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Positron Emission Tomography-Computed Tomography in the Detection of Axillary Lymph Node Metastasis in Patients with Early Stage Breast Cancer

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Objective: The status of axillary lymph nodes (ALNs) is the most important prognostic factor in breast cancer. The purpose of this study was to evaluate the clinical usefulness of ALN involvement by means of positron emission tomography-computed tomography (PET-CT) compared with breast sonography and mammography in patients with early breast cancer.
Methods: This study involved 108 breast cancer patients with non-palpable ALNs. All patients had PET-CT, breast sonography and mammography imaging before sentinel lymph node (SLN) biopsy. After SLN biopsy, all patients underwent complete ALN dissection. ALNs were evaluated by standard hematoxylin and eosin staining techniques. The findings of PET-CT, breast sonography and mammography imaging of 108 patients were compared with pathologic findings after surgery. Sensitivity, specificity and accuracy of individual diagnostic modalities were compared. Diagnostic accuracy was evaluated applying receiver operating characteristic (ROC) curve areas.
Results: The sensitivity, specificity and accuracy of PET-CT imaging were 48.5%, 84% and 73.2%, respectively. The sensitivity, specificity and accuracy of breast sonography were 51.5%, 89.3% and 77.8%, respectively. The sensitivity, specificity and accuracy of mammography were 33.3%, 96% and 76.9%, respectively. For involvement of ALNs, PET-CT imaging, breast sonography and mammography had areas under the ROC curve of 0.662, 0.704 and 0.647, respectively.
Conclusions: Compared with the combination of breast sonography and mammography, PET-CT was less sensitive and had less accuracy in detecting ALN metastasis. Consequently, PET-CT is not a reliable non-invasive modality for assessing ALN involvement that can replace ALN dissection or SLN biopsy before decisions are made on appropriate systemic interventions.

Key words: positron emission tomography-computed tomography – sonography – mammography – axillary lymph node – breast cancer

INTRODUCTION

Breast cancer is the most common female malignancy. Its incidence has been increasing in Europe, the United States and Korea, but recently the incidence is declining because of reduction of hormonal replacement therapy and the fatality rate is also decreasing (1–4). This is probably a result of more effective treatment strategies, as well as the detection of disease at an early stage (3). New diagnostic modalities, surgical techniques and various adjuvant approaches lead to longer survival in patients with breast cancer than ever before. The management and prognosis of breast cancer depends on the size and grade of the primary tumor, estrogen receptor status, axillary lymph node (ALN) involvement and the presence of metastatic disease. Among these factors, the most reliable prognostic indicator for recurrence and survival at the time breast cancer is initially diagnosed is the presence and extent of metastasis to the ALNs (5,6).

Currently, several techniques are used in the diagnosis and staging of breast cancer, including mammography, breast

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sonography, chest radiography, computed tomography (CT), sentinel lymph node (SLN) biopsy, complete ALN dissection, magnetic resonance imaging and isotope bone scanning. For nodal staging, ALN dissection has been performed in most women with invasive breast cancer, although SLN biopsy has recently increased in frequency as an alternative procedure (7,8). While ALN dissection provides staging and prognostic information, ALN has well-known risks, including lymphedema (12%) and upper arm dysfunction or discomfort in more than one-half of the patients (9).

SLN biopsy, introduced by Krag et al. (10) and Giuliano et al. (7) in the early 1990s, represents a new standard of care for ALN staging in patients with early-stage, clinically node-negative breast cancer. SLN biopsy has decreased the morbidity of staging by avoiding unnecessary ALN dissection, and probably measurably improved the accuracy of staging as well. Importantly, SLN biopsy is also an invasive ALN staging method and there is no reliable non-invasive method of evaluation of lymph node status in patients with breast cancer (11). It would be of great clinical benefit if a reliable non-invasive method of determining ALN status was available. The utility of positron emission tomography-computed tomography (PET-CT) with 18F-fluoro-2-deoxy-D-glucose (18F-FDG) has been currently proven for various human malignancies (12), and various studies have shown that PET-CT is a sensitive and specific diagnostic tool for the detection of ALN metastases in breast cancer (13).

The purpose of this study was to evaluate the clinical usefulness of non-invasive ALN staging by means of PET-CT compared with other non-invasive methods (breast sonography and mammography) in patients with early breast cancer.

PATIENTS AND METHODS

Patients

Between March and November 2003, 108 patients with breast cancer and non-palpable ALN were enrolled in this study. Our institutional review board approved our research study and waived the informed consent requirement because this was a retrospective study. All the patients had cytologically or histologically proven breast cancer based on core needle biopsy or fine needle aspiration specimens. After PET-CT imaging, breast sonography and mammography were performed preoperatively, and all patients underwent SLN biopsy. All SLN biopsies were followed by ALN dissection, including level I and II nodes. Micrometastasis or isolated tumor cell cases were excluded in this study.

Methods

PET-CT Imaging

All patients underwent a high-resolution preoperative PET-CT examination (Advance Nxi; GE Medical, Milwaukee, WI, USA). The patients were asked to fast for at least 6 h before the examination. Serum glucose levels were measured to ensure euglycemia ($<$120 mg/dl). Five millicuries of FDG were then injected with saline infusion. One hour after the injection, a whole-body scan and abdominal tomoscintigraphy were systematically performed in the supine position, followed by thoracic tomoscintigraphy in the prone position with the arms in extension. The standard uptake value (SUV) was decay-corrected tissue activity divided by the injected dose per patient body and was calculated using the following formula: SUV = activity in region of interest/decay factor of F-18 (MBq/ml)/injected dose (MBq/kg body weight).

SLN biopsy

After the induction of general anesthesia, patients received a subdermal injection of 5 ml of isosulfan blue dye below the periareolar skin, followed by breast massage for 5 min. Five minutes after the injection, an SLN biopsy was performed through an incision in accordance with ALN dissection just below the axillary hairline. The SLN was located by following a blue lymphatic channel to the lymph node. SLN biopsy was followed by standard ALN dissection.

Histopathologic Evaluation

Each half-sentinel node was sectioned at 3 mm intervals. Each 3 mm section was analyzed by four additional levels of 150 μm and four parallel sections. One level was used for hematoxylin and eosin staining. The size of nodal metastases was estimated with an eyepiece micrometer. Immunohistochemical staining was not performed rountinely.

Analysis

The evaluation of results was based on the calculated sensitivity, specificity and accuracy relative to the histopathologic status of the ALNs, as follows: sensitivity, TP/(TP + FN); specificity, TN/(TN + FP); positive predictive value, TP/(TP + FP); negative predictive value, TN/(TN + FN); and accuracy, (TP + TN)/(TP + FP + FN + TN), where TP is the true-positive, TN the true-negative, FP the false-positive and FN the false-negative.

The diagnostic accuracies of the non-invasive methods (mammography, breast sonography and PET-CT) and ALN involvement were evaluated applying receiver operating characteristic (ROC) curve and under the curve areas.

RESULTS

Characteristics of Patients

During the study period, 108 patients were enrolled. The patient demographics and tumor characteristics are listed in Table 1. The patients' mean age was 48.6 years (range, 27–75 years) and the mean tumor size was 19.2 mm (range,

Table 1. Characteristics of patients

Characteristics	No. of patients (%)
All cases	108 (100)
Age (years)	
Mean	48.6
Range	27–75
Tumor size (mm)	
Mean	19.2
Range	3–70
Histology	
Ductal	100 (92.6)
Lobular	1 (0.9)
Others	7 (6.5)
Estrogen receptor status	
Positive	65 (60.2)
Negative	43 (39.8)
Progesterone receptor status	
Positive	59 (54.6)
Negative	49 (45.4)

3–70 mm). One hundred patients (92.6%) had invasive ductal carcinoma, one patient (0.9%) had lobular carcinoma and seven patients (6.5%) had other tumor types (six mucinous carcinomas and one medullary carcinoma). Estrogen receptor status was positive in 65 patients (60.2%) and progesterone receptor status was positive in 59 patients (54.6%). Seventy-seven patients (71.3%) were clinical stage T1, 29 patients were T2 (26.9%) and 2 patients were T3 (1.8%). Metastasis was found in the ALNs of 33 patients (30.6%). Eighteen patients (54.5%) had clinical stage N1, 10 patients (30.3%) had N2 and 5 patients (15.2%) had N3 disease.

Comparative Detection Performance of Non-Invasive Methods and SLN Biopsy in Breast Cancer

The SUV of ALNs ranged from 0.00 to 7.01. The SUV of the ALN cut-off value gained by the ROC curve was 0.6400 (Table 2). PET-CT was positive if the SUV was ≥0.64, and the PET-CT sensitivity and specificity were 48.5% and 84%, respectively (Fig. 1).

As shown in Table 3, mammography, breast sonography, PET-CT and an SLN biopsy sensitivities for ALNs were 33.3%, 51.5%, 48.5% and 78.8%, respectively. The specificity of mammography, breast sonography, PET-CT and SLN biopsy for ALNs was 96%, 89.3%, 84% and 98.7%, respectively. The accuracy of PET-CT (73.2%) was lower than the other diagnostic tools. A combination of non-invasive modalities had a sensitivity of 63.6%, a specificity of 78.6% and an accuracy of 74.1%.

Table 2. Coordinates of the curve

Positive if greater than or equal to (a)	Sensitivity	1-specificity
−1.0000	1.000	1.000
0.3000	0.515	0.187
0.6050	0.485	0.173
0.6400	0.485	0.160
0.6850	0.455	0.160
0.7500	0.455	0.147
0.8500	0.455	0.107
0.9500	0.455	0.067
1.0500	0.424	0.053
1.1300	0.424	0.040
1.1800	0.394	0.040
1.2450	0.364	0.040
1.2950	0.333	0.040
1.3950	0.242	0.027
1.5450	0.212	0.027
1.7300	0.182	0.027
1.8800	0.152	0.027
2.0000	0.121	0.027
2.1300	0.091	0.027
2.3450	0.091	0.013
2.7650	0.061	0.013
3.9000	0.030	0.013
5.1200	0.000	0.013
6.4400	0.000	0.000

(a) The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

As shown by the ROC curves continuously obtained from the three imaging modalities and the SLN biopsy for the involvement of ALNs (Fig. 2), the area under the curve of mammography, breast sonography, PET-CT and SLN biopsy was 0.647, 0.704, 0.662 and 0.887, respectively (Table 4).

DISCUSSION

The presence of ALN metastases is commonly accepted as the most important prognostic factor in patients with breast cancer. In general, adjuvant chemotherapy is recommended in patients with ALN metastases. It has been suggested that detection of tiny foci of disease in ALNs may be important in determining prognosis and treatment. It is now accepted that SLN biopsy allows ALN dissection to be carried out selectively, rather than routinely (14). However, complications following ALN dissection and radiation therapy have been reported to occur in 40–70% of all patients. These

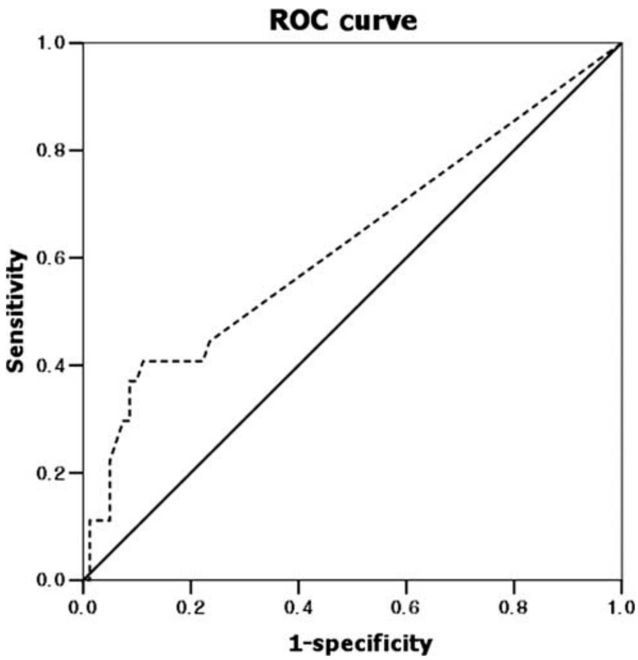

Figure 1. ROC curves obtained from SUV of ALNs in PET-CT. ROC, receiver operating characteristic; SUV, standard uptake value; ALNs, axillary lymph nodes; PET-CT, positron emission tomography-computed tomography.

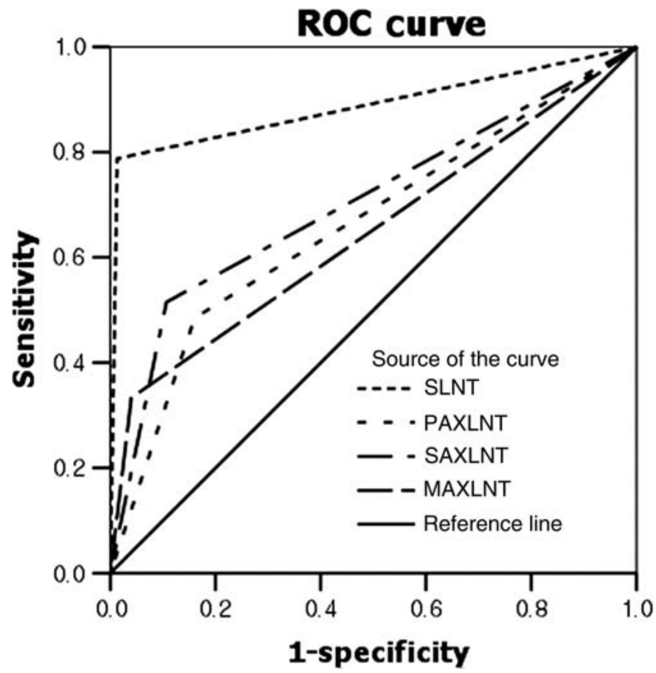

Figure 2. ROC curves obtained from three imaging modalities and SLN biopsy for the involvement of ALNs. SLN, sentinel lymph node.

complications include seromas, infections, pain, arm edema, breast edema or nerve injuries (15,16).

Non-invasive imaging techniques with sufficient sensitivity in detecting ALN metastases would prevent patients without lymph node metastases from suffering these complications. Classical non-invasive imaging techniques for detecting ALN metastases are mammography and breast sonography. In addition, PET-CT has also been widely used. PET-CT is an imaging method that provides a quantitative portrayal of the *in vivo* biodistribution of a radioactive tracer, such as the glucose analog 18F-FDG (17).

Studies of ALN staging by PET-CT have reported sensitivities of between 25% and 100% (18). It is that axillary surgery would be unnecessary in patients with negative scans of the axilla, with resulting clinical and economic benefits. In a study of 117 patients, Schirrmeister et al. (3) noted that, although PET was accurate in screening for lymph node metastasis, there was a false-negative rate of 20% and an overall sensitivity of 80% in detecting nodal

Table 3. Comparative detection performance of individual diagnostic modalities

	ALN(+)	ALN(−)	Total	Sensitivity (%)	Specificity (%)	Accuracy (%)
Mammo-positive	11	3	14	33.3	96	76.9
Mammo-negative	22	72	94			
BSG-postitive	17	8	25	51.5	89.3	77.8
BSG-negative	16	67	83			
PET-CT-positive	16	12	28	48.5	84	73.2
PET-CT-negative	17	63	80			
SLN-positive	26	1	27	78.8	98.7	92.6
SLN-negative	7	74	81			
M + BSG + P-positive	21	16	37	63.6	78.6	74.1
M + BSG + P-negative	12	59	71			
Total	33	75	108			

ALN, axillary lymph node; BSG, breast sonogram; M, mammogram; P, PET-CT; SLN, sentinel lymph node biopsy.

Table 4. Area under the curve of individual diagnostic methods

Test result variable(s)	Area	Std error	Asymptotic sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
PET-CT	0.662	0.060	0.007	0.545	0.780
SLN biopsy	0.887	0.044	0.000	0.802	0.973
Mammography	0.647	0.062	0.015	0.525	0.769
Breast sonography	0.704	0.059	0.001	0.588	0.820

disease. Greco et al. (19) suggested that FDG-PET could avoid histologic assessment of ALN status in patients with early-stage breast cancer (stage T1); however, the results of our study do not support this view.

We evaluated PET-CT, mammography and breast sonography in the detection of ALN metastases in patients with early-stage breast cancer undergoing SLN biopsy. The sensitivity of PET-CT was only 48.5%, using ALN dissection and histologic examination as a reference. The sensitivity of PET-CT was lower than breast sonography (51.5%). In addition, the specificity of PET-CT was 84%, which was also lower than breast sonography (89.3%) and mammography (96%). Therefore, the accuracy of PET-CT (73.2%) was lower than breast sonography (77.8%) and mammography (76.9%). The area under the curve gained from the ROC (0.662) was also a lower value than breast sonography (0.704). This result of the study clearly indicates that PET-CT does not have the spatial resolution to assess the axilla accurately. Preferably, among non-invasive methods of detecting ALN metastasis, breast sonography was the most effective diagnostic value as our result; however, it is also insufficient instead of SLN biopsy or ALN dissection.

Ohta et al. (20) investigated the efficacy of PET-CT alone, breast sonography alone and the two modalities combined in the detection of ALN metastatic disease. The combination of PET-CT and breast sonography had the best overall accuracy at 85%, followed by PET-CT alone (82%) and breast sonography alone (79%).

In the present study, the combination of mammography, breast sonography and PET-CT had a sensitivity, specificity and accuracy of 63.6%, 78.6% and 74.1%, respectively. Combination of the three diagnostic modalities was more sensitive than breast sonography alone. However, accuracy was lower than breast sonography alone, by reason of low specificity (78.6%). Although the accuracy of the combination modality was low, it was higher than PET-CT alone. This result means that PET-CT alone for ALN staging in early breast cancer is not reliable. Furthermore, even if we use a combination modality composed of three non-invasive diagnostic imaging techniques, it cannot substitute with an invasive method, such as SLN biopsy or ALN dissection.

In conclusion, breast sonography for ALN staging in early breast cancer had high diagnostic accuracy in non-invasive methods. The combination of mammography, breast sonography and PET-CT leads to an increase in sensitivity, but does not lead to an increase in accuracy. Therefore, a non-invasive method alone is not possible for ALN staging in early breast cancer.

CONCLUSION

In early breast cancer, PET-CT is not a reliable non-invasive test of ALN involvement that can replace ALN dissection or SLN biopsy before decisions are made on appropriate systemic interventions. At present, no non-invasive imaging modality exists that screens the axilla with sufficient sensitivity. Therefore, histologic evaluation of ALN status is still required for the detection of lymph node metastases. A combination of non-invasive modalities can more closely approximate an invasive method for detecting ALN metastasis with respect to sensitivity.

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Conflict of interest statement

None declared.

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