Clinical Significance of ^{18}F -FDG-PET in Invasive Lobular Carcinoma

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Abstract. The diagnostic utility of ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) for breast cancer is controversial. The histological type or tumor size of breast cancer has been reported to be associated with a greater likelihood of positive FDG uptake. Compared to invasive ductal carcinomas (IDCs), invasive lobular carcinomas (ILCs) have a lower level of FDG uptake and are detected at a significantly lower sensitivity. The role of preoperative FDG-PET for ILCs may, thus, be limited. Few data evaluating the significance of FDG-PET in ILCs are available. Here, we evaluated the clinical significance of FDG-PET for ILC patients. We retrospectively investigated the cases of 196 consecutive patients with primary breast cancer who were diagnosed as having ILC ($n=15$) or IDC ($n=181$) and underwent FDG-PET preoperatively. Fifteen (7.7%) of patients were histopathologically diagnosed as ILC. A univariate analysis revealed that tumor size, extent of tumor, estrogen receptor (ER) expression and progesterone receptor (PgR) expression were significantly different between the ILC and IDC groups. The maximum standardized uptake value (SUV_{max}) values of the primary tumors were not significantly different between the two groups but, regardless of the larger size of tumor or ductal spread, the SUV_{max} was relatively lower in the ILC group compared to the IDC group. The tumors in two ILC cases showed no FDG uptake. Among the ILC cases, there were linear associations between SUV_{max} and tumor size and between SUV_{max} and the nuclear grade by Pearson

correlation ($r=0.447$, $p=0.048$ and $r=0.519$, $p=0.024$, respectively). Our findings imply that the preoperative FDG uptake in ILC may be reflective of the tumor size and the nuclear grade of the tumor. FDG uptake may be useful and predictive of aggressive features or prognosis in ILC patients.

^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been widely used for diagnosing the stage or recurrence in breast cancer; however, the diagnostic utility of FDG-PET for breast cancer is controversial (1-9). FDG-PET has high specificity but mediocre sensitivity for identifying primary breast cancer; it can detect breast cancers with a sensitivity of 66%-96% and a specificity of 83%-100% (1-5). 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% (5).

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 (5). Invasive lobular carcinomas (ILCs) have a lower level of FDG uptake and are detected at significantly lower sensitivity than invasive ductal carcinomas (IDCs) (10-15). Several studies reported that ILCs showed a limited FDG uptake and that the role of preoperative FDG-PET in ILC may, thus, be limited (11). Few data evaluating the significance and usefulness of FDG-PET in ILC are available in the existing literature.

Our previous study revealed that small-size tumor invasion and lower nuclear grade were significant factors associated with FDG uptake in primary breast cancers, including IDCs and ILCs (5). That study revealed that histological type, including ILC, was not significantly associated with FDG uptake in the primary tumor (5). In the present study, we evaluated the clinical significance and usefulness of FDG-PET in ILC.

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Key Words: FDG-PET, invasive lobular carcinoma, breast cancer, size, nuclear grade.

Patients and Methods

Patients. We retrospectively investigated the cases of 196 consecutive patients with primary breast cancer who were diagnosed as having ILC or IDC and underwent FDG-PET preoperatively at 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 196 patients, 15 (7.7%) were diagnosed as having ILC. The patients underwent FDG-PET/computed tomography 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, size of the invasive primary tumor, size of extent of tumor, presence of lymphatic or vascular invasion, nuclear grade, estrogen receptor (ER) expression 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 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 (16, 17).

Statistical analysis. The breast cancer cases were divided into two groups on the basis of histology, *i.e.* ILC and IDC. 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 investigate possible relationships between the SUV_{max} and the tumor size or nuclear grade, we computed the Pearson coefficient of correlation and performed a linear regression analysis of the data. Differences were considered significant when $p < 0.05$.

Results

In total, 196 cases were included in the analysis. In 15 patients (7.7%), the histopathological examination revealed ILC. We divided the 196 cases with breast cancer into two groups based on the histology of the primary tumor, *i.e.* ILC (n=15) and IDC (n=181). Table I shows the patients' characteristics and summarizes the results of the univariate analysis conducted to determine the differences in clinicopathologic variables between ILC and IDC. The univariate analysis revealed that tumor size, extent of tumor, ER and PgR expressions were significantly different between the ILC and IDC groups. The SUV_{max} values of the primary tumor were not significantly different between the two groups; however, despite the larger size of tumor and extent of tumor, the SUV_{max} values were relatively lower in the ILC group compared to the IDC group.

In two ILC cases, there was no FDG uptake in the tumors (Figure 1). Most of the ILC cases showed FDG uptake, although it was relatively lower than the intake of the IDC

Table I. Patients' characteristics and clinicopathological features in invasive ductal carcinoma and invasive lobular carcinoma.

	ILC (n=15)	IDC (n=181)	<i>p</i>
Age (years)	61.2±11.5	59.3±12.1	0.558
CEA	2.17±0.77	2.40±2.08	0.640
CRP	0.05±0.01	0.13±0.56	0.529
SUV _{max}	2.25±1.99	3.44±3.03	0.137
Tumor size of invasion (mm)	40.5±31.3	18.1±11.0	<0.001
Size of extent of tumor (mm)	52.6±29.5	30.2±18.7	<0.001
Node metastases (n)	7	47	0.155
ER (n)	15	113	0.008
PgR (n)	14	105	0.016
HER2 (n)	0	32	0.157
Nuclear grade 3 (n)	3	65	0.336
ly (n)	7	75	0.903
v (n)	1	40	0.279

Values are expressed as mean±SD. n, Number; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ly, lymphatic invasion; v, vascular invasion; CRP, C-reactive protein; CEA, carcinoembryonic antigen; SUV_{max}, maximum standardized uptake value; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

cases (Figure 2). Among the ILC cases, there were linear associations between SUV_{max} and tumor size and between SUV_{max} and nuclear grade ($r=0.447$, $p=0.048$ and $r=0.519$, $p=0.024$, respectively) (Figure 3).

Discussion

As noted in the Introduction, there are many reports of preoperative evaluations using FDG-PET for breast cancer but the diagnostic utility of FDG-PET for breast cancer is controversial (1-9). It was recently reported that FDG-PET may be useful in predicting prognosis or aggressive features in breast cancer patients (5, 13, 15, 18-20); however, there is a lack of data regarding the associations between FDG uptake and prognostic factors in ILC. As can be seen from our present findings and those of other studies, ILCs have a limited uptake, which is sometimes not significant. The lower FDG uptake of ILCs has been explained as being due to diffuse infiltrative growth patterns, a low tumor cell density, a low level of GLUT1 expression and a decreased proliferation rate (10, 12, 15).

However, we herein observed that, among the ILC cases, there were linear associations between SUV_{max} and tumor size, as well as nuclear grade, a finding consistent with our previous study of IDCs (5). Our previous study revealed that, in IDC cases, low nuclear grade was significantly negatively associated with FDG-PET uptake, as was the small size of tumor invasion (5). FDG-PET measures glucose metabolism,

Figure 1. Cases without FDG uptake in tumors. *a.* Absence of FDG uptake in right breast cancer on PET-CT in a 53-year-old female. Histopathological examination revealed invasive lobular carcinoma. The tumor size was 16 mm. *b.* Absence of FDG uptake in left breast cancer on PET-CT in a 85-year-old female. Histopathological examination revealed invasive lobular carcinoma. The tumor size was 27 mm.

Figure 2. Cases with FDG uptake in tumors. *a.* FDG uptake (SUV_{max} 1.4) in right breast cancer on PET-CT in a 75-year-old female. Histopathological examination revealed invasive lobular carcinoma. The tumor size was 15 mm. *b.* FDG uptake (SUV_{max} 1.4) in left breast cancer on PET-CT in a 79-year-old female. Histopathological examination revealed lobular carcinoma. The tumor size was 85 mm.

Figure 3. Association between SUV_{max} and tumor size and, also, between SUV_{max} and nuclear grade. There were linear associations between SUV_{max} and tumor size (*a*) and nuclear grade (*b*), when using a Pearson correlation ($r=0.447$, $p=0.048$ and $r=0.519$, $p=0.024$, respectively).

which reflects the biological aggressiveness of cancers (4, 8, 13, 15, 18-20) and its use may, thus, provide biological information about a tumor's growth potential. In fact, several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in breast cancer patients (5, 13, 15, 18-20).

ILCs are less conspicuous than IDCs on FDG-PET, but our present findings indicate that FDG-PET may also be useful for predicting the prognosis or aggressive features in ILC patients. In the two ILC cases without FDG uptake, there was no recurrent disease even though neither of the patients underwent chemotherapy. Two (15.4%) of the other 13 cases of ILC showing FDG uptake had disease recurrence. These findings indicate that FDG-negative ILCs may have a better prognosis than FDG-positive cases. We suggest that FDG-PET, as a predictor, may indicate a lower risk of recurrent disease in ILC patients with FDG negativity.

This study has several limitations, with the major one being that it was a retrospective analysis encompassing a relatively small number of cases. Additional research is needed to explore other benefits and drawbacks of FDG-PET evaluations of ILCs; however, the present study provides the first report describing the features and the additional usefulness of the FDG uptake of ILCs as a predictor of the nuclear grade or prognosis among patients with ILC.

In conclusion, the present study demonstrated that the finding of preoperative FDG uptake in ILC may be reflective of the tumor size and nuclear grade of the tumor. In light of our results, FDG uptake may be predictive of aggressive features or prognosis among patients with ILC.

Conflicts of interest

The Authors declare that they have no competing financial interests.

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References

- Flanagan FL, Dehdashti F and Siegel BA: PET in breast cancer: *Semin Nucl Med* 28: 290-302, 1998.
- Cooper KL, Harnan S, Meng Y, Ward SE, Fitzgerald P, Papaioannou D, Wyld L, Ingram C, Wilkinson ID and Lorenz E: Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: A systematic review and meta-analysis. *Eur J Surg Oncol* 37: 187-198, 2011.
- Peare R, Staff RT and Heys SD: The use of FDG-PET in assessing axillary lymph node status in breast cancer: A systematic review and meta-analysis of the literature. *Breast Cancer Res Treat* 123: 281-290, 2010.
- Koolen BB, van der Leij F, Vogel WV, Rutgers EJ, Vrancken Peeters MJ, Elkhuisen PH and Valdés Olmos RA: Accuracy of 18F-FDG PET/CT for primary tumor visualization and staging in T1 breast cancer. *Acta Oncol* 53: 50-57, 2014.
- 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.
- Groves AM, Shastry M, Ben-Haim S, Kayani I, Malhotra A, Davidson T, Kelleher T, Whittaker D, Meagher M, Holloway B, Warren RM, Ell PJ and Keshtgar M: Defining the role of PET-CT in staging early breast cancer. *Oncologist* 17: 613-619, 2012.
- Hodgson NC and Gulenchyn KY: Is there a role for positron emission tomography in breast cancer staging? *J Clin Oncol* 26: 712-720, 2008.
- Fujii T, Yajima R, Tatsuki H, Oosone K and Kuwano H: Implication of 18F-Fluorodeoxyglucose uptake of affected axillary lymph nodes in cases with breast cancer. *Anticancer Res* 36: 393-397, 2016.
- Fujii T, Yajima R, Tatsuki H and Kuwano H: Prediction of extracapsular invasion at metastatic sentinel nodes and non-sentinel lymph nodal metastases by FDG-PET in cases with breast cancer. *Anticancer Res* 36: 1785-1789, 2016.
- Jung NY, Kim SH, Hoi BB, Kim SH and Sung MS: Associations between the standardized uptake value of 18F-FDG PET/CT and the prognostic factors of invasive lobular carcinoma: In comparison with invasive ductal carcinoma. *World J Surg Oncol* 13: 113, 2015.
- Heudel P, Cimorelli S, Montella A, Bouteille C and Moggetti T: Value of PET-FDG in primary breast cancer based on histopathological and immunohistochemical prognostic factors. *Int J Clin Oncol* 15: 588-593, 2010.
- Bos R, van Der Hoeven JJ, van Der Wall E, van Der Groep P, van Diest PJ, Comans EF, Joshi U, Semenza GL, Hoekstra OS, Lammertsma AA and Molthoff CF: Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. *J Clin Oncol* 15: 379-387, 2002.
- Gil-Rendo A, Martinez-Regeira F, Zornoza G, Garcia-Velloso MJ, Beorlegui C and Rodriguez-Spiteri N: Association between 18F-fluorodeoxyglucose uptake and prognostic parameters in breast cancer. *Br J Surg* 96: 166-170, 2009.
- Avil N, Rose 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* 15: 3495-3502, 2000.
- Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, Yamamoto M, Hama Y, Tamura K, Ishida J, Abe Y and Mochizuki H: Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. *Jpn J Clin Oncol* 38: 250-258, 2008.
- 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.
- Shousha S: Oestrogen receptor status of breast carcinoma: Allred/H score conversion table. *Histopathology* 53: 346-347, 2008.

- 18 Aogi K, Kadoya T, Sugawara Y, Kiyoto S, Shigematsu H, Masumoto N and Okada M: Utility of ^{18}F FDG-PET/CT for predicting prognosis of luminal-type breast cancer. *Breast Cancer Res Treat* 150: 209-217, 2015.
- 19 Ohara M, Shigematsu H, Tsutani Y, Emi A, Masumoto N, Ozaki S, Kadoya T and Okada M: Role of FDG-PET/CT in evaluating surgical outcomes of operable breast cancer – usefulness for malignant grade of triple-negative breast cancer. *Breast* 22: 958-963, 2013.
- 20 Sanli Y, Kuyumcu S, Ozkan ZG, Isik G, Karanlik H, Guzelbey B, Turkmen C, Ozel S, Yavuz E and Mudun A: Increased FDG uptake in breast cancer is associated with prognostic factors. *Ann Nucl Med* 26: 345-350, 2012.

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