^{18}F-fluorodeoxyglucose uptake as predictor for invasion in preoperatively diagnosed breast ductal carcinoma *in situ*: Significance in cases without mass formation

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Abstract. A diagnosis of ductal carcinoma *in situ* (DCIS) at needle biopsy often changes to that of invasive ductal carcinoma as the definitive pathological diagnosis following the surgical procedure. The present study sought to identify the factors associated with invasive disease in cases diagnosed as DCIS on needle biopsy by analyzing ^{18}F-fluorodeoxyglucose-proton emission tomography (FDG-PET) findings. The present study retrospectively investigated the cases of 24 consecutive patients with primary breast cancer who were preoperatively diagnosed with DCIS by needle biopsy. The cases were divided into two groups based on the presence of invasion in the primary tumor. Among the 24 patients, 13 (54.7%) patients had invasive carcinoma and 11 (45.8%) had DCIS. The analysis revealed that the presence of FDG uptake in the tumor was the only independent predictor of presence of the invasive disease. No cases without FDG uptake exhibited invasion and all of these were ultimately diagnosed as DCIS. In the present study, all cases, including DCIS, with a nodular growth pattern demonstrated FDG uptake in the tumors, and all cases without FDG uptake were interpreted as having a diffuse growth pattern. The present findings suggested that the presence of FDG uptake in the tumor can be considered a predictor for invasion in cases with DCIS by needle biopsy, particularly in cases with a diffuse growth pattern. Patients preoperatively diagnosed as DCIS without mass formation and without FDG uptake in the tumor may avoid sentinel lymph node biopsy.

Introduction

In previous 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 types of malignancies, including breast cancer, for tumor staging, tumor restaging, the detection of recurrence and monitoring treatment responses (1-4). However, use of FDG-PET for detection of primary breast cancer is currently not advised, predominantly due to its low sensitivity in small carcinoma and ductal carcinoma *in situ* (DCIS) (5,6). The majority of FDG-PET studies have been performed on patients with invasive breast cancer, since DCIS has been reported to be poorly imaged by FDG-PET (7,8). Only a few reports regarding the role of FDG-PET in the detection of DCIS of the breast exist (9,10), and the standardized uptake value (SUV) pattern of DCIS of the breast on FDG-PET examination remains to be fully understood.

Accurate diagnosis of invasion around DCIS lesions is important for appropriate surgical planning. The diagnosis of DCIS at needle biopsy often changes to invasive ductal carcinoma as the definitive pathological diagnosis following the surgical procedure. Diagnosis of invasive breast cancer in cases preoperatively diagnosed as DCIS by needle biopsy ranges between 0-59% (11-13). Therefore, several previous studies have attempted to predict which DCIS lesions at core needle biopsy (CNB) will reveal invasion at final excision histology. Metaanalysis of predictors of invasive ductal carcinoma revealed that tumor size, tumor grade, mammographic features and palpability were associated with invasion in cases with DCIS by needle biopsy (11); however, no established factors exist to identify cases with invasion. The present study sought to identify the factors associated with invasive disease in DCIS diagnosed on needle biopsy by analyzing FDG-PET findings. The present study reported the assessment of the efficiency of FDG uptake in patients with diffuse-type DCIS diagnosed by needle biopsy.

Patients and methods

Patients and methods. The present study retrospectively investigated the cases of 24 consecutive patients with primary breast cancer who were preoperatively diagnosed as DCIS by needle biopsy and who underwent FDG-PET preoperatively at the Department of General Surgical Science, Gunma University (Gunma, Japan) between January 2009 and January 2015. All patients underwent radical breast surgery. Patients with previously diagnosed breast cancer

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or incomplete clinical information were excluded. 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 SUV_{max} of primary tumors was calculated in a routine clinical manner. No patients succumbed to surgical complications. Informed consent was obtained from all patients.

The details extracted from the database were age, palpability, primary tumor size (lesion of tumor or ductal spread), type of tumor (mass formation or diffuse), nuclear grade, mammographic mass, estrogen (ER) or progesterone (PgR) status, human epidermal growth factor receptor 2 (HER2/neu) expression, SUV_{max} of the primary tumor and visibility of detected lesion on the FDG-PET. The ER and PgR status was assessed by ALLRED scores, and an ALLRED score of 3 or higher was defined as ER- and PgR-positive (14,15).

Statistical analysis. The breast cancer cases were divided into two groups on the basis of the presence of invasion in the primary tumor or DCIS. A univariate statistical analysis was performed using Fisher's exact test or the χ^2 test with Yates' correction. To compare the two groups, Student's t-test was performed. To test the independence of the risk factors, variables were entered into a multivariate logistic regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

FDG uptake is a factor associated with invasion in cases initially diagnosed as DCIS by needle biopsy. The present study analyzed the cases of 24 consecutive patients with breast cancer diagnosed as DCIS by needle biopsy and underwent FDG-PET preoperatively. The patients with breast cancer were divided into two groups based on the presence of invasion in the primary tumor. Among the 24 patients, 13 (54.7%) patients had invasive carcinoma and 11 (45.8%) had DCIS. Table I summarizes not only the patient characteristics, but also the results of the analysis performed to determine the associaiton between the presence of invasion and clinicopathological variables. The univariate analysis revealed that the presence of FDG uptake in the tumor (P=0.003) and ER expression (P=0.030) were statistically significant factors. The SUV_{max} of the primary tumor tended to be higher in patients with invasion, although the difference was not statistically significant. As observed, palpability, mammographic mass, grade and lesion size were not statistically significant factors in the present study. The multivariate analysis revealed that only the presence of FDG uptake in the tumor (P=0.002) was an independent risk factor of the presence of invasion. ER expression (P=0.902) lost its significance in the multivariate analysis. In the present study, none of the cases without detection by FDG-PET exhibited invasion; all 6 cases without FDG uptake were diagnosed as DCIS.

FDG uptake in patients with diffuse spread without mass formation, not with mass formation, was associated with invasion. All 6 cases without FDG uptake were diagnosed as DCIS and were the diffuse-spread type without mass formation. The present study divided the cases of patients into two subgroups based on the presence of mass formation in the primary tumor (mass formation or diffuse pattern without mass formation). Among the 24 patients, 12 (50.0%) exhibited mass formation. Table II summarizes not only the patient characteristics, but also the results of the univariate analysis performed to determine the association between the clinicopathological variables and the presence of invasion in the tumor in patients with diffuse-type tumor without mass formation (Fig. 1). The univariate and multiple analyses revealed that the presence of FDG uptake in the primary tumor and ER expression were statistically significant factors in cases with a diffuse growth pattern. As observed, palpability, mammographic mass, grade and lesion size were not statistically significant factors in the diffuse-type tumor. All cases with mass formation had FDG uptake (Fig. 2); thus, the presence of the FDG uptake in primary tumors with mass formation had no significance with regard to invasive disease vs. DCIS (Table III). Nuclear grade was associated with invasion in cases with mass formation, similar to findings in previous studies (16).

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

Characteristic	DCIS (n=11)	IDC (n=13)	P-value
Age, years	58.0±12.9	58.9±9.7	0.562
Palpitation, n	5	7	0.500
Mass detected by MMG, n	2	6	0.156
Mass formation, n	4	8	0.207
Lesion size, mm	36.0±21.6	33.8±18.8	0.399
Not detected by FDG-PET, n	6	0	0.003
SUV_{max}	1.5±2.4	2.1±1.1	0.778
ER	11	8	0.030
PgR	10	7	0.059
HER2	1	6	0.059
Nuclear grade, n			
1	6	5	0.131
2	5	4	
3	0	4	

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; MMG, mammography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; SUV, standardized uptake value; ER, estrogen; PgR, progesterone; HER2, human epidermal growth factor receptor 2. The data are presented as the mean ± standard deviation.

Discussion

FDG-PET has been widely used for staging and identifying recurrence in various types of cancer. FDG-PET can differentiate breast cancer from benign lesions with a sensitivity of 66-96% and a specificity of 83-100% (4). In the present series, the overall sensitivity for detection of all breast cancer is 91.5% (172/188). FDG-PET measures glucose metabolism, which reflects the biological aggressiveness of cancer. FDG-PET can provide biological information about the tumor growth potential. Infiltrating ductal carcinoma has a higher level of FDG uptake

Table II. Patients' characteristics and clinicopathological features associated with invasion in cases without mass formation.

Characteristic	DCIS (n=7)	IDC (n=5)	P-value
Age, years	53.6±11.7	54.4±8.8	0.547
Palpitation, n	3	2	0.689
Mass detected by MMG, n	0	2	0.152
Lesion size, mm	39.6±22.3	49.2±17.9	0.759
Not detected by FDG-PET, n	6	0	0.008
SUV_{max}	0.3±0.8	2.4±0.4	0.999
ER	7	2	0.045
PgR	6	2	0.152
HER2	1	3	0.152
Nuclear grade, n			
1	2	3	0.162
2	5	1	
3	0	1	

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; MMG, mammography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; SUV, standardized uptake value; ER, estrogen; PgR, progesterone; HER2, human epidermal growth factor receptor 2. The data are presented as the mean ± standard deviation.

Table III. Patients characteristics and clinicopathological features associated with invasion in cases with mass formation.

Characteristic	DCIS (n=4)	IDC (n=8)	P-value
Age, years	65.8±11.0	61.6±9.2	0.273
Palpitation, n	2	5	0.576
Mass detected by MMG, n	2	4	0.727
Lesion size, mm	29.8±18.8	24.1±11.4	0.286
Not detected by FDG-PET, n	0	0	NS
SUV_{max}	3.6±2.7	2.0±1.3	0.113
ER	4	6	0.424
PgR	4	5	0.255
HER2	0	3	0.255
Nuclear grade, n			
1	4	2	0.050
2	0	3	
3	0	3	

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; MMG, mammography; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; SUV, standardized uptake value; ER, estrogen; PgR, progesterone; HER2, human epidermal growth factor receptor 2. The data are presented as the mean ± standard deviation.

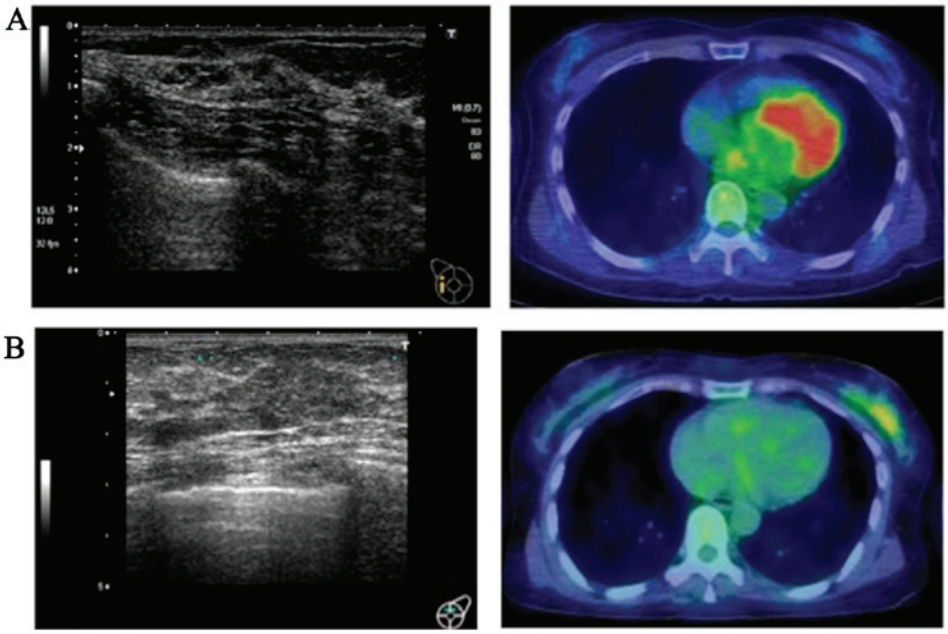

Figure 1. Cases with diffuse growth pattern, without mass formation. (A) A 58-year-old female. Ultrasonography revealed a hypoechoic lesion without mass formation. ^{18}F-fluorodeoxyglucose uptake was not detected in the right breast. Histopathological examination revealed ductal carcinoma *in situ*. (B) A 46-year-old female. Ultrasonography revealed a hypoechoic lesion without mass formation. ^{18}F-fluorodeoxyglucose uptake was detected in the left breast (SUV_{max}=2.3). Histopathological examination revealed invasive ductal carcinoma and papillotubular carcinoma.

and therefore is detected with significantly higher sensitivity compared with DCIS. The present study aimed to investigate the critical role of FDG-PET for differentiated diagnosis of invasive disease in DCIS diagnosed on needle biopsy. The present data demonstrated that the absence of FDG uptake in the tumor was a statistically significant factor for predicting DCIS, particularly in cases of diffuse-type disease without mass formation. The present results suggested that patients preoperatively diagnosed

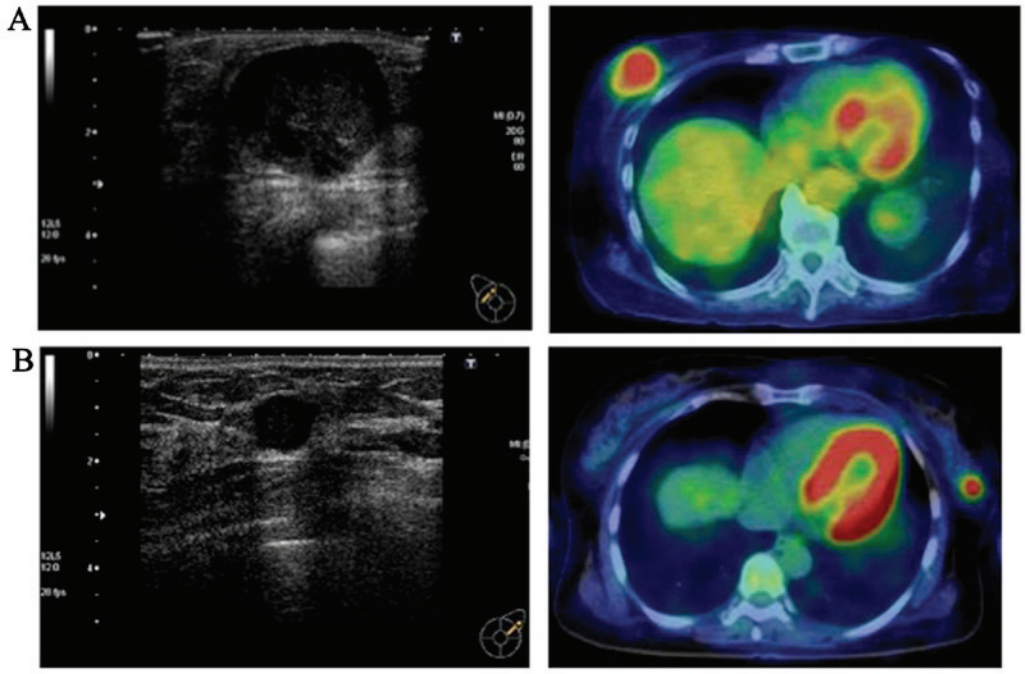

Figure 2. Cases with mass formation. (A) A 78-year-old female. Ultrasonography revealed a tumor with mass formation. ^{18}F-fluorodeoxyglucose uptake was detected in the tumor (SUV_{max}=8.2). Histopathological examination revealed ductal carcinoma *in situ*. (B) A 53-year-old female. Ultrasonography revealed a tumor with mass formation. ^{18}F-fluorodeoxyglucose uptake was detected in the tumor (SUV_{max}=5.8). Histopathological examination revealed invasive ductal carcinoma and papillotubular carcinoma.

as DCIS without mass formation and without FDG uptake in the primary tumor may safely forego sentinel lymph node biopsy. This possibility must be investigated in further studies.

In the present study, the SUV_{max} of the primary tumor was not associated with the presence of invasion. A previous study suggested that SUV_{max} on FDG-PET is useful for predicting the underestimation of invasive ductal carcinoma (IDC) in cases of DCIS at biopsy (10). The SUV_{max} is used as a semi-quantitative indicator of FDG uptake; however, the SUVmax is influenced by numerous factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells (3,17,18). Several studies have reported that SUV_{max} correlates with the size of a tumor to a certain level, according to the resolution of the PET scanner, known as the partial volume effect (19). Furthermore, the SUVmax of patients with a nodular growth pattern is significantly higher compared with those with a diffuse growth pattern (20,21). In the present study, all cases with a nodular growth pattern had FDG uptake in the tumors (Fig. 1), and all cases without FDG uptake had a diffuse growth pattern. FDG uptake may be determined predominantly by the number of viable tumor cells (20,22), which notably suggests that mass formation promotes FDG uptake. FDG uptake reflects not only the biological aggressiveness of tumors, but also the tumor cell density of intraductal carcinoma (9). These findings combined with the present results suggested that FDG-PET is useful for the prediction of invasion of DCIS in cases with diffuse growth pattern (Fig. 2), but not with mass formation (Fig. 1).

The present study has several potential limitations. The major limitation is that it uses retrospective methods of data collection. In addition, the number of cases was relatively small. However, the clinical implications of the data obtained are very important. Only a few reports have discussed the role of FDG-PET in the detection of DCIS, since the majority of FDG-PET studies in the literature have been performed on cases with IDC. To the best of our knowledge, this is the first report describing the usefulness of FDG-PET as predictor of invasion of preoperatively diagnosed diffuse-growth-type DCIS. Additional research is required to investigate the significance of FDG uptake in patients in predicting the presence of invasion in patients clinically diagnosed with DCIS.

In conclusion, the present findings suggested that the presence of FDG uptake in the tumor can be considered a predictor for invasion in cases with DCIS by needle biopsy, particularly in those with a diffuse growth pattern. Patients preoperatively diagnosed as DCIS without mass formation and without FDG uptake in the tumor can be spared sentinel lymph node biopsy.

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References

1. Fletcher JW, Djulbegovic B, Soares H, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, *et al*: Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 49: 480-508, 2008.
2. Groves AM, Shastry M, Ben-Haim S, Kayani I, Malhotra A, Davidson T, Kelleher T, Whittaker D, Meagher M, Holloway B, *et al*: Defining the role of PET-CT in staging early breast cancer. Oncologist 17: 613-619, 2012.

3. Fujii T, Yajima R, Yamaguchi S, Tsutsumi S, Asao T and Kuwano H: Is it possible to predict malignancy in cases with focal thyroid incidentaloma identified by 18F-Fluorodeoxyglucose positron emission tomography? Am Surg 78: 141-143, 2012.
4. Flanagan FL, Dehdashti F and Siegel BA: PET in breast cancer. Semin Nucl Med 28: 290-302, 1998.
5. Rostom AY, Powe J, Kandil A, Ezzat A, Bakheet S, el-Khwsky F, el-Hussainy G, Sorbris R and Sjoklint O: Positron emission tomography in breast cancer: A clinicopathological correlation of results. Br J Radiol 72: 1064-1068, 1999.
6. Avil N, Rosé CA, Schelling M, Dose J, Kuhn W, Bense S, Weber W, Ziegler S, Graeff H and Schwaiger M: Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: Use and limitations. J Clin Oncol 18: 3495-3502, 2000.
7. Quon A and Gambhir SS: FDG-PET and beyond: Molecular breast cancer imaging. J Clin Oncol 23: 1664-1673, 2005.
8. Vincenzi B, Calvieri A, Santini D, Altomare V and Tonini G: Occasional FDG-PET recognition of in situ breast cancer. Ann Oncol 18: 1584-1585, 2007.
9. Azuma A, Tozaki M, Ito K, Fukuma E, Tanaka T and O'uchi T: Ductal carcinoma in situ: Correlation between FDG-PET/CT and histopathology. Radiat Med 26: 488-493, 2008.
10. Shigematsu H, Kadoya T, Masumoto N, Matsuura K, Emi A, Kajitani K, Amioka A and Okada M: Role of FDG-PET/CT in prediction of underestimation of invasive breast cancer in cases of ductal carcinoma in situ diagnosed at needle biopsy. Clin Breast Cancer 14: 358-364, 2014.
11. Brennan ME, Turner RM, Ciatto S, Marinovich ML, French JR, Macaskill P and Houssami N: Ductal carcinoma in situ at core-needle biopsy: Meta-analysis of underestimation and predictors of invasive breast cancer. Radiology 260: 119-128, 2011.
12. Houssami N, Ciatto S, Ellis I and Ambrogetti D: Underestimation of malignancy of breast core-needle biopsy: Concepts and precise overall and caregory-specific estimates. Cancer 109: 487-495, 2007.
13. Jackman RJ, Burbank F, Parker SH, Evans WP III, Lechner MC, Richardson TR, Smid AA, Borofsky HB, Lee CH, Goldstein HM, *et al*: Stereotactic breast biosy of nonpalpable lesions: Determinants of ductal carcinoma in situ underestimation rates. Radiology 218: 497-502, 2001.
14. Allred DC, Harvey JM, Berardo M and Clark GM: Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 11: 155-168, 1998.
15. Shousha S: Oestrogen receptor status of breast carcinoma: Allred/H score conversion table. Histopathology 53: 346-347, 2008.
16. Fujii T, Yajima R, Tsuboi M, Higuchi T, Obayashi S, Tokiniwa H, Nagaoka R, Takata D, Horiguchi J and Kuwano H: Clinicopathological features of cases with primary breast cancer not identified by 18F-FDG-PET. Anticancer Res 36: 3019-3022, 2016.
17. Choi JY, Lee KS, Kim HJ, Shim YM, Kwon OJ, Park K, Baek CH, Chung JH, Lee KH and Kim BT: Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: Clinical significance and improved characterization. J Nucl Med 47: 609-615, 2006.
18. Matsuzu K, Segade F, Matsuzu U, Carter A, Bowden DW and Perrier ND: Differential expression of glucose transporters in normal and pathologic thyroid tissue. Thyroid 14: 806-812, 2004.
19. Hoffman EJ, Huang SC and Phelps ME: Quantitation in positron emission computed tomography: 1. Effect of object size. J Comput Assist Tomogr 3: 299-308, 1979.
20. Avril N, Menzel M, Dose J, Schellin M, Weber W, Jänicke F, Nathrath W and Schwaiger M: Glucose metabolism of breast cancer assessed by 18F-FDG PET: Histologic and immunohistochemical tissue analysis. J Nucl Med 42: 9-16, 2001.
21. Owaki T, Kijima Y, Yoshinaka H, Uenososno Y, Yoshioka T, Natsugoe S and Aikou T: Ductal carcinoma in-situ of the breast detected by [F-18] fluorodeoxyglucose positron emission tomography. Breast Cancer 13: 210-213, 2006.
22. Higashi K, Clavo AC and Wahl RL: Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. J Nucl Med 34: 414-419, 1993.