Clinicopathological Features of Cases with Primary Breast Cancer not Identified by ^{18}F-FDG-PET

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Abstract. *Several studies have reported that high F18-fluorodeoxyglucose (FDG) uptake is predictive of poor prognosis and aggressive features in patients with breast cancer. While these studies evaluated the prognostic value for cases with high FDG uptake, they did not elucidate the meaning of FDG negativity in primary breast cancer. In this study, we evaluated the clinicopathological features of breast cancer cases without FDG uptake. We retrospectively investigated the cases of 219 consecutive patients with primary breast cancer who underwent FDG-positron emission tomography (PET) preoperatively. Among the 219 patients, 25 (11.4%) did not have FDG uptake in the tumor. The 219 cases with breast cancer were divided into two groups based on the presence of FDG uptake in the primary tumor. The present univariate analysis revealed that histology, small invasive tumor size, high estrogen receptor (ER) or progesterone receptor (PgR) expression, low nuclear grade and absence of lymph node metastasis were significantly associated with negative FDG uptake in the primary tumor. On the other hand, the size of ductal spread was not significantly different between the two groups. Multivariate analysis revealed that small-size tumor invasion and lower nuclear grade were statistically significant. Among the 25 cases without FDG uptake, there was no recurrent disease in spite of there being no case that underwent chemotherapy, while 4 cases among the 194 cases with FDG uptake had disease recurrence. Our findings imply that preoperative FDG negativity in primary breast cancer is effective in predicting better prognosis, but is less effective in predicting ductal spread. Cases without FDG uptake in the primary tumor may have a lower risk of recurrent disease and may be able to safely avoid adjuvant chemotherapy.*

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In recent years, the clinical applications of positron emission tomography (PET) have undergone explosive growth. PET using F18-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 (1-9). Regarding breast cancer, there are many reports of preoperative evaluation with FDG-PET; however, its diagnostic utility for breast cancer is controversial (3-9). FDG-PET measures glucose metabolism, which reflects the biological aggressiveness of cancers (8-16). Thus, FDG-PET may provide biological information about the tumor growth potential. In fact, several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer (10-16). However, all these studies focused on the prognostic value in cases with high FDG uptake but did not focus on this specific issue in cases without FDG uptake in primary breast cancer (10-16). There have been few studies to assess the clinicopathological features of breast cancer cases that were negative for FDG uptake. FDG uptake is not detected in some cases with primary breast cancer; thus, FDG-PET can be considered less sensitive than other modalities (8, 9). For the evaluation of breast cancer by FDG-PET, an understanding of FDG negativity, as well as positive FDG avidity, is important. In this study, we evaluated the clinicopathological features of cases with FDG-negative breast cancer. We examined whether certain clinical factors, including tumor size or other clinicopathological features, were associated with FDG-negative breast cancer.

Patients and Methods

Patients. We retrospectively investigated the cases of 219 consecutive patients with primary breast cancer who underwent FDG-PET preoperatively at Gunma University, from January 2010

Table I. *Patients' characteristics and clinicopathological features associated without FDG uptake in primary tumor.*

	FDG uptake		Univariate analysis	Multivariate analysis
	Absent (n=25)	Present (n=194)	*p*-Value	*p*-Value
Age (years)	58.9±11.7	59.2±13.0	0.823	
Histology (n)			0.005	0.332
IDC	18	163		
ILC	2	13		
DCIS	5	7		
Other	0	11		
Tumor size of invasion (mm)	9.3±6.5	20.3±15.4	<0.001	0.014
Size of ductal spread (mm)	25.3±19.4	33.6±21.0	0.006	
ER-positive (n)	25	122	<0.001	0.134
PgR-positive (n)	22	114	0.009	0.687
HER2-positive (n)	1	35	0.135	
Nuclear grade 3 (n)	1	74	0.002	0.032
ly-positive (n)	6	80	0.149	
v-positive (n)	3	39	0.485	
Node metastases-positive (n)	1	58	0.012	0.123
CEA	1.95±1.33	2.49±2.26	0.798	
CRP	0.06±0.1	0.19±0.71	0.776	

Values are expressed as mean±SD. n, Number; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; ly, lymphatic invasion: v, vascular invasion: CRP, C-reactive protein; CEA, carcinoembryonic antigen.

to October 2015. All patients had undergone radical breast surgery. Patients with incomplete clinical information and male patients were excluded. Among the 219 patients, 25 (11.4%) had no FDG uptake in the tumor. Patients underwent FDG-PET/computed tomography (CT) as part of the routine standard of care, without deviating from the main protocol. The maximum standardized uptake value (SUV_{max}) of primary tumors was calculated in a routine clinical fashion. Written consent was obtained from all patients for the use of their records and imaging in future studies.

The details extracted from the database were age, histological type, size of invasive primary tumor, size of ductal spread, lymphatic or vascular invasion, nuclear grade, estrogen receptor (ER) and progesterone receptor (PgR) expression status, human epidermal growth factor receptor 2 (HER2) score of the primary tumor, axillary lymph node status, SUV_{max} of the primary tumor and visibility of detected lesion by FDG-PET. The ER and PgR status were assessed by ALLRED scores, with an ALLRED score of 3 or higher defined as indicating ER and PgR positivity (17, 18).

Statistical analysis. The breast cancer cases were divided into two groups on the basis of FDG uptake in the primary tumor. We conducted a univariate statistical analysis using Fisher's exact test or the χ^2 test with Yates' correction. To compare the two groups, Student's *t*-test was used. Differences were considered significant when $p<0.05$. To test the independence factors related with negative FDG uptake, the variables were entered into a multivariate logistic regression model with a likelihood of $p<0.05$.

Results

In total, 219 cases were included in the analysis. In 25 patients (11.4%), no FDG uptake was detected by FDG-PET (Figure 1). Thus, the false negative rate of FDG-PET for primary breast cancer was 11.4% in this study. The mean SUV_{max} of all breast cancer cases was 3.39±3.96 (range=0-43.2) overall. The 219 cases with breast cancer were divided into two groups based on the presence of FDG uptake in the primary tumor. Table I shows the patients' characteristics and summarizes the results of the univariate and multivariate analysis conducted to determine the relationships between negative FDG uptake in the primary tumor and various clinicopathologic variables. The present univariate analysis revealed that histology, small tumor size, high ER or PgR expression, low nuclear grade and absence of lymph node metastasis were significantly associated with negative FDG uptake in the primary tumor. The analysis revealed that the size of tumor invasion was a statistically significant factor; however, the size of ductal spread did not significantly differ between the two groups. Multivariate analysis revealed that only the small size of tumor invasion and lower nuclear grade were the statistically significant. Among the 25 cases without FDG uptake, there was no recurrent disease in spite of the fact that none of them underwent chemotherapy; meanwhile, four cases among the 194 with FDG uptake had disease recurrence. The overall median follow-up period was 52.2 months.

Discussion

FDG-PET has been widely used for diagnosing staging or recurrence in breast cancer; however, its diagnostic utility for breast cancer is controversial (3-9). FDG-PET can differentiate

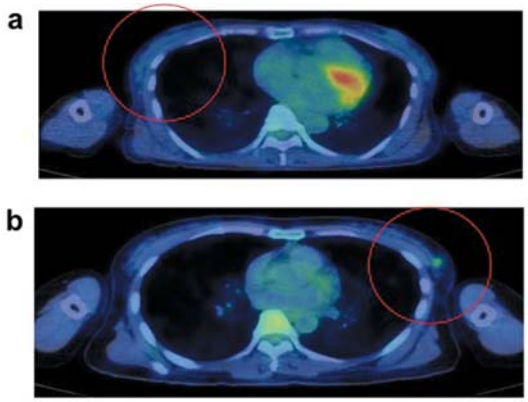

Figure 1. *a. Absence of FDG uptake in primary right breast cancer on PET-CT in a 57-year-old female. Histopathological examination revealed invasive ductal carcinoma, scirrhous carcinoma. The tumor size was 18 mm. b. FDG uptake (SUVmax=2.1) in primary left breast cancer on PET-CT in a 45-year-old female. Histopathological examination revealed invasive ductal carcinoma, scirrhous carcinoma. The tumor size was 6 mm.*

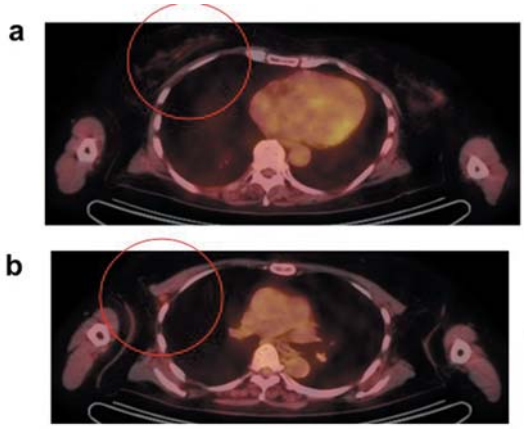

Figure 2. *Case of negative FDG uptake in primary right breast cancer (a) on PET-CT in a 68-year-old female who had axillary lymph node metastasis (b). Histopathological examination revealed invasive ductal carcinoma and scirrhous carcinoma. The tumor size was 11 mm. FDG uptake in the primary tumor was negative. Lymph node metastases were confirmed histopathologically.*

breast cancers from benign lesions with a sensitivity of 66-96% and a specificity of 83-100% (3, 5, 6, 8). In our study, the overall sensitivity for detection of all breast cancers was 88.6% and the false negative rate of FDG-PET evaluation of primary breast cancer was 11.4%. FDG-PET has high specificity but mediocre sensitivity for identifying primary breast cancer. From these findings, use of FDG-PET for detection of primary breast cancer is not currently advised. However, in recent years, several studies have reported that high FDG uptake may be predictive of poor prognosis and aggressive features in patients with breast cancer (10-16). As described above, in these previous studies, the focus was on primary tumor's high SUV_{max}; there have been few studies to assess the factors associated with FDG negativity of primary breast cancer. Thus, the present study was undertaken to expand the benefit of FDG-PET evaluation for patients with breast cancer, focusing on the clinicopathological features of FDG-negative breast cancer cases.

SUV_{max} is used as a semi-quantitative indicator of FDG uptake as SUV_{max} is influenced by many factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells (2, 9, 19, 20). Several studies have reported that SUV_{max} is correlated with the size of a tumor to a certain level, according to the resolution of the PET scanner, known as the partial volume effect (21). FDG-PET evaluation of tumor is not predictive of small metastases or micrometastases (8, 9). In this study, small-size tumor invasion was also strongly associated with FDG negativity of the primary tumor due to the partial volume effect. On the other hand, the size of tumor's ductal spread was not associated with FDG avidity of the primary tumor, which suggested that FDG-PET evaluation was not sufficient for assessment of tumor spread.

Besides the partial volume effect, FDG-PET measures glucose metabolism (22), which reflects the biological aggressiveness of cancers. FDG-PET evaluation of tumors was not predictive of relatively small metastases (8, 9); however, even in the current cases with a tumor size ≤10 mm, we showed that 77.2% (44/57) of tumors could be visualized with FDG-PET. In the current study, multivariate analysis revealed that low nuclear grade was statistically significantly associated with FDG-PET negatively, besides the small size of tumor invasion. Among the 25 cases without FDG uptake, there was no recurrent disease despite the fact that none of these patients underwent chemotherapy; meanwhile, 4 cases among 194 cases with FDG uptake had disease recurrence. These findings reflect that FDG-negative breast cancer may have better prognosis than FDG-positive breast cancer. Among the 25 cases without FDG uptake, there was one node-positive case; however, this case had no recurrent disease, even without chemotherapy. From these results, node-positive patients without FDG uptake in primary tumor (Figure 2), even though that combination is relatively rare, may not have an increased risk of recurrent disease and may be able to avoid adjuvant chemotherapy.

This study has several potential limitations, the major ones being that it was a retrospective analysis and the number of cases was relatively small. Additional research is needed to explore other benefits and drawbacks of FDG-PET evaluation of primary breast cancer; however, to the best of our

knowledge, this is the first report describing the features of FDG-negative breast cancer and the additional usefulness of FDG-PET as a predictor in primary breast cancer patients as FDG negativity may indicate a lower risk of recurrent disease.

In conclusion, we have demonstrated that the finding of preoperative FDG-negative primary breast cancer is effective in predicting a better prognosis but is less effective in predicting ductal spread. From our findings, cases without FDG uptake could potentially avoid adjuvant chemotherapy; yet, analyses of large randomized trials are warranted to evaluate the usefulness of FDG-PET as a prognostic factor in breast cancer patients without FDG uptake.

Conflicts of Interest

The Authors declare that they have no competing financial interests.

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