Prediction of Extracapsular Invasion at Metastatic Sentinel Nodes and Non-sentinel Lymph Nodal Metastases by FDG-PET in Cases with Breast Cancer

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Abstract. *We have previously reported that the presence of an extracapsular invasion (ECI) at sentinel lymph nodes (SLNs) is a strong predictor of non-SLN metastasis in breast cancer. We hypothesized that ^{18}F-fluorodeoxyglucose (FDG) uptake by metastatic SLNs reflects invasive disease, or ECI. In this study, we evaluated the association of FDG uptake with ECI on SLNs and the possibility of FDG-positron-emission tomography (PET) assessment of axillary non-SLN metastases. We retrospectively investigated the cases of 156 consecutive patients with primary breast cancer who underwent SLN biopsy and FDG-PET preoperatively. Among 35 patients (22.4%) in whom the presence of SLN metastases was diagnosed, 10 cases (28.6%) had FDG uptake in the axillary lesion. The sensitivity, specificity, overall accuracy, and false-negative rates in the diagnosis of SLN status by FDG-PET were 28.6%, 99.2%, 83.3%, and 71.4%, respectively. The false-positive rate of FDG-PET evaluation was 0.8%. The 35 cases with lymph node metastases were divided into two groups based on the presence of FDG uptake in the axillary lesions. None of the clinicopathological features of the primary tumor were significantly associated with FDG uptake in the axillary lesion. The present analysis revealed that only tumor size of the metastatic lymph node was significantly associated with FDG uptake in the axillary lesion. The two groups were not significantly different in terms of presence of ECI and non-SLN metastasis. Among the 35 cases with SLN metastases, 13 cases (37.1%) had non-SLN metastasis. Only ECI was a predictor of non-SLN involvement. FDG uptake in the axilla was not associated with non-SLN metastasis in this study. In conclusion, FDG-PET evaluation of lymph nodes is not a sufficient indicator of ECI at SLN metastasis or non-SLN metastasis, suggesting that axillary lymph node dissection cannot be avoided. However, since the positive predictive value for SLN metastasis is high, positive FDG uptake in the axillary lesions may be useful for avoiding SLN biopsy.*

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Sentinel lymph node (SLN) biopsy has been developed as a minimally invasive operative procedure to precisely determine the presence of axillary lymph node metastases in patients with clinically negative nodes (1-6). Accurate intraoperative diagnosis of SLN metastasis enables for selection of patients who require axillary lymph node dissection (ALND), thus avoiding unnecessary additional surgery in patients with false-negative results. However, numerous studies have shown that SLNs may be the only positive lymph nodes in 40% to 70% of cases of node-positive breast cancer (3, 7-11). Thus, if patients without additional metastases in non-SLN after SLN biopsy could be accurately selected among the patients with positive SLNs, it might be possible to spare the axilla after SLN biopsy and avoid unnecessary axillary lymph node dissection in these selected patients (12-14). The recent results of the American College of Surgeons Oncology Group Z0011 trial suggested that some women would be safe from recurrence without further axillary treatment if they have fewer than three involved SLNs with no extracapsular spread (15). We previously reported that the presence of extracapsular invasion (ECI) at SLNs is a strong predictor of non-SLN metastasis in breast cancer (3, 4). The ability of metastatic nodes to recruit degradation factors that permit cancer cells to break through the lymph node capsule is an important process in lymphatic spread (3, 4). Thus, ECI may be a key process following distant lymph node metastasis.

In recent years, the clinical applications of positron-emission tomography (PET) have undergone explosive growth. PET using ^{18}F-fluorodeoxyglucose (FDG) is a non-invasive whole-body imaging technique used to evaluate

various kinds of malignancies, including breast cancer, for tumor staging and restaging, detection of recurrence, and monitoring treatment responses (16-20). FDG-PET can provide biological information on the tumor growth potential. Infiltrating ductal carcinoma has a higher level of FDG uptake and therefore is detected with significantly higher sensitivity than ductal carcinoma *in situ* (DCIS). We previously found that the presence of FDG uptake in the tumor can be considered a predictor for invasion in cases with DCIS by needle biopsy (unpublished data). We hypothesized that FDG uptake reflects invasive disease, or ECI, at metastatic SLNs. In this study, we evaluated the association of FDG uptake with ECI at SLNs and furthermore, evaluated the possibility of FDG-PET assessment of axillary non-SLN metastases.

Patients and Methods

We retrospectively investigated the cases of 156 consecutive patients with primary breast cancer who underwent SLN biopsy and FDG-PET preoperatively at the Department of General Surgical Science, Gunma University, Japan, from January 2010 to February 2015. All patients had undergone radical breast surgery. Patients with previously diagnosed breast cancer or incomplete clinical information were excluded, and male patients were excluded. Among the 156 patients, 35 (22.4%) had SLN metastases. In all 35 cases, the presence of lymph node metastasis was confirmed pathologically. None of the patients had received preoperative chemotherapy. Patients underwent FDG-PET/computed tomography as part of the routine standard-of-care, and no changes to the standard-of-care were made. The maximum standardized uptake value (SUV_{max}) of primary tumors was calculated in routine clinical fashion. Informed consent was obtained from all patients.

The details extracted from the database were the age, histological type, primary tumor size, lymphatic or vascular invasion, estrogen (ER) and progesterone (PgR) receptor expression status, human epidermal growth factor receptor 2 (HER2) score of the primary tumor, SUV_{max} of the primary tumor, axillary lymph node status, and visibility of the detected lesion by FDG-PET. The ER and PgR statuses were assessed by Allred scores, and Allred scores of 3 or higher were defined as ER- and PgR-positive.

Statistical analysis. The breast cancer cases with SLN metastasis were divided into two groups on the basis of the presence of FDG uptake in the axillary lesion. The cases with metastatic SLNs were then further divided into two groups based on the presence of metastases in the non-SLNs. We conducted a univariate statistical analysis using Fisher's exact test or the χ^2 test with Yates' correction. To compare the two groups, we used Student's *t*-test. Differences were considered significant when $p<0.05$.

Results

The presence of FDG uptake was associated with the size of tumor in metastatic SLNs, but not with ECI or non-SLN metastasis. In total, 156 cases were included in the analysis. In 35 patients (22.4%), the presence of SLN metastases was diagnosed by histological examination with standard hematoxylin and eosin staining. Among the 35 cases with SLN metastases, 10 (28.6%) had FDG uptake in the axillary lesion. As shown in Table I, the sensitivity, specificity, overall accuracy, and false-negative rates in the diagnosis of SLN status by FDG-PET were 28.6% (10/35), 99.2% (120/121), 83.3% (130/156), and 71.4% (25/35), respectively. The false-positive rate of FDG-PET evaluation was 0.8%. The mean SUV_{max} of metastatic SLNs was 0.6 (range=0-9.0) overall.

The 35 cases with lymph node metastases were divided into two groups based on the presence of FDG uptake in the axillary lesions. Table I shows the patient characteristics and summarizes the results of the univariate analysis conducted to determine the relationship between the clinicopathological variables and FDG uptake in the axillary lesions. As can be seen, none of the clinicopathological features of the primary tumor, including primary tumor size, SUV_{max} or biomarkers, was significantly associated with FDG uptake. The present analysis revealed that only the tumor size of the metastatic lymph node was significantly associated with FDG uptake in the axillary lesion. The presence of ECI or non-SLN metastasis was not significantly different between the two groups.

Non-SLN metastasis was associated with ECI, but not with FDG uptake in the axillary lesion. The 35 cases with metastatic SLNs were divided into two groups based on the presence of metastasis in the non-SLNs. Among the 35 cases with SLN metastases, 13 (37.1%) also had non-SLN metastasis. Table II shows the patients' and tumor characteristics and summarizes the results of the univariate and multivariate analyses conducted to determine the relationship between the clinicopathological variables and the presence of non-SLN metastasis. Age, histological grade, number of positive SLNs, ER status and HER2 status were not predictors of metastatic involvement of non-SLNs. In the univariate analysis, ECI and metastatic tumor size at the SLNs, lymphatic invasion and the histological type of the primary tumor were factors significantly associated with the presence of cancer cells in non-SLNs. Multivariate analysis demonstrated that only ECI was a predictor of non-SLN involvement. FDG uptake in the axilla was not associated with non-SLN metastasis in this study.

Discussion

FDG-PET has been widely used for diagnosing staging and recurrence in various types of cancers however, its diagnostic utility for cancer is controversial (16-20). There exist many reports of preoperative FDG-PET evaluation of patients with breast cancer. FDG-PET has been investigated for its accuracy in the axillary staging of operable primary breast cancer (11-16). FDG-PET has a high specificity but mediocre sensitivity for identifying axillary lymph node

Table I. *Patients' characteristics and clinicopathological features associated with ^{18}F-fluorodeoxyglucose (FDG) uptake in axillary lymph nodes. Values are expressed as the mean±SD, or frequency.*

Characteristic	FDG uptake in axilla		*p*-Value
	Present (n=10)	Absent (n=25)	
Age (years)	54.0±11.6	57.4±11.8	0.226
Postmenopausal (n)	6	17	0.802
CEA (ng/ml)	3.8±5.4	2.8±2.3	0.765
CRP (mg/dl)	0.06±0.04	0.08±0.19	0.333
Primary tumor			
Histology			0.281
IDC	8	21	
ILC	1	4	
Other	1	0	
Tumor size (mm)	23.3±14.1	30.8±19.0	0.142
SUV_{max}	5.3±3.5	3.1±1.9	0.986
ER (n)	10	20	0.164
PgR (n)	10	18	0.072
HER2 (n)	0	5	0.164
Nuclear grade 3	3	9	0.530
ly (n)	9	16	0.129
v (n)	3	5	0.411
Axillary node metastasis			
Tumor size (mm)	10.8±5.0	4.3±3.6	<0.001
Number of nodal metastases	2.9±2.2	2.1±2.4	0.806
1 Nodal metastasis (n)	4	17	0.126
1-3 Nodal metastases (n)	7	21	0.916
Micrometastasis (n)	1	8	0.182
ECI (n)	5	8	0.262
Non-SLN metastasis (n)	5	8	0.262

IDC, Invasive ductal carcinoma; ILC, invasive lobular carcinoma; SUV_{max}, maximum standardized uptake value; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ly, lymphatic invasion; v, vascular invasion; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECI: extracapsular invasion. SLN, sentinel lymph node.

Table II. *Patients' characteristics and clinicopathological features associated with non-sentinel lymph node (SLN) metastasis. Values are expressed as the mean±SD, or frequency.*

Characteristic	Non-SLN metastasis		*p*-Value
	Present (n=13)	Absent (n=22)	
Age (years)	54.0±8.6	57.9±13.2	0.180
Postmenopausal (n)	10	13	0.243
CEA (ng/ml)	2.3±1.3	3.6±4.3	0.161
CRP (mg/dl)	0.05±0.05	0.09±0.21	0.213
Primary tumor			
Histology (n)			0.029
IDC	8	22	
ILC	4	1	
Other	1	0	
Tumor size (mm)	30.5±22.3	27.3±14.2	0.693
SUV_{max}	3.7±2.2	3.8±2.9	0.449
ER (n)	13	17	0.081
PgR (n)	12	17	0.257
HER2 (n)	1	4	0.374
Nuclear grade 3	5	7	0.483
ly (n)	11	5	0.003
v (n)	4	5	0.541
Axillary node metastasis			
Tumor size (mm)	8.4±4.5	4.8±4.8	0.042
Number of nodal metastases	1.7±1.3	1.1±0.2	0.983
ECI (n)	10	3	0.001
FDG uptake (n)	5	5	0.365

IDC, Invasive ductal carcinoma; ILC, invasive lobular carcinoma; SUV_{max}, maximum standardized uptake value; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ly, lymphatic invasion; v, vascular invasion; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECI: extracapsular invasion: FDG, ^{18}F-fluorodeoxyglucose.

metastases in breast cancer. In our series, positive FDG uptake was a good predictor of axillary disease (16). FDG-PET may help identify patients with a high axillary lymph node burden (16). Since FDG-PET measures glucose metabolism, which reflects the biological aggressiveness of cancer, FDG-PET could provide a good indication of invasive potential. We evaluated the hypothesis that the FDG avidity of lymph nodes was associated with ECI of nodal metastases and lymphatic metastatic spread, and evaluated whether FDG-PET could be useful for predicting non-SLN metastasis. We found that FDG uptake was not a predictor for metastasis of non-SLNs. Our results revealed that FDG uptake was associated with the tumor size of metastatic lymph nodes, but not with ECI or the number of lymph node metastases. Several studies have reported that FDG uptake is correlated with the size of tumors to a certain extent, according to the resolution of the PET scanner, known as the partial-volume effect (16, 21). These findings reflect the fact that FDG uptake in lymph nodes may be determined mainly by tumor size (16), but not ECI or lymphatic spread. Tumor size was associated with lymphatic invasion, which may reflect lymphatic spread, but the number of nodal metastases and ECI may have fallen short of a statistically significant association because the size of the tumor is the main factor affecting nodal FDG uptake. Furthermore, in some cases, there was marked lymphatic spread regardless of the small size of the metastases. The size of lymph node metastases does not always reflect lymphatic spread. In patients with melanoma, there is a consensus in the literature that FDG-PET cannot replace SLN biopsy for regional lymph nodal staging (22). Therefore, the FDG-PET evaluation was not sufficient for evaluation of axillary lymphatic spread, suggesting that axillary lymph node dissection cannot be avoided, even in cases with negative FDG uptake in axillary lesions by FDG-PET.

We previously reported that the presence of ECI at SLNs is a strong predictor of non-SLN metastasis in breast cancer (3, 4); likewise, in the current study, ECI at the SLNs was an independent risk factor of non-SLN metastasis. ECI at metastatic SLNs is consistently associated with non-SLN metastasis (23-26); our findings essentially support those of these previous studies.

On the other hand, FDG-PET has high specificity for identifying axillary lymph node metastases in breast cancer. In the current study, the false-positive rate of FDG-PET evaluation of lymph node metastasis was only 0.6%. Our findings imply that macrometastasis of lymph nodes can be detected by FDG-PET, and in cases with FDG uptake in lymph nodes, lymph node metastasis may be highly suspected. Therefore, FDG-PET analysis may be useful for avoiding SLN biopsy in cases with positive FDG uptake in the axillary lesion.

This study has several potential limitations, the major ones being that it was a retrospective analysis and that the number of cases was relatively small. Additional research is needed to explore other benefits and drawbacks of FDG-PET evaluation of axillary lymph node metastasis.

In conclusion, we demonstrated that preoperative FDG-PET evaluation of lymph nodes is not sufficient for evaluation of ECI at SLN metastasis or non-SLN metastasis, suggesting that axillary lymph node dissection cannot be avoided. However, the positive predictive value for SLN metastasis is high, so that positive FDG uptake in the axillary lesions may be useful for avoiding SLN biopsy.

Conflicts of Interest

The Authors declare that they have no competing financial interests.

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