FDG-PET for the Detection of Recurrent or Metastatic Breast Cancer

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FDG-PET is known to be a non-invasive imaging technique, which is capable of identifying primary tumors and metastases with high sensitivity and accuracy. The aim of this study was to evaluate the diagnostic accuracy of whole-body FDG-PET imaging for the detection of recurrent or metastatic breast cancer after surgery. Whole-body FDG-PET imaging was performed on 27 patients with suspected recurrent breast carcinoma. PET images were evaluated qualitatively for each patient and lesion. FDG-PET scans showed that there were 61 reference sites of malignant or benign lesions in 27 patients. In a patient-based analysis, FDG-PET scans correctly identified 16 of 17 patients with recurrent or metastatic disease and 8 of 10 without recurrence, resulting in a sensitivity, specificity and accuracy of 94%, 80% and 89%, respectively. In a lesion-based analysis, FDG-PET scans correctly identified 46 of 48 lesion sites with recurrent or metastatic disease and 11 of 13 without recurrence. Overall sensitivity, specificity and accuracy for all lesion sites were 96%, 85% and 93%, respectively. FDG-PET scans revealed unsuspected recurrent or metastatic diseases in 8 of 27 (30%) of patients and 11 of 20 (55%) distant metastatic lesions. In 13 patients, treatment was altered by the outcome of the PET scan. We concluded that whole-body FDG-PET scan is a useful diagnostic imaging modality for the detection of recurrent or metastatic breast carcinoma in patients suspected of having recurrent disease after primary surgery. (Journal of Korean Breast Cancer Society 2000;1:000~000)

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The follow-up of breast cancer patients after primary surgery is important in both detecting locally recurrent disease and distant metastatic disease. Early detection of recurrences and metastases has a significant influence on therapy and the correct selection of treatment modalities can be expected to have a significant impact on overall survival. Currently, mammography, ultrasonography, CT, bone scan, and chest X-rays are used for the early detection of recurrent diseases in the breast and to detect regional and distant metastases. However, the evaluation of the postsurgical breast, particularly in patients who have had breast-conserving surgery is sometimes difficult by mammography because of scar formation. Occult distant metastasis can also be missed, even by CT and MR, because detection with conventional imaging methods is based solely on the presence of morphological changes. Given this situation, whole-body FDG-PET imaging appears to be particularly useful in detecting recurrent disease and the screening of occult distant metastases. FDG-PET, one of the nuclear medicine techniques, has added unique functional information to the anatomical characterization of disease provided by conventional imaging methods. Several clinical studies have shown that FDG-PET is both sensitive and specific in both detecting primary breast cancers and for differentiating between breast cancers and benign lesions. FDG-PET also has been used to evaluate the tumor's response to chemotherapy or hormone therapy. We have previously reported that FDG-PET is a highly sensitive, accurate diagnostic tool for the detection of the primary breast mass and axillary lymph node metastasis, when compared with physical examination and mammography.

The aim of this study was to evaluate the diagnostic accuracy of PET imaging for the detection of recurrent or metastatic breast carcinoma in patients suspected of having recurrent or metastatic disease after primary surgery.

Materials and Methods

1. Patients

The study group consisted of 27 female patients (range 28-62 years, mean age 46 years) with breast cancer who underwent primary surgery with or without adjuvant chemotherapy or radiation therapy and were referred to the Seoul National University Hospital between January 1997 and December 1998 with either a clinical suspicion of disease recurrence or systemic disease. The mean time interval between the diagnosis of breast cancer and the FDG-PET scan was 31 month (range 2 month to 7 year). Lesions that were already biopsied or known to have recurrent breast cancer before the FDG-PET scan were excluded from the data analysis. Patients were also excluded when the result of their PET scan could not be confirmed by clinical, histological, or radiological evaluation.

Overall, 27 patients with suspected recurrent or metastatic breast carcinoma were examined. The primary clinical indications, which were used to decide which patients should be examined by FDG-PET were as follows: - loco-regional palpable mass lesions (14 patients), abnormal mammography findings (one patient), abnormal whole-body bone scans (10 patients) and other radiological abnormalities (2 patients).

The histories of all patients were documented and physical examinations were undertaken, in addition two or more tests were performed for staging purposes. These included: - mammography, ultrasonography, whole-body bone scan, or thorax/-abdomen CT and/or MRI. Positive PET findings of local and/or regional lymph node recurrence were confirmed by histology following surgery and/or biopsy or fine-needle aspiration cytology of the lesions. Confirmation of distant metastasis (bone,
lung, and liver) was based on a biopsy of the lesions, if this was possible. If not, lesions with the morphological characteristics of tumors by two or more conventional imaging studies and by clinical and radiological follow up evidence of disease progression over a period of at least 6 months, after the FDG-PET scan, were considered to be the result of distant metastasis.

2. FDG-PET techniques

PET scans were performed using an ECAT EXACT 47 model (Siemens, Knoxville, Tenn.). Patients fasted overnight and 30 minutes before scanning. 10 mg of valium was administered orally to reduce FDG uptake in the neck muscles. They were asked to stay in the supine position, resting, with eyes closed. A bolus of 370-555 MBq F-18-FDG was injected intravenously 60 minutes before imaging. Patients were imaged on the ECAT EXACT 47 scanner in a number of imaging sequences, which encompassed the entire whole body in steps. All patients were asked to void just before scanning, which extended from the bottom of the pelvis up to the bottom of the cerebellum. After scanning for six minutes, the table height was increased by 16.5cm and the acquisition process re-started. Regional transmission images using a germanium-68 source and emission images were also obtained for 30 minutes if any image gave the suspicion of a lesion. Standardized uptake value (SUV) was calculated as follows:

\[
\text{SUV} = \frac{\text{Region's radioactivity concentration (Bq/ml) \times injected dose (Bq)/patient's weight (g)}}}{\text{}}
\]

3. Image analysis

All PET images were evaluated visually on a high-resolution monitor by two experienced nuclear physicians, who reached a consensus. A lesion site was defined as any anatomical site with a clinical, radiological or PET abnormality, which suggested the possibility of recurrences or metastasis of breast cancer. Many other anatomical sites, which were negative by all imaging studies, were not included in the data analysis. PET imaging was also analyzed by the quantitative use of SUV. The result of FDG-PET was considered positive when a lesion showed a SUV value of more than 3.0 or if FDG uptake had increased abnormally and was higher than in the surrounding normal tissue. Effects that the PET examination had upon the method of treatment were documented.

Results

Based upon the clinical, pathological and radiological information obtained from the FDG-PET scans, 61 reference sites of malignant or benign lesions were identified in 27 patients. In a patient based analysis, 17 patients were confirmed to have recurrent or metastatic breast carcinoma, and 10

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<th>Table 1. Patient-based Analysis of FDG-PET Scans</th>
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<td>PET finding</td>
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<tr>
<td>Positive(n=18)</td>
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<td>Negative(n=9)</td>
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<th>Table 2. Lesion-based Analysis of FDG-PET Scans</th>
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<td>Tumor site</td>
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<tr>
<td>Local recurrences</td>
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<td>Lymph nodes</td>
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<tr>
<td>Bone</td>
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<tr>
<td>Lung</td>
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<td>Liver</td>
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<td>Total</td>
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patients had no evidence of recurrence. The FDG-PET scan correctly identified 16 of the 17 patients with recurrent or metastatic disease and 8 of the 10 without recurrence or metastasis, resulting in a sensitivity and a specificity of 94% and 80%, respectively. The corresponding positive and negative predictive values and the accuracy of FDG-PET scans were all 89% (Table 1).

Whole-body FDG-PET scans of the involved organs were also analyzed. In a lesion-based analysis, 48 sites were confirmed to be recurrent or metastatic lesions, and 13 sites were without evidence of recurrence. The FDG-PET scans correctly identified 46 of 48 lesion sites with recurrent or metastatic disease and 11 of 13 without recurrence (Table 2).

Overall sensitivity, specificity and accuracy in all lesion sites were 96%, 85% and 93%, respectively (Table 3). The positive and negative predictive value for all lesion sites was 96% and 85%, respectively. Of the eight local recurrence lesions, 7 were assigned as positive for malignancy but in one lesion site recurrence was overlooked. In 19 lesion sites regional lymph node recurrences were found, one lesion site was false-negative and one false-positive. Sensitivity, specificity and accuracy of local recurrences was 88%, 100% and 92%, respectively, and in regional lymph node recurrences 95%, 67% and 91%, respectively. In addition, bone metastases was identified in 9 lesion sites but in one lesion site was false-positive, resulting in a sensitivity, specificity and accuracy of 100%, 83% and 93%, respectively. Lung and liver metastases were found in 7 and 4 lesion sites respectively, with a sensitivity and accuracy of 100% in each case. When the lesion sites were classified by patterns of recurrence and metastasis, a relatively high sensitivity of FDG-PET scans in terms of the detection of distant metastatic lesions was found; the sensitivity and specificity in terms of loco-regional recurrence were 93% and 86%, respectively, and in terms of distant metastasis 100% and 83%, respectively.

In addition to the qualitative visual evaluation of FDG uptake in recurrent/metastatic breast cancer lesions, PET imaging was also analyzed quantitatively by SUV. Among a total of 61 reference sites, SUVs could be calculated for 51. Of the lesion sites with recurrent or metastatic disease, all but 2 lesion sites were found to be due to hypermetabolic lesions with SUVs greater than 3.0. Two false-negative lesions showed no FDG uptake. These were small-sized lesions less than 1 cm in diameter. On the other hand, among the lesion sites without recurrence all sites, except one, were less than 3.0 by SUV. The one false-positive lesion was due to rib uptake with an SUV of 3.25, which was later confirmed to be due to a rib fracture.

To further evaluate the causes of false-negative or false-positive results, misdiagnosed lesions were re-

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<th>Tumor site</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
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<tbody>
<tr>
<td>Local recurrences</td>
<td>88</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>95</td>
<td>67</td>
<td>91</td>
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<tr>
<td>Bone</td>
<td>100</td>
<td>83</td>
<td>93</td>
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<tr>
<td>Lung</td>
<td>100</td>
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<tr>
<td>Liver</td>
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<td>-</td>
<td>100</td>
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<tr>
<td>Total</td>
<td>96</td>
<td>85</td>
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viewed in detail. False-negative lesions included one local recurrence and one lymph node recurrent lesion. These two lesions were palpable but small, less than 1 cm in diameter. They showed no FDG uptake but were confirmed to be positive for malignancy by histological examination. False-positive lesions included one bone lesion and one mediastinal lymph node site. Of these lesions, the underlying cause for false-positive uptake of the rib was confirmed to be due to a fracture on a follow-up clinical and radiological evaluation. The cause of the mediastinal lymph node uptake could not be precisely identified but, the lesion was likely to be due to increased skeletal muscle uptake, mimicking a lymph node lesion and confirmed to be without recurrence by a one year follow-up imaging study.

FDG-PET scans revealed unsuspected recurrent or metastatic diseases in 8 of 27 (30%) patients (Fig. 1 and 2). Of these, 7 were of distant metastatic disease. These unsuspected lesions were as follows: - two metastatic lesions of bone, five of lung, four of liver and three of lymph node. Overall, 14 of totally 46 (30%) identified malignant lesion sites were of unsuspected lesions. Importantly, 11 of 20 (55%) identified distant metastatic lesion sites were unsuspected lesions and only detected by FDG-PET scan. In 13 of 27 (48%) patients, treatment was altered as a direct result of the PET examination.

Discussion

Although remarkable developments and general progress have been made in conventional imaging techniques and optimal multidisciplinary treatment modality, breast cancer is still associated with significant mortality, and its prognosis is not good. This is in part attributed to shortcomings in the methods currently used for the early detection of recurrent disease, i.e. the staging, and monitoring treatment response of breast cancer⁵.
The careful follow-up of breast cancer patients after primary surgery is important to both detect locally recurrent disease and distant metastatic disease, which are generally considered to be incurable. Although the benefits of the early detection of recurrence or distant metastases have not been well established, it is unquestionably true that the early detection of recurrence and metastases has a significant influence on therapy. In addition, recent clinical studies have demonstrated that high-dose chemotherapy with autologous bone marrow transplantation showed higher response rates and an increase in the number of long-term survivors by 10-30% in cases of recurrent/metastatic breast cancer. This stresses the need for improved imaging methods to detect early metastatic breast cancer. Furthermore, the evaluation of the postsurgical breast, particularly in patients who have had breast-conserving surgery, with conventional imaging methods is sometimes difficult because of scar formation. In this type of situation, wholebody FDG-PET imaging appears to be particularly useful in the detection of recurrent disease and in the screening for occult distant metastases. FDG-PET has emerged as a non-invasive imaging technique, which in the case of breast cancer, is able to identify primary tumors and metastases with a high degree of sensitivity and accuracy. With the growing interest in breast conservation surgery, FDG-PET scan may be a good tool to follow up irradiated breasts and may be useful in differentiating between fat necrosis and recurrent breast cancer. For these reasons we undertook this study to examine the feasibility of using the FDG-PET technique for the restaging of breast cancer in patients suspected of having loco-regional recurrences or distant metastases after primary surgery.

Our data demonstrates that the FDG-PET scan allowed the correct identification of 16 of 17 patients with recurrent or metastatic disease and 8 of 10 patients without recurrence or metastasis, resulting in a sensitivity, specificity and accuracy of 94%, 80% and 89%, respectively. The corresponding positive and negative predictive values of FDG-PET scans were all 89%. When the findings of whole-body FDG-PET scan were analyzed according to the involved organs or lesion sites, we identified 61 reference sites of malignant or benign lesions in 27 patients. Of these lesion sites, 48 sites were confirmed to be recurrent or metastatic lesions, and 13 sites were without evidence of recurrence. The FDG-PET scans correctly identified 46 of 48 lesion sites with recurrent or metastatic disease (true positive) and 11 of 13 without recurrence (true negative). Overall sensitivity, specificity and accuracy in all lesion sites were 96%, 85%, and 93%, respectively. FDG-PET scans also revealed unsuspected recurrent or metastatic diseases in 8 of 27 (30%) patients. Overall, 14 (30%) of the total of 46 identified malignant lesion sites were unsuspected lesions. Importantly, 11 (55%) of 20 identified distant metastatic lesion sites were unsuspected lesions but detected by FDG-PET scan. In 13 (48%) of 27 patients, treatment modality was altered by the outcome of the PET examination. Of these, six patients received unexpected chemotherapy because of unsuspected metastatic disease. Seven patients suspected of having metastatic disease were saved from additional treatment because they were proved to be without metastasis by PET scan.

Many clinical reports have suggested that FDG-PET is more sensitive than conventional staging methods at detecting the true extent of disease and that FDG-PET can reveal unsuspected metastatic disease in breast cancer patients. When the lesion sites were classified by patterns of recurrence and metastasis, sensitivity and specificity in terms of loco-regional recurrence were 93% and 86%, respectively, and in terms of distant metastasis 100% and 83%, respectively. In summary, FDG-PET was
found to have a relatively high sensitivity for the detection of distant metastatic lesions. The value of the whole body method becomes clear, as it allows a reliable assessment to be made of the true extent of the disease and enables better informed decision making upon treatment selection.

In this study, we found that FDG-PET scan is a useful diagnostic imaging modality for the detection of recurrent and metastatic breast carcinoma in patients suspected of having recurrent disease after surgery and for the assessment of the true extent of disease.

It is of significance that FDG-PET showed high sensitivity in the detection of metastatic bony lesions, because skeletal metastasis of breast cancer is the most common form of distant metastasis and cause of potential morbidity. Whole-body bone scintigraphy, on the other hand, is less likely to detect bone metastases at an early stage. Cook et al reported that FDG-PET is superior to whole-body bone scintigraphy in the detection of osteolytic breast cancer metastases (osseous metastases) and is therefore more likely to detect metastases at an early stage. In contrast, Moon et al suggested that a combination of whole-body FDG-PET and whole-body bone scans is a more effective tumor survey method for most body tissues of patients with suspected recurrent or metastatic breast cancer, because of the relatively low sensitivity of FDG-PET for the detection of metastatic bony lesions.

It is also expected that FDG-PET imaging can provide more objective criteria for differentiating between malignant and benign lesions by quantitative analysis. In our quantitative evaluation using SUV, we found that among the lesions with recurrent disease, all but 2 lesion sites were hypermetabolic, with SUV greater than 3.0 and for those lesion sites without recurrence all but one site were less than 3.0 by SUV. However, because of the small number of reference sites without recurrence for each of the involved organs, statistical comparisons between the malignant and benign lesions could not be performed. Although quantitative measurements of FDG uptake, such as the determination of tumor/nontumor ratios or SUV offer more objective and relatively observer-independent methods for differentiating between malignant and benign lesions, many investigators have suggested that these quantitative techniques provide no definite diagnostic advantage over the qualitative analysis of FDG uptake. Clinically, quantitative methods have been frequently used for longitudinal comparison studies, such as for the determination of tumor response to chemotherapy or hormone therapy but more study is needed to determine whether FDG-PET is capable of predicting tumor responsiveness reliably.

Compared with many other PET studies, this study resulted in relatively low specificities in terms of both patient- and lesion-based analyses. This is largely due to the exclusion of many anatomical lesion sites that were found to be recurrence-negative by all imaging studies. In this work only two false positive lesions were found, but other reports have suggested that one of the major drawbacks of FDG-PET scan in breast cancer is the high false-positive rate of lymph nodes. A major reason for the high level of false-positives in lymph nodes, is that suspicious lesions in the neck are misclassified because of the high index of suspicion for metastases in this location and the increased muscle uptake, which mimics lymph node lesions. To improve the specificity of FDG-PET scans, it is necessary to prepare patients carefully and to be aware of potential skeletal neck muscle uptake. This is particularly important when the involvement of lymph nodes in the neck or mediastinum is suspected clinically. One of the false-positive lesions in this study was due to mediastinal lymph node uptake. This was also believed to have been caused by increased muscle uptake.
This study has some limitations. One is that not all regions were prospectively examined using the other conventional imaging modalities, and, therefore, PET findings were not directly comparable with those of conventional study. Another limitation is due to a referral bias, because only more difficult cases, which were not resolved by conventional imaging, tended to be referred for FDG-PET.

Although, the use of the FDG-PET scan as a screening test for breast cancer is as yet impractical because of its high cost, one of the most important advantages of whole-body PET imaging is its ability to evaluate the entire body in one examination. Therefore, for patients with suspected distant metastatic diseases, it is cost effective to perform whole body examinations by PET imaging.

In conclusion, whole-body FDG-PET scan is able to identify local recurrence, lymph node metastases and distant metastases with high sensitivity, acceptable specificity and high accuracy. Whole-body FDG-PET scan is, therefore, an excellent diagnostic modality for the detection of recurrent or metastatic breast carcinoma in those patients suspected of having recurrent disease after primary surgery. In our opinion whole-body FDG-PET imaging is of particular value as it enables a more reliable assessment to be made of the true extent of disease, moreover, this information influences treatment selection. Further study is needed to assess the clinical impact of FDG-PET imaging in the management of recurrent/metastatic breast cancer and particularly its consequences on prognosis.

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References


