| 95% confidence interval          | 51-85         | 66-95          | 47-93         | 35-100                 |
| Accuracy, %¶                    | 73            | 88             | 78            | 96                     |
| 95% confidence interval          | 58-85         | 76-96          | 52-94         | 76-100                 |

*Clinical examination revealed palpable axillary lymph nodes in 18 patients, four with conglomerate masses. In axillary PET imaging, 2-(fluorine-18)-fluoro-2-deoxy-D-glucose uptake was classified as unlikely (n = 31) or definite (n = 20) to represent axillary lymph node metastases. Statistical analysis in the last two columns is calculated for primary breast carcinomas of stage pT1 (<2 cm) and larger tumors (more advanced than stage pT1).

†Sensitivity is the ability of the test to detect disease in patients who actually have the disease.

‡Specificity is the ability of the test to rule out disease in patients who do not have the disease.

§Positive predictive value is the ability of the test to detect patients with disease among all patients with positive test results.

¶Negative predictive value is the ability of the test to detect patients without disease among all patients with negative test results.

¶Accuracy is the ability of the test to detect true outcomes (positive and negative) among all test results.
tumors larger than 2 cm (greater than stage pT1), the sensitivity of axillary PET imaging increased to 94% and the corresponding specificity was 100%.

The disease in five patients with false-negative PET results was histologically identified as being of stage pN1. Two of these patients had micrometastases with lymph node metastases smaller than 0.2 cm classified as stage pN1a, two had up to three lymph node metastases with a maximum diameter of 1.0 cm classified as stage pN1b, and one had four lymph node metastases with a maximum diameter of 1.2 cm classified as stage pN1bii.

In a comparison of PET findings with results from clinical examination, 12 patients had positive PET scans and palpable axillary lymph nodes. Eight of nine patients who had positive PET scans, but who were found to be negative upon clinical examination, had surgically proved lymph node metastases. Of 30 patients with negative PET scans, six patients had palpable lymph nodes, but the lymph nodes from only two of these patients turned out to be positive upon histologic examination.

When the PET results regarding the number of tumor-involved lymph nodes in the patients were compared with those identified by axillary lymph node dissection, PET imaging could identify only one of four patients with one lymph node metastasis, four of six with two to five lymph node metastases, and all patients with more than five lymph node metastases (Table 3).

Table 3. Positron emission tomography (PET) results in relation to the number of tumor-involved lymph nodes in 20 patients with axillary lymph node metastases compared with axillary lymph node dissection as reference

<table>
<thead>
<tr>
<th>No. of tumor-involved lymph nodes</th>
<th>Total No. of patients</th>
<th>No. of patients with true-positive results</th>
<th>No. of patients with false-negative results</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>2-5</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>&gt;5</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>100</td>
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</table>

The smallest tumor-infiltrated lymph node visualized by PET was 0.8 cm in diameter. One false-positive PET scan was observed in a patient with a fibroadenoma. The PET scan of the breast was negative, but a moderately increased F-18 FDG uptake was seen in the axilla region.

In addition, axillary PET imaging provided diagnostic information on the extent of the disease in 12 (29%) of the 41 patients with breast cancer. In nine patients, we noted focally increased F-18 FDG uptake in level III of the axilla. Lymph node metastases were confirmed by surgery in six of these patients, whereas histologic findings were not available in the other three patients because these patients had undergone primary chemotherapy. Focal F-18 FDG uptake was observed in the periclavicular region in five patients, and three patients had retrosternal foci suggestive of internal mammary lymph node metastases. In one patient, a skin metastasis, which was later confirmed by histologic examination, was positive in PET imaging; in another patient, foci in the lung were also seen on a computed tomography scan. F-18 FDG uptake was increased in the spine in two patients and in the sternum in one patient; subsequent bone scan and x-ray confirmed these findings.

Discussion

This study showed that PET using the radiolabeled glucose analogue F-18 FDG allowed highly accurate detection of axillary lymph node involvement predominantly in patients with locally advanced breast cancer. Results of PET imaging, using axillary lymph node dissection as a reference, provided a sensitivity of 79% and a specificity of 96% for detection of metastases in all patients studied. Sensitivity increased to 94% in a subgroup of patients with primary breast tumors larger than 2 cm in diameter (more advanced than stage pT1). In eight patients found to have no evidence of axillary lymph node involvement on the basis of a physical examination, PET correctly identified metastases. A positive predictive value of 100% was observed in patients with enlarged lymph nodes and positive PET imaging.

This study suggests that PET imaging was more accurate than alternative diagnostic techniques. Comparing the sensitivity and specificity of clinical examination with those of ultrasound, Bruneton et al. (27) found a sensitivity of 45% for clinical examination and 73% for ultrasound and a specificity of 97% for both procedures combined. They concluded that ultrasound
depicted only lymph node enlargement but provided no information about malignancy. March et al. (22) performed thoracic computed tomography in 35 consecutive patients with suspected breast cancers. Correlation of the results with axillary lymph node dissection in 20 patients resulted in a sensitivity of 50% and a specificity of 75%. However, the computed tomography was limited to the detection of the level of axillary lymph node involvement or extracapsular lymph node extension only if lymph nodes were enlarged.

A variety of malignant tumors, including breast cancer, have demonstrated enhanced F-18 FDG uptake by PET imaging as evidence of increased glucose metabolism (7-18). Wahl et al. (17) investigated 12 patients with advanced breast cancer and noted increased F-18 FDG uptake also in axillary lymph node metastases. Nieweg et al. (23) found in five of the 11 breast cancer patients they studied metastatic lymph node involvement in the axilla, displaying a tumor-to-normal tissue ratio ranging from 7.9 to 29.4. The smallest lymph node that they were able to visualize by use of PET was 0.8 cm in diameter. Whole-body PET imaging has also been successfully used to detect axillary lymph node metastases (24). Because of the limited number of patients, no data about the diagnostic accuracy of PET imaging were calculated in these studies. In 18 breast cancer patients, Adler et al. (18) reported a sensitivity of 90% and a specificity of 100% for PET imaging of axillary lymph nodes. Nine of 10 cases with positive results at axillary lymph node dissection had positive PET scans. Although the study by Adler et al. represents the largest reported patient group up to now, it is limited because it included only a small, preselected patient population with a high prevalence of advanced breast cancer.

Positive PET scans defined axillary lymph node metastases with a very high specificity. In our study, only one false-positive PET scan of the axilla was found. In this case, the primary breast tumor showed no increased F-18 FDG uptake and was later identified as a fibroadenoma. Moderately increased F-18 FDG uptake in the axilla of this patient may be explained most likely by an inflammatory reaction from a rabies vaccination given 2 weeks before PET imaging. As has been reported elsewhere (25-27), inflammatory processes may result in increased F-18 FDG uptake. Abscesses, soft-tissue infections, tuberculosis, and sarcoidosis have also been reported to result in increased F-18 FDG uptake in PET imaging (25-27). These observations, however, suggest that increased F-18 FDG uptake may not be entirely specific for malignant tissue.

Carter et al. (2) reported a statistically significant relationship between size of primary breast cancer and the extent of axillary lymph node metastases. Our investigation demonstrated that the sensitivity of PET imaging of axillary lymph nodes depended on the extent of lymph node involvement and that the technique was limited in terms of its ability to visualize small lymph node metastases. Of 18 patients with breast cancer of stage pT1, only two of six with histologically proved axillary lymph node metastases could be identified, resulting in a sensitivity of 33%. This low sensitivity may be explained by partial volume effect, meaning that the F-18 FDG uptake is underestimated in objects smaller than twice the spatial resolution of the imaging technique, which is 5-8 mm in the case of PET (28).

In a small breast cancer (stage pT1), there is only a low probability, ranging from 7% to 15%, of axillary lymph node involvement (29). Moreover, most axillary lymph node metastases consist of only one or two tumor-involved lymph nodes, reflecting primarily micrometastases. Might PET imaging be substituted for axillary lymph node dissection in these patients? Axillary lymph node dissection is mainly performed as a staging procedure, because axillary lymph node status is a strong prognostic indicator and, therefore, is used to determine the need for adjuvant therapy. Our data indicate that PET imaging does not provide the spatial resolution necessary to accurately assess the axillary lymph node status in patients with small metastases. If only one lymph node was affected, the sensitivity of PET imaging was 25%. None of the patients with micrometastases (stage pN1a) were identified. However, in view of the technical limitations of currently available imaging modalities, it cannot be expected that early lymph node involvement can be detected by means other than microscopic in vitro analysis.

More than 50% of all breast cancer patients present with primary tumors larger than 2 cm in diameter (greater than stage pT1) (2). Our study showed that PET imaging allowed detection of axillary lymph node metastases with high accuracy in these patients. In our opinion, however, axillary lymph node dissection cannot be abandoned in patients with negative PET scans because of the limitations discussed above. On the other hand, in cases with positive PET scans, axillary lymph node dissection plays an important role in the locoregional control of tumor growth and in the identification of extracapsular lymph node extension that cannot be identified with PET. Furthermore, evaluation of the number of tumor-involved lymph nodes is often not possible in PET images, especially in cases with lymph node conglomeration. These limitations in spatial resolution may be important in the decision-making process with regard to the mode and intensity of adjuvant treatment, including autologous bone marrow transplantation.

What clinical role could PET imaging play in the future? PET imaging allows preoperative staging. Moreover, it may give additional information concerning the extension of lymph node metastases beyond levels I and II in the axillary lymph node region. Currently, there are no noninvasive modalities available to accurately identify involvement of level III or spread to supraclavicular or internal mammary lymph nodes. Identification of these lymph node metastases has important implications for local treatment (e.g., in the planning of radiation therapy in these regions). In the current study, additional diagnostic information about the extent of disease was found in 12 (29%) of 41 of the breast cancer patients showing tumor involvement of axillary level III, periclavicular, and retrosternal lymph nodes, and the PET technique used also allowed skin, bone, and lung metastases to be visualized. This means that a single procedure, PET imaging, can provide information about the extent of primary breast cancer as well as of metastatic tumor sites. Considering that PET imaging using whole-body techniques provides staging from the head and neck region to the lower extremities, PET may be more cost-effective than other currently used diagnostic procedures, which include x ray, ultrasound, computed tomography, or magnetic resonance imaging. Further studies, however, are required to compare the accuracy and cost-
effectiveness of PET imaging with those of other imaging methods currently available for staging procedures.

References


Notes

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