Clinicopathological Features of Ductal Carcinoma *In Situ* from ^{18}F-FDG-PET Findings

TAKAAKI FUJII, KEIKO YANAI, SHOKO TOKUDA, YUKO NAKAZAWA, SASAGU KUROZUMI,
SAYAKA OBAYASHI, REINA YAJIMA, TOMOKO HIRAKATA and HIROYUKI KUWANO

*Division of Breast and Endocrine Surgery, Department of General Surgical Science,
Graduate School of Medicine, Gunma University, Gunma, Japan*

Abstract. *Aim: The presence of ductal carcinoma in situ (DCIS) can increase the risk of developing an invasive ductal carcinoma (IDC), but it is difficult to predict what will occur if a DCIS is left untreated. We reported the usefulness of* [18]*F-fluorodeoxyglucose positron emission tomography (FDG-PET) for DCIS, and that the presence of FDG uptake in the tumor could be considered a predictor of invasive potential in patients with DCIS. In this study, we retrospectively evaluated the clinicopathological features of DCIS by using FDG-PET findings, and we evaluated the possibility of using FDG-PET in DCIS cases as a biomarker of which lesions will go on to become invasive. Patients and Methods: We investigated the cases of 185 consecutive patients with primary breast cancer who were diagnosed as having DCIS or IDC and underwent FDG-PET preoperatively. Results: We divided the cases into two groups on the basis of histology; DCIS vs. IDC (n=171). The DCIS cases were divided into two groups on the basis of FDG uptake in the primary tumor. Fourteen of the 185 patients (7.4%) were revealed to have a DCIS. The analysis revealed that the SUV_{max} and the number of cases not detected by FDG-PET were significantly different between the DICS and IDC groups. The extent of the primary tumor was not significantly different between the two groups. In six cases (42.9%) of the 14 DCIS cases, no FDG uptake was detected by FDG-PET. The extent of tumor did not significantly differ between the two groups. In addition, all six cases without FDG uptake were of the diffuse-spread type, without mass formation. All eight cases with mass formation had FDG uptake. Conclusion: Our present findings suggest that the*

FDG-PET uptake reflects tumor burden or tumor density, which should be considered to be associated with the presence of invasion.

Ductal carcinoma *in situ* (DCIS) is a pre-cancer or non-invasive cancer of the breast. DCIS does not spread beyond the duct into any of the surrounding tissue in the breast. The presence of DCIS could increase the risk of developing an invasive ductal carcinoma (IDC), but it is difficult to predict what will occur if a DCIS is left untreated. There is no biomarker that can be used to predict which lesions will go on to become invasive or instead remain stable 'non-invasive' disease.

In recent years, clinical applications of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) have undergone explosive growth for diagnosing the stage or recurrence in breast cancer; however, the diagnostic utility of FDG-PET for breast cancer is controversial (1-11). Several research groups have conducted that the use of FDG-PET for the detection of primary breast cancer is currently not advised, mainly because of its low sensitivity in cases of smaller carcinoma or histology, including lobular carcinoma or DCIS (1-4). The majority of FDG-PET studies have been carried out on patients with invasive breast cancer because DCIS has been reported to be poorly imaged by FDG-PET (5, 6). FDG-PET measures glucose metabolism, which reflects the biological aggressiveness of cancers (1, 2, 10-14). 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 (1, 2, 10-14).

There exist only few reports regarding the role of FDG-PET in the detection of DCIS of the breast (15-17), and the standardized uptake value (SUV) pattern of DCIS of the breast on FDG-PET examination is not fully understood. The findings of our previous study, demonstrated (1) the usefulness of FDG-PET for DCIS and (2) that the presence of FDG uptake in the tumor could be considered a predictor

for invasive potential in cases with DCIS cases (17). In the present study, we evaluated the clinicopathological features of DCIS obtained using FDG-PET findings, and we considered the possibility for additional usefulness of FDG-PET in DCIS cases as a biomarker to predict which lesions will go on to become invasive.

Patients and Methods

We retrospectively investigated the cases of 185 consecutive patients with primary breast cancer who were diagnosed as having DCIS or IDC and underwent FDG-PET preoperatively at the Gunma University (Gunma, Japan), in the period from January 2010 to October 2015. All patients had undergone radical breast surgery.

We excluded patients with incomplete clinical information, those who underwent preoperative chemotherapy, and male patients. Among the 185 patients, 14 (7.6%) were diagnosed as having DCIS. The 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 each primary tumor 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, the size of the invasive primary tumor, the size of extent of tumor, the presence of lymphatic or vascular invasion, the nuclear grade, the estrogen receptor (ER) expression and progesterone receptor (PgR) expression status, the human epidermal growth factor receptor 2 (HER2) score of the primary tumor, the axillary lymph node status, the SUV_{max} of the primary tumor, and the visibility of the detected lesion by FDG-PET. The ER and PgR expressions were assessed by ALLRED scores, with an ALLRED score of ≥3 defined as indicating ER and PgR positivity (18, 19).

Statistical analysis. We divided the breast cancer cases into two groups on the basis of histology, *i.e.* DCIS *versus* IDC. We divided the DCIS cases 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. Student's *t*-test was used to compare the two groups. Differences were considered significant when $p<0.05$. To test the independence factors related to negative FDG uptake, we entered the variables with a likelihood of $p<0.05$ into were entered into a multivariate logistic regression model.

Results

Presence of FDG uptake was not associated with tumor extension in patients with IDC and DCIS. A total of 185 cases were included in the analysis. In 14 patients (7.4%), the histopathological examination revealed DCIS. We divided the 185 breast cancer cases into two groups based on the histology of the primary tumor, *i.e.*, DCIS (n=14) and IDC (n=171). Table I summarizes the patients' characteristics and the results of the univariate analysis conducted to determine differences in clinicopathologic variables between DCIS and IDC. The univariate analysis revealed that the SUV_{max} and the number of cases not detected by FDG-PET

were significantly different between the DICS and IDC groups. The extent of primary tumor was not significantly different between the two groups.

FDG uptake in the DCIS patients was associated with mass formation. In six (42.9%) of the 14 DCIS cases, no FDG uptake was detected by FDG-PET. We divided the 14 DCIS cases into two groups based on the presence of FDG uptake in the primary tumor. Table II summarizes both the patients' characteristics and the results of the univariate analysis conducted to determine the relationships between negative FDG uptake in the primary tumor and various clinicopathologic variables. The univariate analysis revealed that age was significantly associated with negative FDG uptake in the primary tumor; however, the multivariate analysis revealed that age was not a significant factor, and the extent of the tumor did not differ significantly between the two groups. In addition, all six of the cases without FDG uptake were the diffuse-spread type, without mass formation, whereas all eight of the cases with mass formation had FDG uptake.

Discussion

FDG-PET has high specificity but mediocre sensitivity for identifying primary breast cancer, and it can differentiate breast cancers from benign lesions with 66%-96% sensitivity and 83-100% specificity (3, 4, 7). In our previous study, the overall sensitivity for the detection of all breast cancers was 88.6% and the false-negative rate of the FDG-PET evaluation of primary breast cancer was 11.4% (3). Many studies have evaluated factors associated with the FDG avidity of the primary tumor in breast cancer and the tumor size or histological type of breast cancer has been reported to be associated with a greater likelihood of FDG uptake (3).

Several studies have reported that the SUV_{max} correlates with the size of a tumor to a certain value, according to the resolution of the PET scanner, known as the partial volume effect (20). However, our present analysis revealed that the extent of the tumor did not significantly differ between the DCIS and IDC groups. The FDG uptake may be determined mainly by the number of viable tumor cells (21, 22), but not by ductal spread. Thus, the FDG-PET evaluation was not sufficient for evaluating the ductal spread of a tumor. However, the SUV_{max} of patients with a nodular growth pattern is significantly higher than the SUV_{max} of patients with a diffuse growth pattern (13, 22, 23). In the present study, all cases with a nodular growth pattern had FDG uptake in the tumors, and all of the cases without FDG uptake had a diffuse growth pattern. The FDG-PET findings reflected the tumor burden or tumor density, which should be considered to be associated with the presence of invasion.

FDG-PET measures glucose metabolism, which reflects biological information about the tumor growth potential.

Table I. *Patients characteristics and clinicopathological features associated with invasion.*

	DCIS (n=14)	IDC (n=171)	*p*-Value
Age (years)	60.6±12.6	59.2±12.2	0.697
CEA (ng/ml)	1.67±0.92	2.52±2.46	0.238
CRP (mg/dl)	0.08±0.13	0.12±0.52	0.749
SUV_{max}	1.49±2.10	3.26±2.79	0.022
not detected by FDG-PET	6	17	0.002
Extention of tumor (mm)	38.8±29.6	30.9±12.3	0.165
Node metastases (n)	0	44	0.065
ER (n)	14	147	0.276
PgR (n)	11	136	0.796
HER2 (n)	2	28	0.862
Nuclear grade 3 (n)	2	62	0.171
ly (n)	0	97	<0.001
v (n)	0	43	0.070

Values are expressed as mean±SD. IDC, Invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; CRP, C-reactive protein; CEA, carcinoembryonic antigen.

Table II. *Patients characteristics and clinicopathological features associated with FDG uptake in DCIS.*

	FDG uptake		
	Absent (n=6)	Present (n=8)	*p*-Value
Age (years)	51.0±10.7	67.8±8.6	0.011
CEA (ng/ml)	0.97±0.43	2.34±0.62	
CRP (mg/dl)	0.10±0.16	0.05±0.05	0.574
Extention of tumor (mm)	40.3±24.0	37.6±33.1	0.878
ER (n)	6	8	-
PgR (n)	5	6	0.615
HER2 (n)	1	1	0.692
Grade (n)			0.896
low	3	5	
intermediate	2	2	
high	1	1	

Values are expressed as mean±SD. IDC, Invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; CRP, C-reactive protein; CEA, carcinoembryonic antigen.

DCIS patients have shown a lower level of FDG uptake, and DCISs are detected at a significantly lower sensitivity than IDCs. In the present study, the SUV_{max} of the primary tumors and the presence of FDG uptake in the tumors were associated with the presence of invasion. Infiltrating ductal carcinomas have a higher level of FDG uptake and are therefore detected with significantly higher sensitivity compared to DCISs.

In our previous study, the presence of FDG uptake in the tumor could be considered as a predictor for invasion in DCIS cases confirmed by needle biopsy. That finding, combined with our present results, suggests that FDG uptake reflects not only the biological aggressiveness of tumors but also the tumor cell density of intraductal carcinoma, which may reflect tumor invasion or future invasion, and that FDG-PET is thus useful for the prediction of the invasion of DCIS. This possibility should be investigated in further studies.

This study has several potential limitations. The major limitation is the retrospective method of data collection. The number of cases was also relatively small. However, the clinical implications of the data we obtained are very important. There have been only a few reports about the role of FDG-PET in DCIS because the majority of prior FDG-PET studies were carried out on IDC patients. To the best of our knowledge, this is the first report describing the usefulness of FDG-PET as a biological predictor of invasion in patients with DCIS. Additional research is needed to explore the significance of FDG uptake for predicting invasion in patients diagnosed with DCIS.

In conclusion, our present findings suggest that the results of an FDG-PET evaluation reflect tumor burden or tumor density. In patients with DCIS, the presence of FDG uptake in the tumor may be considered a predictor of future invasion.

Acknowledgements

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