^{18}F-FDG Uptake by Metastatic Axillary Lymph Nodes on Pretreatment PET/CT as a Prognostic Factor for Recurrence in Patients with Invasive Ductal Breast Cancer

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This study assessed the maximum standardized uptake value of metastatic axillary lymph nodes in patients with invasive ductal breast cancer (IDC) to determine the pretreatment prognostic value of ^{18}F-FDG PET/CT for disease-free survival (DFS). **Methods:** Sixty-five female IDC patients who had undergone pretreatment ^{18}F-FDG PET/CT and had pathologically confirmed axillary lymph node involvement without distant metastasis were enrolled. All patients showed complete remission after first-line treatment. To obtain nodal SUVmax, a transaxial image representing the highest ^{18}F-FDG uptake was carefully selected and a region of interest was manually drawn on the ^{18}F-FDG–accumulating lesion. Clinicopathologic parameters such as age, TNM stage, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 status, and primary-tumor and nodal SUVmax on PET were analyzed for their usefulness in predicting recurrence. Combinatorial effects and interactions between variables that were significant by univariate analysis were examined using multivariate Cox proportional-hazards models. **Results:** Twelve of 65 patients (18.5%) experienced recurrence during follow-up (median follow-up, 36 mo; range, 21–57 mo). Nodal SUVmax was significantly higher in patients with recurrence than in those who were disease-free (recurrence group: 5.2 ± 2.3, vs. disease-free group: 1.9 ± 1.9, $P < 0.0001$). A receiver-operating-characteristic curve demonstrated a nodal SUVmax of 2.8 (sensitivity, 91.7%; specificity, 86.8%; area under the curve, 0.890) to be the optimal cutoff for predicting DFS. Univariate analysis revealed that T stage, N stage, estrogen receptor status, and primary-tumor and nodal SUVmax correlated significantly with DFS. Among these 5 variables, only nodal SUVmax was found to be a single determinant of DFS by multivariate analysis (hazard ratio, 31.54; 95% confidence interval, 2.66–373.39; $P = 0.0065$). **Conclusion:** Nodal SUVmax on pretreatment ^{18}F-FDG PET/CT may be an independent prognostic factor for disease recurrence in patients with IDC.

Key Words: ^{18}F-FDG PET/CT; lymph nodes; SUV; breast cancer; prognosis

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According to the American Cancer Society, breast cancer is the most frequently diagnosed solid malignancy in women in the United States and the second most common cause of cancer-related mortality. It was estimated that 230,480 new cases of invasive breast cancer would be diagnosed in 2011 and that approximately 39,520 patients were expected to die from breast cancer (*1*). Although it is curable when detected early, about one third of women with breast cancer eventually die of the disease. However, breast cancer is a remarkably heterogeneous disease. Therefore, precise prediction of prognosis and selection of optimal treatment are important.

Traditionally, pathologic determination of tumor size, histologic tumor grade, axillary lymph node (LN) involvement, endocrine (hormonal) receptor status, and human epidermal growth factor receptor 2 (HER2) status have been used as prognostic factors for patients with breast cancer. Among these prognostic factors, it has long been recognized that involvement of locoregional LNs by metastatic carcinoma is one of the most important in breast cancer (*2,3*), because this factor is highly associated with subsequent development of distant metastases. Despite the prognostic value of LN metastasis, the precise preoperative status of LN metastasis can be difficult to gauge.

PET with ^{18}F-FDG has been widely used in clinical practice for diagnosis, staging, treatment monitoring, and detection of disease recurrence in breast cancer patients (*4*). ^{18}F-FDG PET enables the semiquantitative metabolic characterization of tissues by calculating the degree of ^{18}F-FDG uptake, known as standardized uptake value (SUV), which may help to predict tumor behavior. ^{18}F-FDG PET/CT has also been suggested to have a considerable prognostic util-

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ity in various cancers (*5–9*). Previously, we investigated the prognostic value of ^{18}F-FDG uptake by the primary tumor in patients with invasive ductal breast cancer (IDC). In that study, primary-tumor maximum SUV (SUVmax) exhibited a strong relationship with known prognostic parameters of breast cancer and could be used as a good surrogate marker for the prediction of progression in patients with IDC (*10*). Recently, a few studies have shown that ^{18}F-FDG uptake by LNs as well as by the primary tumor is an important prognostic factor in patients with oral cavity squamous cell carcinoma (*11*) and locally advanced cervical cancer (*12*). In patients with breast cancer, ^{18}F-FDG PET/CT is not yet sensitive enough to replace sentinel node biopsy to detect axillary LN involvement, but the high specificity of ^{18}F-FDG PET/CT is useful in determining the extent of local and systemic disease (*13*). As to its prognostic value, however, the degree of ^{18}F-FDG uptake in metastatic axillary LNs on ^{18}F-FDG PET/CT has not been fully investigated in patients with IDC.

The aim of the present study was to investigate the relationship between nodal SUVmax and known prognostic parameters of breast cancer. We also sought to determine the prognostic value of nodal SUVmax for disease-free survival (DFS) in patients in whom primary IDC with axillary LN involvement had been diagnosed.

MATERIALS AND METHODS

Patients

From June 2006 to March 2009, 184 patients underwent ^{18}F-FDG PET/CT to determine the clinical stage of primary IDC before initial treatment. Of these patients, 84 patients were pathologically confirmed to have axillary LN involvement and received standard treatment in our institution. Of the 84 patients, 15 whose disease progressed or persisted while they were undergoing neoadjuvant chemotherapy and surgery were excluded. We also excluded 4 patients with distant metastasis found at the period of initial diagnosis. Finally, 65 women (mean age, 49.4 ± 10.0 y; range, 31–71 y) were enrolled in this study. In all patients, breast-conserving surgery or modified radical mastectomy with axillary LN dissection was performed, depending on tumor size, location, multicentricity, patient preference, and the result of sentinel LN biopsy. Systemic chemotherapy was given with a taxane-based regimen consisting of doxorubicin (Adriamycin; Pharmacia) and cyclophosphamide followed by docetaxel, preoperatively or postoperatively. Radiotherapy was given after surgery, and hormonal therapy was given to patients with hormonal receptor–positive breast cancer. Patients with HER2–positive breast cancer were treated with trastuzumab (Herceptin; Genentech) for 1 y postoperatively. In the follow-up period, mammography, breast sonography, MRI, CT, whole-body bone scanning, and ^{18}F-FDG PET/CT were used for the diagnosis of disease recurrence, metastasis, and progression. All suggestive lesions were confirmed histologically by fine-needle aspiration cytology. The nodal SUVmax was compared with clinicopathologic parameters including tumor size, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, axillary LN metastasis, and stage. Tumors were classified and staged according to the World Health Organization classification and the TNM staging system. In patients receiving neoadjuvant chemotherapy, pathologic T and N staging may be influenced by systemic therapy before surgical procedures; thus, for these patients we used the pretreatment clinical staging system. The study was approved by the Ethics Committee of the hospital.

^{18}F-FDG PET/CT Acquisition Protocol

All patients fasted for at least 6 h, and blood glucose levels were checked before the administration of ^{18}F-FDG. Patients with elevated blood glucose levels had their examinations rescheduled and blood glucose concentration was managed to be less than 150 mg/dL in all subjects. Approximately 8.1 MBq of ^{18}F-FDG per kilogram of body weight were injected intravenously, and patients were advised to rest for 1 h before acquisition of the PET/CT image. PET/CT scans were performed using a Reveal RT-HiREZ 6-slice CT apparatus (CTI Molecular Imaging) and a 16-slice CT Discovery STE apparatus (GE Healthcare). Before the PET scan, for attenuation correction a low-dose CT scan was obtained without contrast enhancement from the skull vertex to the knee, with the patient supine and breathing quietly. PET scans with a maximum spatial resolution of 6.5 mm (Reveal PET/CT) and 5.5 mm (Discovery PET/CT) were also obtained from the skull vertex to the knees, at 3 min per bed position. PET images obtained by the Reveal PET/CT and Discovery PET/CT scanners were reconstructed with a 128 × 128 matrix, an ordered-subset expectation maximum iterative reconstruction algorithm (4 iterations, 8 subsets), a gaussian filter of 5.0 mm, and a slice thickness of either 3.0 mm (Reveal PET/CT) or 3.27 mm (Discovery PET/CT).

Image Analysis

The PET/CT images were interpreted by 2 experienced nuclear medicine physicians, and a final consensus was reached for all patients. Regions of interest were manually placed over the area of maximal activity on slices of the primary breast tumor lesions and axillary LNs in attenuation-corrected images, and the SUVmax within the region of interest was obtained. Especially in the case of low ^{18}F-FDG uptake (SUVmax $<$ 2) on the axillary area, the region of interest was carefully drawn over the corresponding axillary LNs on CT images. The SUVmax was calculated using the following formula: SUVmax = maximum activity in region of interest (MBq/g)/[injected dose (MBq)/body weight (g)].

Immunohistochemistry

Immunohistochemical staining was performed on tissue slices from formalin-fixed, paraffin-embedded representative breast tumors. ER, PR, and HER2 expression was assessed by immunohistochemistry using commercial monoclonal antibodies for ER (1:200 dilution; Neomarker), PR (1:4,500 dilution; Neomarker), and HER2 (1:300 dilution; DakoCytomation); the iView DAB detection kit (Ventana Medical Systems) was used as a secondary antibody. The results were recorded according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists (*14*). Cases with a HER2 immunohistochemical staining score of more than 2 were tested by HER2 gene amplification using the fluorescence in situ hybridization method. HER2 positivity was defined as an immunohistochemical staining score of 3+ or, in the case of an immunohistochemical staining score of 2+, as positive findings on fluorescence in situ hybridization.

Statistical Analyses

Numeric data are expressed as the mean ± SD. To identify an optimal cutoff for primary-tumor and nodal SUVmax for the pre-

diction of progression, receiver-operating-characteristic (ROC) analysis was performed. Moreover, to reveal the prognostic trend according to nodal SUVmax, patients were divided into groups according to 2 tentative thresholds (2.5 and 5.0): group 1 (nodal SUVmax $<$ 2.5), group 2 (2.5 $\leq$ nodal SUVmax $<$ 5.0), and group 3 (nodal SUVmax $\geq$ 5.0). DFS was calculated using the Kaplan–Meier method. The Cox proportional-hazards model was used for the multivariate analyses. The additional prognostic value of nodal SUVmax was evaluated by means of ROC, integrated discrimination improvement (IDI), and net reclassification improvement (NRI) (*15*). SAS software, version 9.2 (SAS Institute), was used for the statistical analysis. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

The characteristics of the study participants are listed in Table 1. Among the 65 patients, 10 (15.4%) received neoadjuvant chemotherapy before surgical treatment, 63 (96.9%) received adjuvant chemotherapy, and 38 (58.5%) received radiation therapy. N stage was categorized by the staging system of the American Joint Committee on Cancer: 40 patients (61.5%) in N stage 1, 16 (24.6%) in N stage 2, and 9 (13.8%) in N stage 3. There were 36 patients (55.4%) in stage II and 29 (44.6%) in stage III IDC (Table 1). At the time of analysis, no patients had died during the median follow-up of 36 mo (range, 21–57 mo). Among the 65 patients, 53 (81.5%) were disease-free and 12 (18.5%) had disease recurrence. Three patients showed locoregional recurrence, and 9 patients showed systemic recurrence. Median DFS was 13.5 mo (range, 4–29 mo) in patients with disease recurrence.

Relationship Between Nodal SUVmax and Clinicopathologic Parameters

Table 1 shows nodal SUVmax differences according to the clinicopathologic parameters. The mean nodal SUVmax of the 65 patients was 2.5 $\pm$ 2.3 (range, 0.5–12.3) and was significantly higher in ER-negative tumors (P = 0.0011) and PR-negative tumors (P = 0.0046) than in ER-positive tumors and PR-positive tumors, respectively. The mean nodal SUVmax was significantly different among the N-stage groups (P = 0.003) and was increased by increases in N stage. Also, mean nodal SUVmax was significantly different among the T-stage groups (P = 0.043). However, there was no significant difference in nodal SUVmax according to HER2 status (P = 0.5544). The mean nodal SUVmax was significantly higher in stage III (3.3 $\pm$ 2.6) than in stage II (1.9 $\pm$ 1.9) (P = 0.011).

DFS Analysis

Nodal and primary-tumor SUVmax was significantly higher in patients with disease recurrence than in those who were disease-free. The mean nodal SUVmax of the disease-free group was 1.9 $\pm$ 1.9, and that of the recurrence group was 5.2 $\pm$ 2.3 (95% confidence interval of difference, 2.0–4.6, $P < 0.0001$). The mean primary-tumor SUVmax of the disease-free group was 5.5 $\pm$ 3.5, and that of the recurrence group was 8.9 $\pm$ 5.8 (95% confidence interval of difference, 0.7–5.9, P = 0.0128) (Fig. 1).

TABLE 1
Patient Characteristics and Comparisons of Nodal SUVmax According to Clinicopathologic Parameters

Characteristic	No. of patients (%)	Nodal SUVmax* (mean $\pm$ SD)	*P*
T stage†			0.043
T1	29 (44.6)	1.8 $\pm$ 1.6	
T2	29 (44.6)	2.9 $\pm$ 2.8	
T3	4 (6.2)	4.9 $\pm$ 2.3	
T4	3 (4.6)	3.5 $\pm$ 2.3	
ER			0.0011
Positive‡	48 (73.8)	2.0 $\pm$ 1.9	
Negative	17 (26.2)	4.1 $\pm$ 2.8	
PR			0.0046
Positive‡	46 (70.8)	2.0 $\pm$ 1.9	
Negative	19 (29.2)	3.8 $\pm$ 3.1	
HER2§			0.5544
Positive‖	20 (30.8)	2.8 $\pm$ 3.0	
Negative	45 (69.2)	2.4 $\pm$ 2.0	
N stage†			0.003
N1	40 (61.5)	1.8 $\pm$ 1.8	
N2	16 (24.6)	3.2 $\pm$ 2.2	
N3	9 (13.8)	4.5 $\pm$ 3.4	
Stage†			0.011
II	36 (55.4)	1.9 $\pm$ 1.9	
III	29 (44.6)	3.3 $\pm$ 2.6	
Disease group			$<$0.0001
Disease-free	53 (81.5)	1.9 $\pm$ 1.9	
Recurrence	12 (18.5)	5.2 $\pm$ 2.3	

*SUVmax of axillary LN.
†Staging system of American Joint Committee on Cancer (seventh edition).
‡According to immunohistochemical staining for ER/PR.
§Human epidermal growth factor receptor 2.
‖Immunohistochemical 3+ or, in case of immunohistochemical 2+, positive on fluorescence in situ hybridization for HER2 gene amplification.

An ROC curve demonstrated that a nodal SUVmax of 2.8 was the optimal cutoff for predicting DFS (sensitivity, 91.7%; specificity, 86.8%; area under the curve, 0.890; SE, 0.0633) (Fig. 2A). Meanwhile, an ROC curve demonstrated that a primary-tumor SUVmax of 6.9 was the optimal cutoff for predicting DFS (sensitivity, 58.3%; specificity, 75.5%; area under the curve, 0.699; SE, 0.0830) (Fig. 2B).

Kaplan–Meier analysis revealed that T stage (1, 2 vs. 3, 4), N stage (1 vs. 2, 3), ER status (+ vs. −), primary-tumor SUVmax ($\leq$6.9 vs. $>$6.9), and nodal SUVmax ($\leq$2.8 vs. $>$2.8) were significantly correlated with DFS (Table 2). However, age ($<$45 vs. $\geq$45 y) and HER2 status (+ vs. −) were not associated with DFS. A statistically significant trend toward higher recurrence in a stepwise manner in accordance with groups with higher nodal SUVmax was revealed not only for 2 groups by optimal cutoff (2.8) (Fig. 3A) but also for the entire patient population by 2 tentative cutoffs (Fig. 3B).

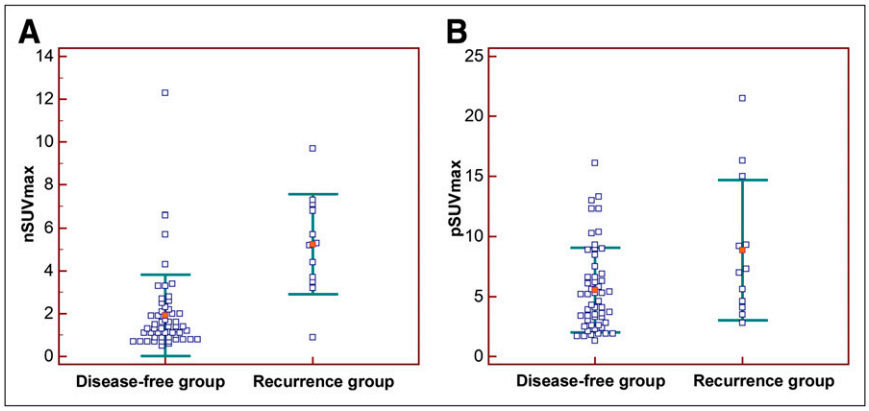

FIGURE 1. Comparison of SUVmax between disease-free and recurrence groups of IDC patients. (A) SUVmax of metastatic axillary LN (nSUVmax) was significantly higher in patients with disease recurrence than in patients who were disease-free ($P < 0.001$). Mean nodal SUVmax (1.9 in disease-free group and 5.2 in recurrence group) are indicated with orange boxes. (B) Primary-tumor SUVmax (pSUVmax) was significantly higher in patients with disease recurrence than in patients who were disease-free ($P = 0.0128$). Mean primary-tumor SUVmax (5.5 in disease-free group and 8.9 in recurrence group) is indicated with orange boxes. Error bars represent SD.

In the multivariate analysis using Cox proportional-hazards models, only nodal SUVmax was found to be a single determinant of DFS (hazard ratio, 31.54; 95% confidence interval, 2.66–373.39; $P = 0.0065$) (Table 2).

In patients receiving neoadjuvant chemotherapy, the status of axillary LNs may be different after systemic therapy. Thus, subgroup analysis was performed on patients who underwent surgical treatment initially before any systemic therapy. Among these 55 patients, 49 (89.1%) were disease-free and 6 (10.9%) had disease recurrence. Also, an ROC curve demonstrated a nodal SUVmax of 2.8 to be the optimal cutoff for predicting DFS (sensitivity, 83.3%; specificity, 87.8%; area under the curve, 0.832; SE, 0.0040) and an ROC curve demonstrated a primary-tumor SUVmax of 3.4 to be the optimal cutoff for predicting DFS (sensitivity, 100%; specificity, 36.7%; area under the curve, 0.599; SE, 0.0969). Univariate analysis by Kaplan–Meier analysis revealed that nodal SUVmax ($\leq$2.8 vs. $>$2.8) correlated significantly with DFS. However, primary-tumor SUVmax ($\leq$3.4 vs. $>$3.4) was not associated with DFS. Among 4 variables—pathologic T stage [1, 2 vs. 3, 4], pathologic N stage (representing the number of involved axillary LNs) [1 vs. 2, 3], ER status [+ vs. −], and nodal SUVmax [$\leq$2.8 vs. $>$ 2.8])—only nodal SUVmax was found to be a single determinant of DFS by multivariate analysis (hazard ratio, 20.53; 95% confidence interval, 1.54–273.91; $P = 0.0230$) (Table 3).

For the model incorporating established risk factors (T stage, N stage, and ER status) in all 65 patients, the c-statistic for DFS was 0.903 without nodal SUVmax and 0.946 with nodal SUVmax ($P = 0.123$, Fig. 4). Although the result of the traditional approach using ROC comparison was not significant, IDI and NRI showed significant improvement in the accuracy of risk prediction for DFS rates when nodal SUVmax was added to established risk factors ($P = 0.001$ for IDI, $P < 0.001$ for NRI).

DISCUSSION

Many studies have conclusively revealed that breast cancer patients who have histologically confirmed LN involvement have a significantly poorer prognosis than those without nodal metastases (*16–18*). However, an accurate LN status can be obtained only after surgery, which is frequently associated with significant morbidity and mortality. In addition, this factor does not completely explain the extent of variability in the clinical course, because breast cancer is composed of a growing number of recognized biologic subtypes. In contrast, not only is ^{18}F-FDG PET a noninvasive diagnostic modality, but ^{18}F-FDG uptake also indicates the degree of tumor glucose metabolism,

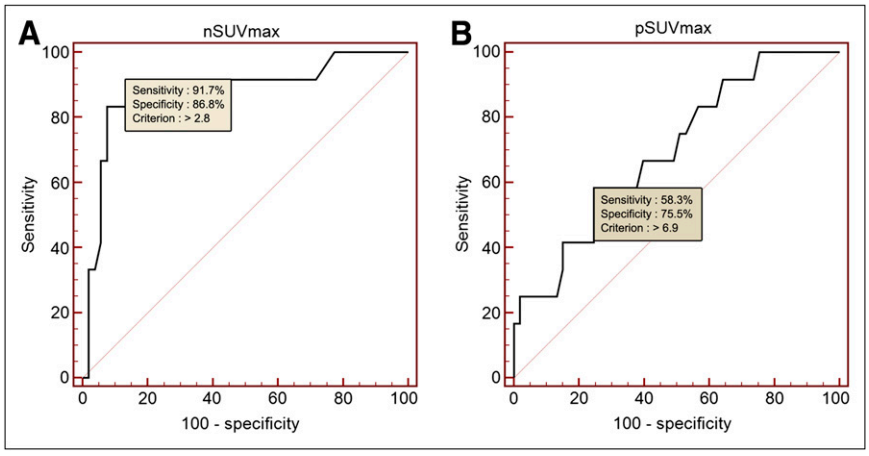

FIGURE 2. ROC curve for predicting recurrence in patients with invasive ductal breast cancer. (A) Nodal SUVmax: optimal cutoff, 2.8; area under curve, 0.890; SE, 0.0633. (B) Primary-tumor SUVmax: optimal cutoff, 6.9; area under curve, 0.699; SE, 0.0830.

TABLE 2
Factors Associated with DFS

Risk factor for recurrence	Total no. of patients	Patients with disease recurrence	Median DFS (mo)	Univariate analysis			Multivariate analysis		
				P	Hazard ratio	95% CI* for hazard ratio	*P*	Hazard ratio	95% CI* for hazard ratio
Age (y)									
<45	21	3	34.0	—	1.00	—			
≥45	44	9	34.0	0.6071	1.41	0.42–4.73			
T stage									
T1, T2	58	8	34.0	—	1.00	—	—	1.00	—
T3, T4	7	4	22.0	0.0029	5.10	0.70–37.14	0.8573	1.16	0.23–5.97
N stage									
N1	40	3	35.5	—	1.00	—	—	1.00	—
N2, N3	25	9	30.0	0.0055	5.20	1.61–16.85	0.9797	0.98	0.15–6.27
ER									
Positive	48	5	35.5	—	1.00	—	—	1.00	—
Negative	17	7	32.0	0.0017	5.17	1.30–20.57	0.2805	2.21	0.53–9.25
HER2									
Negative	45	9	34.0	—	1.00	—			
Positive	20	3	34.0	0.6472	0.74	0.28–2.51			
Primary-tumor SUVmax†									
≤6.9	45	5	35.0	—	1.00	—	—	1.00	—
>6.9	20	7	29.0	0.0121	3.88	1.08–13.99	0.9757	1.02	0.27–3.91
Nodal SUVmax‡									
≤2.8	47	1	36.0	—	1.00	—	—	1.00	—
>2.8	18	11	22.0	<0.0001	38.95	9.94–152.59	0.0065	31.54	2.66–373.39

*Confidence interval.
†SUVmax of primary tumor.
‡SUVmax of axillary LN.

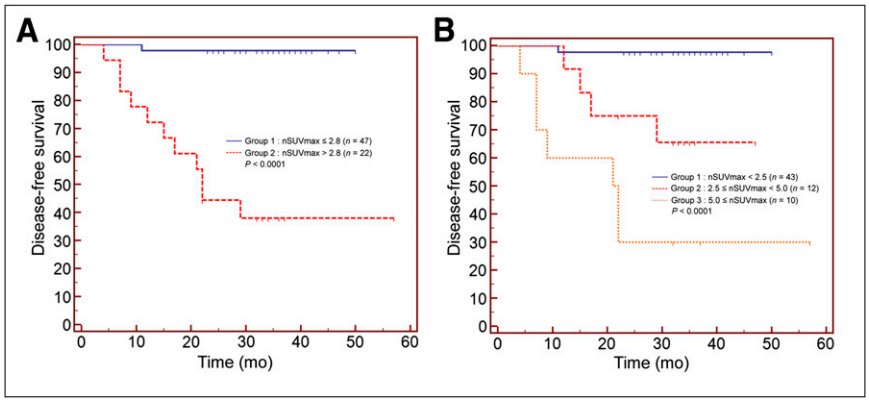

FIGURE 3. Kaplan–Meier analysis of DFS according to nodal SUVmax. (A) Two groups by optimal cutoff (2.8). (B) Three groups by 2 tentative thresholds (2.5 and 5.0).

which represents the aggressiveness of the malignant lesion (*19*). Therefore, quantitative ^{18}F-FDG uptake can be a valuable adjunct to conventional preoperative clinical assessment.

There have been several reports suggesting that breast cancers in which the primary tumor shows high ^{18}F-FDG uptake have higher relapse and mortality rates than breast cancers with low uptake (*20–22*). In our previous study (*10*), the group with a high primary-tumor SUVmax had a significantly worse prognosis, but LN status was the most powerful prognostic factor since all patients with disease progression were LN-positive. Although the prognostic value of nodal SUVmax was not evaluated in the previous study, we found an interesting point. Among patients with involved LNs, those who were destined to develop disease recurrence had a significantly higher nodal SUVmax than did those who were to remain disease-free. Inoue et al. revealed that primary-tumor SUVmax was marginally significant in multivariate analysis, but the combination of primary-tumor SUVmax and focal ^{18}F-FDG uptake in the axillary region was a highly significant prognostic factor, being independent of T and N factors in multivariate analysis (*22*). However, there was no definite cutoff for ^{18}F-FDG uptake in the axillary region. The results of our study showed that primary-tumor SUVmax was not significant but nodal SUVmax was the only predictive factor for DFS in multivariate analysis, and the optimal cutoff for nodal SUVmax to differentiate progression was 2.8.

Why might nodal SUVmax help predict outcomes in the absence of a major diagnostic modality for primary staging? First, many authors have reported that increased tumoral uptake of ^{18}F-FDG correlates closely with the density of viable carcinoma cells, microvessel density, and proliferative activity (*23–25*). These reports suggest that glucose hypermetabolism detected by ^{18}F-FDG using PET would reflect the dense proliferation of highly malignant cells. Second, LN involvement has been known to be the most important prognostic factors in breast cancer. We postulated that these combinational effects highlight the prognostic significance of nodal SUVmax. Recent studies on oral cavity squamous cell carcinoma and locally advanced cervical cancer indicate that high ^{18}F-FDG uptake by LNs predicts a worse outcome (*11,12*). In line with these reports, we presently report that high nodal SUVmax is significantly associated with poor prognosis in breast cancer patients.

The use of area under the ROC curve (AUC) in the prediction of binary events has achieved attractiveness, as the test characteristics of sensitivity and specificity are relevant to discriminating high-risk subjects from low-risk subjects. Analyzing differences in the AUC is a common method of comparing 2 models for prognostic risk prediction. Although having many advantages, AUC has some disadvantages in comparing these models. Typically, it is difficult for a new marker to significantly change the value of AUC (*26,27*). For this reason, Pencina et al. introduced IDI and NRI (*15*). The IDI measures the ability of the new model to improve average sensitivity without sacrificing average specificity. And NRI measures the correctness of reclassification of subjects based on their predicted probabilities of events using the new model with the option of imposing meaningful risk categories. Although difference in AUC was not statistically significant, IDI and NRI, which were presented to evaluate the added predictive ability of a new marker over traditional ROC comparison,

TABLE 3
Subgroup Multivariate Analysis of Participants Who Underwent Surgical Treatment Before Any Systemic Therapy

Variable	Hazard ratio	95% confidence interval	*P*
Pathologic T stage (1, 2 vs. 3, 4)	3.98	0.48–32.93	0.2028
Pathologic N stage (1 vs. 2, 3)	0.68	0.08–6.24	0.7379
ER status (+ vs. −)	0.61	0.10–3.78	0.5982
Nodal SUVmax (≤2.8 vs. >2.8)	20.53	1.54–273.91	0.0230

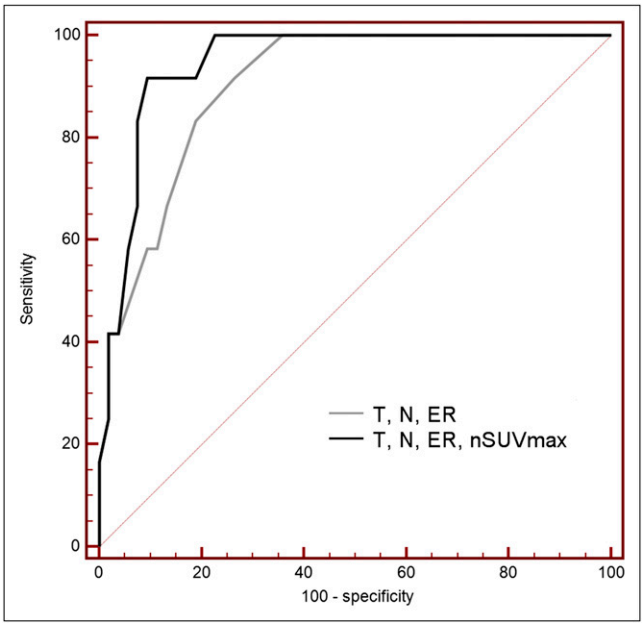

FIGURE 4. Graphs of ROC curve analysis show additional value of nodal SUVmax for predicting DFS rates. Curves are based on risk-prediction models incorporating established risk factors (T stage, N stage, and ER status) that either included nodal SUVmax (nSUVmax; black line) or did not (gray line). Although c-statistics of traditional approach using ROC comparison were not significant (0.903 for risk model without nodal SUVmax and 0.946 with nodal SUVmax, $P = 0.123$), IDI and NRI showed significant improvement in accuracy of risk prediction for DFS rates when nodal SUVmax was added ($P = 0.001$ for IDI, $P < 0.001$ for NRI).

showed a significant improvement in the accuracy of risk prediction for DFS rates when nodal SUVmax incorporated established risk factors (T stage, N stage, and ER status). These results suggest that PET findings at the axillary LN could provide useful information for risk stratification in patients with breast cancer. It might be possible to discriminate aggressive forms of cancers from indolent ones, as well as the stage, by ^{18}F-FDG PET/CT before primary systemic therapy. However, breast cancer is a remarkably heterogeneous disease. Therefore, various aspects of ^{18}F-FDG uptake can be shown according to histologic subtypes (*20*), and the prognosis of the breast cancer is also dependent on histologic subtypes (*28*). Since the entire patient population of this study was IDC patients with axillary LN involvement, our results cannot be generalized to every breast cancer patient and might be restricted to IDC patients.

Preclinical and clinical studies indicate that HER2 overexpression may have prognostic value. HER2 gene amplification or protein overexpression independently predicted decreased DFS time and lower overall survival rates (*29*). The results of our study, however, did not show a significantly shorter DFS by univariate analysis in patients who were HER2-positive. The lack of prognostic value for HER2 could be linked to trastuzumab treatment, which was administered to patients with HER2-positive breast cancer for 1 y postoperatively. In addition, coexisting negative prognostic variables may confound study results (e.g., ER status, tumor size, and LN involvement). Finally, the small number of enrolled patients and the relatively short-term follow-up periods can affect the prognostic value for HER2.

Our study had 3 main limitations. First, the fact that only node-positive patients were enrolled may limit the generalizability of our results and prevents the risk stratification from being applicable to patients without LN metastasis. Second, the SUV of small metastatic LNs may be underestimated because of partial-volume effects and the limited resolution of PET (*30*). ^{18}F-FDG uptake reflects both tumor biology and tumor size for lesions smaller than 2 cm. Because most metastatic LNs are small, nodal SUVmax can be underestimated. However, considering that only 1 (2%) of 47 patients with a low nodal SUVmax ($\leq$2.8) experienced disease recurrence during follow-up, and the significant prognostic trend according to nodal SUVmax categorization, the partial-volume effect was negligible in our study. On the other hand, nodal SUVmax in our study was derived from a single scan, and concerns have arisen about intraobserver or interobserver variability and reproducibility in the measurement of SUV (*31*) because it can be affected by several conditions. However, many reports have already proved that measurement of SUV is highly reproducible (*32–34*). Finally, we could not perform survival analysis and determine prognostic significance after relapse because follow-up periods were relatively short. Thus, further prospective multiinstitutional studies are required for nodal SUVmax to be accepted as a decisive prognostic factor for disease recurrence in IDC patients with axillary LN involvement.

CONCLUSION

The present study revealed that nodal SUVmax on ^{18}F-FDG PET/CT before initial treatment could be an independent prognostic factor for disease recurrence in IDC patients with axillary LN involvement. When combined with appropriate risk reduction strategies, the use of improved prognostic models based on PET findings may also benefit IDC patients with axillary LN involvement. Thus, ^{18}F-FDG PET/CT may be used as a method of risk stratification before surgery and can help in the choice of therapeutic strategies.

DISCLOSURE STATEMENT

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